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Abstract

A close link exists between diabetes mellitus (DM) and cardiovascular disease (CVD), which is the most prevalent cause of morbidity and mortality in diabetic patients. Cardiovascular (CV) risk factors such as obesity, hypertension, and dyslipidemia are common in patients with DM, placing them at increased risk for cardiac events. In addition, many studies have found biological mechanisms associated with DM that independently increase the risk of CVD in diabetic patients. Therefore, targeting CV risk factors in patients with DM are critical to minimize the long-term CV complications of the disease. This paper summarizes the relationship between diabetes and CVD, examines possible mechanisms of disease progression, discusses current treatment recommendations, and outlines future research directions.

Introduction

Diabetes confers a two- to fourfold increased risk of coronary heart disease, stroke, and peripheral artery disease. The burden of cardiovascular disease related to diabetes has increased over the past two decades, and macrovascular events remain the leading cause of mortality. Insulin resistance is the major underlying factor for all the features of metabolic syndrome and is considered very crucial in the pathophysiology of vascular damage.¹

The Pathophysiology of CVD in Diabetes

The two key metabolic abnormalities associated with type 2 diabetes mellitus (T2DM) are insulin-resistance and hyperglycemia. Whereas the two main pathophysiologic mechanisms in vascular wall that can lead to CV events are arterial stiffening and atherosclerosis.²

The patients with diabetes mellitus show both accelerated arterial stiffening as well as premature atherosclerotic changes.

Pro-Atherogenic Mechanisms Associated with Hyperglycemia (Flowchart 1)

Different molecular mechanisms associated with hyperglycemia have been identified including:
- Increased glucose flux via polyol pathway
- Activation of protein kinase C (PKC)
- Formation of advanced glycation end products (AGE)
- Increased glucose flux via the hexosamine pathway, and activation of the 12/15-lipoxygenase (12/15-LO) pathway³
- All these mechanisms finally result in increased superoxide formation

Insulin Resistance (Flowchart 1)

Insulin receptors are seen in endothelial cells, macrophages, and vascular smooth muscle cells (SMCs). Insulin resistance has been shown to be due to decreased synthesis or release of NO and increased production of reactive oxygen species, as well as with an increased free fatty acids release from adipose tissue. The increased levels
Flowchart 1: Pathophysiologic mechanisms through which hyperglycemia and insulin resistance can affect the arterial wall

- **Atherosclerosis**
  - \( \uparrow \text{Chronic inflammation} \)
  - \( \uparrow \text{Endothelial permeability} \)

- **Endothelial dysfunction**
  - \( \uparrow \text{Collagen synthesis} \)

- **Arterial wall stiffness**
  - \( \uparrow \text{MMP expression} \)
  - \( \uparrow \text{AGEs generation} \)
  - \( \uparrow \text{Collagen cross-linking} \)
  - \( \uparrow \text{Ang II in SMCs} \)

- **Insulin resistance and hyperinsulinemia**
  - \( \uparrow \text{FFA release} \)
  - \( \uparrow \text{ROS production} \)
  - \( \downarrow \text{NO synthesis/release} \)

- **Diabetes mellitus**
  - \( \uparrow \text{ROS production, } \downarrow \text{NO synthesis} \)
  - \( \downarrow \text{Anti-oxidant intracellular defense} \)

**Obesity and Insulin Resistance**

Impaired nutrition contributes to hyperlipidemia as well as insulin resistance causing hyperglycemia. This leads to alterations in intracellular signaling and cellular metabolism that negatively impact cells. All these effects induce cellular events like:
- Modification of gene expression,
- Dyslipidemia and hyperglycemia,
- Activation of oxidative stress and inflammatory response,
- Endothelial dysfunction, and
- Ectopic lipid accumulation, which is favored by obesity and leads to metabolic deregulation.

In the cardiomyocyte, this damage can be through the following three actions:
- Alteration of insulin signaling,
- Increased substrate accessibility, and
- Inflexibility of metabolism changes.

**Diabetes and Inflammation**

Diabetes is a state of chronic and low-level inflammation. Insulin resistance may be preceded by some immune activation in diabetic and pre-diabetic states and may leads to increase in cardiovascular risk. Along with diabetes, obesity is also associated with increase in the levels of a number of adipokines. Diabetes accelerates the process of natural aging in arterial tree. The correlation between arterial stiffness and CV events or all-cause mortality can be explained by the hemodynamic effects of arterial stiffening. CIMT and Plaque Presence are the surrogate markers of atherosclerosis, plaque indicates an advanced atherosclerotic process (Fig. 1).⁶,⁷

**Endothelial Dysfunction**

Healthy endothelium has the properties of vasodilation, anti-atherogenesis as well as anti-inflammatory. However,
a defective endothelium is associated with an accelerated process of atherosclerosis. Hence, both insulin deficiency as well as insulin resistance promote dyslipidemia along with increased oxidation, glycosylation, and triglyceride enrichment of lipoproteins, which further contributes to increase in atherogenicity and macrovascular disease in diabetes (Fig. 2).8

**Impaired Vascular Repair**

Diabetes retards the *endothelial repair processes*, due to shortage of bone marrow (BM)-derived vascular regenerative cells like circulating progenitor cells (CPCs) as well as *endothelial progenitor cells (EPCs)*.9 EPCs released from the bone marrow are involved in homeostasis of healthy as well as damaged endothelium and in physiologic as well as compensatory angiogenesis. Therefore, a reduction in their number as seen in diabetes is believed to promote the development and progression of cardiovascular disease.10

**Hypercoagulability**

Up to 80% of diabetics die of thrombotic events. In that 75% of these deaths are the result of a myocardial infarction, and the remainders are the result of cerebrovascular events and complications related to PVD.11

**Epicardial Adipose Tissue (EAT)**

EAT is an imaging biomarker (ECHO and CTA), and has gained attention due to its intimate location to the coronary vessels and the myocardium. Associated with prevalent subclinical atherosclerosis, ischemia, and future major adverse cardiac events, EAT is a transducer of the adverse effects of systemic inflammation and metabolic disorders on the heart, and thus represents an important target for therapeutic interventions.12

**Clinical Presentations**

See Table 1.
**Table 1**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Very high risk</td>
<td>Patients with DM and established CVD or</td>
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<tr>
<td></td>
<td>Other target organ damage or</td>
</tr>
<tr>
<td></td>
<td>Three or more major risk factors or</td>
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<tr>
<td></td>
<td>Early onset T1DM of long duration &gt;20 years</td>
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<tr>
<td>High risk</td>
<td>Patients with duration of DM &gt;10 years without any organ damage plus any other additional risk factor</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Young patients (T1DM aged &lt;35 years or T2DM aged &lt;50 years) with duration of DM &lt;10 years, without any other risk factors</td>
</tr>
</tbody>
</table>

**Macrovascular Disease**

Characterized by fibrosis and arterial thickening, as well as vasomotor and endothelial dysfunction, can *increase risk of heart failure (HF)* in diabetes mellitus. Diabetic blood is more likely to be high in triglycerides. Hypertriglyceridemia in diabetes—insulin action regulates lipid flux (Fig. 3).

**Premature Atherosclerosis**

Multiple mechanisms are associated with insulin resistance, which may promote atherosclerosis in type 2 diabetes (Fig. 4):

- *Secretion of adipokines* from adipose tissue (apelin, adiponectin, or leptin),
- *Fatty acid binding protein (FABP)* aP2 secreted from adipocytes, foam cells or macrophages (Mφ),
- *C peptide as a decomposition product of proinsulin*, and
- *Diabetic hyperlipidemia*. Lipoprotein lipase (LPL) is inversely associated with insulin resistance, atherosclerosis, and non-enzymatically glycated hemoglobin (HbA1c).

**Cardiac Clinical Impact**

**Coronary Artery Disease**

Diabetes mellitus is one of the major risk factors for the development of coronary artery disease and adversely
affects overall clinical outcomes. The absolute risk of death due to coronary artery disease is three to five times higher in patients with diabetes when compared to those without diabetes, regardless of their cholesterol concentration. Three-fourths of the diabetics have multivessel disease and the plaques involving multiple coronary segments. Coronary angiography of diabetic patients characterized as showing diffuse narrowing and multivessel disease. Pathologically in diabetics the plaques show larger necrotic cores, increased presence of inflammation as well as advanced coronary artery calcification. Diabetic patients show a less favorable clinical outcome after successful percutaneous coronary intervention, which will be manifested as higher incidence of restenosis of the artery or stent, a higher incidence of myocardial infarction or reinfarction, and a lower survival rate. After coronary artery bypass grafting, diabetic patients had twice the mortality when compared with those without diabetes.

Silent CAD is far more common in patients with DM (10–20%) than those without DM (1–4%). Diabetic nephropathy is one of the key factors due to which there is an increased incidence of silent ischemia in diabetic patients. Risk for HF increases 5-fold in women and 2.4-fold in men in comparison with those without DM (Fig. 5).

Hypertension
Hypertension is very common in patients with T1DM as well as T2DM, with prevalence rates of about 30% and 60%, respectively. Hypertension in diabetic patients is closely associated with the development of diabetic nephropathy (DN).

Diabetes can directly contribute to the development of Diabetic cardiomyopathy (CMP). Annual mortality rates up to 20%. Refer Tables 2 and 3 for recent guidelines and management.

Heart Failure (HF)
So many observational studies have demonstrated an increased risk of HF of about 2–4 folds in diabetics compared with nondiabetics. Beyond the structural or functional changes due to diabetic cardiomyopathy, a
complex underlying, and interrelated pathophysiology exists. In spite of controlling hyperglycemia, the high prevalence of HF in T2DM persists (Fig. 6). There is an increased risk of developing HF both HF with reduced ejection fraction as well as HF with preserved ejection fraction.

A recent network analysis showed that biomarker profiles specific for HFrEF are related to cellular proliferation and metabolism, whereas those specific for HFpEF are related to inflammation and extracellular matrix reorganization. How these pathophysiological differences might translate into different outcomes in those with DM and HFpEF versus HFrEF remains unclear. Refer Tables 2 and 3 for recent guidelines and management.

Diabetic Dyslipidemia
Low HDL, moderate to high LDL. Dyslipidemia is one of the factors by which diabetes can promote atherosclerosis and endothelial dysfunction. Refer Tables 2 and 3 for recent guidelines and management.

Cerebrovascular Disease
Diabetes is a major risk factor for the development of carotid atherosclerosis and stroke, both ischemic as well as hemorrhagic. Data from the Emerging Risk Factors Collaboration suggest that diabetes was associated with an increased risk of ischemic stroke for about 2.27 folds and that of hemorrhagic stroke for about 1.56 folds. Diabetes is already established as a risk factor for cognitive impairment, dementia, and Alzheimer disease (Fig. 4).
Diabetes is also associated with an increased risk of lower limb ischemia for about twofolds, and about 21% of diabetes patients have signs of peripheral artery disease (PAD). The ABI is the most widely used tool to diagnose PAD and its normal range is from 0.9 to 1.3. An ABI lower than 0.9 is commonly used to diagnose PAD both symptomatic and asymptomatic.

**Diabetic Nephropathy**

Efferent arteriolar hyalinosis is the major defect seen in DN. Nonspecific arteriosclerosis may be present, which is associated with more severe glomerular disease. “Matrix to Media ratio” is increased. Significant medial thickness may be associated with hypertension. Neovascularization is seen. Diabetic kidney disease includes glomerular hyperfiltration, progressive albuminuria, declining GFR, and, ultimately, ESRD.

**ANS Dysfunction**

Microcirculation is regulated by central as well as local regulatory mechanisms. Central regulation is through autonomic sympathetic and parasympathetic nerves.

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**TABLE 2**

<table>
<thead>
<tr>
<th>2019 ESC guidelines</th>
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<tbody>
<tr>
<td><strong>Change in recommendations</strong></td>
</tr>
<tr>
<td><strong>BP targets</strong></td>
</tr>
<tr>
<td>BP target &lt;140/85 mm Hg for all</td>
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<tr>
<td><strong>Lipid targets</strong></td>
</tr>
<tr>
<td>In DM at high CV risk, an LDL-C target of &lt;100 mg/dL</td>
</tr>
<tr>
<td>In DM at very high CV risk, an LDL-C target of &lt;70 mg/dL is recommended</td>
</tr>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
</tr>
<tr>
<td>Aspirin for primary prevention is not recommended in DM at low CVD risk</td>
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<td></td>
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<tr>
<td><strong>Glucose-lowering treatment</strong></td>
</tr>
<tr>
<td>Metformin should be considered as first-line therapy in patients with DM</td>
</tr>
<tr>
<td><strong>Revascularization</strong></td>
</tr>
<tr>
<td>DES rather than BMS is recommended in DM</td>
</tr>
</tbody>
</table>
### TABLE 3
New recommendations in the 2019 guidelines

<table>
<thead>
<tr>
<th>CV risk assessment</th>
<th>Resting ECG is recommended in patients with DM with hypertension or suspected CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of CVD</td>
<td>Lifestyle intervention is recommended to delay/prevent conversion from pre-DM to T2DM</td>
</tr>
<tr>
<td>Glycaemic control</td>
<td>Use of self-monitoring of blood glucose should be considered to facilitate optimal glycemic control in T2DM</td>
</tr>
<tr>
<td></td>
<td>It is recommended to avoid hypoglycemia</td>
</tr>
<tr>
<td>BP management</td>
<td>Lifestyle changes are recommended in hypertension</td>
</tr>
<tr>
<td></td>
<td>RAAS blockers rather than beta-blockers/diuretics are recommended for BP control in pre-DM</td>
</tr>
<tr>
<td></td>
<td>Home BP self-monitoring should be considered in patients with DM</td>
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<tr>
<td></td>
<td>24-h ABPM should be considered for BP assessment, and adjustment of antihypertensive treatment</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>In patients at very high risk, with persistent high LDL-C despite treatment with maximum tolerated statin dose in combination with ezetimibe, or in patients with intolerance to statins, a PCSK9 inhibitor is recommended</td>
</tr>
<tr>
<td></td>
<td>Statins may be considered in asymptomatic patients with T1DM aged &gt;30 years</td>
</tr>
<tr>
<td></td>
<td>Statins are not recommended in women of childbearing potential</td>
</tr>
<tr>
<td>Antithrombotic drugs</td>
<td>Prolongation of DAPT beyond 12 months should be considered for ≤3 years in patients with DM at very high risk who have tolerated DAPT without major bleeding complications</td>
</tr>
<tr>
<td>Glucose-lowering treatment</td>
<td>Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death</td>
</tr>
<tr>
<td></td>
<td>Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or very high/high CV risk, to reduce CV events</td>
</tr>
<tr>
<td></td>
<td>Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin is not recommended in patients with T2DM and a high risk of HF</td>
</tr>
<tr>
<td>Revascularization</td>
<td>Same revascularization techniques are recommended in patients with or without DM</td>
</tr>
<tr>
<td>Treatment of HF in DM</td>
<td>Device therapy with an ICD, CRT, or CRT-D is recommended</td>
</tr>
<tr>
<td></td>
<td>Sacubitril/valsartan instead of ACEIs is recommended in HFrEF and DM remaining symptomatic despite treatment with ACEIs, beta-blockers, and MRAs</td>
</tr>
<tr>
<td></td>
<td>CABG is recommended in HFrEF and DM, and two- or three-vessel CAD</td>
</tr>
<tr>
<td></td>
<td>Ivabradine should be considered in patients with HF and DM in sinus rhythm, and with a resting heart rate &gt;70 b.p.m. if symptomatic despite full HF treatment</td>
</tr>
<tr>
<td></td>
<td>Aliskiren (direct renin inhibitor) in HFrEF and DM is not recommended</td>
</tr>
<tr>
<td>DM treatment to reduce HF risk</td>
<td>SGLT2 inhibitors are recommended to lower risk of HF hospitalization</td>
</tr>
<tr>
<td></td>
<td>Metformin should be considered in patients with DM and HF if eGFR &gt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>GLP1-RAs and DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of HF and may be considered</td>
</tr>
<tr>
<td></td>
<td>Insulin treatment in HF may be considered</td>
</tr>
<tr>
<td></td>
<td>DPP4 inhibitor saxagliptin in HF is not recommended</td>
</tr>
<tr>
<td></td>
<td>Thiazolidinediones (pioglitazone and rosiglitazone) in HF are not recommended</td>
</tr>
<tr>
<td>Management of arrhythmias</td>
<td>Attempts to diagnose structural heart disease should be considered in patients with DM with frequent premature ventricular contractions</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia should be avoided as it can trigger arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Diagnosis and management of PAD</td>
</tr>
<tr>
<td></td>
<td>Low-dose rivaroxaban 2.5 mg b.i.d. plus aspirin 100 mg o.d. may be used in patients with DM and symptomatic Lower Extremity Arterial Disease</td>
</tr>
<tr>
<td>Management of CKD</td>
<td>SGLT2 inhibitors are recommended to reduce progression of diabetic kidney disease</td>
</tr>
</tbody>
</table>
Local regulation is by the substances produced by the endothelial cells. Diabetes contributes to defects in the autonomic nervous system, the endothelium, and local metabolism. Incidence of cardiovascular autonomic neuropathy (CAN) increases with age and inadequate glycemic control, which leads to a higher risk of developing both CAN and CVD in diabetes. It is very common in diabetes and is very well correlated with an increased 5-year mortality rate from CVD. The development and progression of CAN may be due to dysregulation of the autonomic nervous system (ANS) associated with increased sympathetic activity as well as elevated inflammatory markers.

**Angiogenesis**

There is a differential expression of *vascular endothelial growth factors (VEGF)* seen in diabetes, which leads to a paradoxical increase in angiogenesis in the retina and decrease in the peripheral limbs and myocardium.

**Conclusion**

T2DM can be called as Coronary Equivalent. Hyperglycemia and Insulin Resistance are important components of metabolic syndrome and control of which will lead to a disease-free life. Main pathophysiology of DM includes Atherosclerosis and Arterial stiffness which in turn leads to various cardiac complications. Major macrovascular complications of DM are due to Lipid dependent & Endothelial Dysfunction whereas microvascular will be ANS dependent.

Strategies to prevent or delay the progression of diabetic microvascular complications mainly depends on:

- Elimination of hyperglycemia,
- Inhibition hyperglycemia induced vascular dysfunction,
- Neutralization of inflammation and oxidative stress, and
- Activation of tissue-specific protective factors.

Lifestyle management which includes Weight Reduction, Medical nutrition therapy, Physical activity, Tobacco cessation along with blood pressure control, Lipids regulation, Antiplatelet agents, and Glycemic control are recommended for Primary prevention of cardiovascular diseases in diabetic population. Diabetic cardiovascular disease is an upcoming specialty in medicine which is rapidly growing in developed as well as developing nations.

**References**

Abstract
The discovery of insulin earmarked the first effective treatment for diabetes. Till today insulin is an injectable agent. Modifications in the insulin peptide chain and genetic engineering have lead to the evolution of a variety of innovative insulins. Insulin analogues have several advantages over purified animal insulin. Research is ongoing for insulins which can be injected at a reduced frequency apart from non-injectable methods of administration. This chapter highlights all the major milestones and advances in the development of insulin over the last century.

Introduction
The word “Insulin” corresponds to the Latin word “Insula” meaning “island”, so-called because of its formation in the island cells of the pancreas, the islets of Langerhans. Insulin was discovered in 1921 and is soon completing 100 year of its discovery. Insulin, over many decades, has enabled us to understand what we currently know of the disease called diabetes mellitus. With the discovery of insulin, it was for the first time that we got an effective treatment for diabetes; this also led to further research, gaining of knowledge in diabetes pathophysiology and management, in turn helping us to make advances in finding out other therapy options for treatment of this disease. Insulin is the first effective treatment available for diabetes and still retains its importance, despite the advent of other drug classes like sulfonylureas, biguanides, Thiazolidinediones, DPP-4i, SGLT-2i, GLP-1RA, etc. This is the journey of insulin in the past 99 years and what the future holds for it.

Diabetes—The Era before Insulin
Diabetes is not a new disease, the earliest account of its mention is found in Egyptian “Ebers Papyrus” written around 522 B.C., ancient Indian, and Chinese texts also mention this disease. The credit for naming this disease “diabetes” mostly goes to Greek physician “Demetrius of Apamea” (129–199 AD) or to “Aretaeus of Cappadocia (129–199 AD) from the word meaning “passing through.” Thomas Willis, a British doctor, was credited for coining the term “diabetes mellitus” in 1674, mellitus denoting the sweetness of the patient’s urine. In 1776, in Liverpool, physician named Matthew Dobson discovered that “urine of diabetic patients is sweet because of the presence of sugar.” In the latter part of 19th century, many scientists worked to explore the intricacies behind diabetes mellitus—in 1869, Paul Langerhans, a German medical student, discovered groups of cells in the pancreas, unknown at that time and was later named as “Islets of Langerhans” once it was discovered that insulin is produced by these island of cells.

Discovery of Insulin
In 1889, German researchers, Joseph von Mering and Oskar Minkowski while experimenting on dogs found out that if a dog’s pancreas is removed it provokes severe symptoms of diabetes. Inferring from experiments that
pancreatic extracts can elevate the symptoms of diabetes, Minkowski tried injecting the powdered extracts of pancreas, but the toxicity of the extracts was too much to provide any suitable results. This understanding led to multiple attempts at treating diabetes. Many scholars tried using pancreatic extracts for treating diabetes like American pathologist, Lydia Maria Adams DeWitt (1906) and German physician George Ludwig Zuelzer (1908). Paulesco, a Romanian endocrinology experimenter, in 1916 reported that “the aqueous solution of pancreatic extracts leads to improvement in experimentally induced diabetes,” but unfortunately he could not complete his experiments due to the ongoing World War I at that time.

In 1920, Frederick Banting, a young Canadian orthopedic surgeon, got inspired by the works of other scientists in extracting insulin from pancreas and developed some of his own thoughts and theories. With his ideas, Banting approached John James Richard MacLeod, Professor and head of the department of physiology at University of Toronto. MacLeod gave him laboratory space, 10 dogs to do his experiments, a student assistant, Charles Best, and provided supervision and guidance. Banting started his experiments in May 1921, and by September they reported that removing pancreases in dogs leads to diabetes, which can be cured by giving intravenous injection of pancreatic extracts. Banting named this extract as “Isletin.” In late 1921, Biochemist J. B. Collip, joined the group and was instrumental in purifying Isletin for human use. Considering the importance of these findings, MacLeod allowed human experimentation. On 11th January 1922, a young Canadian patient named Leonard Thompson became the first human being to receive an insulin injection. He was 14-years-old and dying when he received the first famous doses, but without much impact. He developed “sterile abscess” at the site of injection, there was no effect on ketosis and only a mild lowering of glucose levels is seen. Banting, Best, and Collip further purified the pancreatic extracts, and second series of injections were given on 23rd January 1922. This time the results were promising with normalization of glycemia, glycosuria, and Ketosis. Blood glucose levels dropped from 520 mg/dL to 120 mg/dL.

This was hailed as a landmark discovery, resulting in the 1923 Nobel Prize for MacLeod & Banting. The prize also led to a controversy as Best and Collip were excluded. Banting at that time strongly criticized the Nobel Prize committee and decided to share his prize money with Best, in turn MacLeod also decided to share his with Collip. By 1923, the extraction process had been improved, and insulin was commercially available in North America and Europe.

**Insulin Era**

Immediately after discovery, insulin was primarily sourced from animals; particularly bovine and porcine insulin. This was possible because all mammalian insulins are structurally similar, that is, composed of 51 amino acids in two linked polypeptide chains (A and B). In 1955, Fredrick Sanger showed “the sequence of all amino acids in the insulin molecule,” a great feet since it was for the first time that a complete protein had been sequenced, this resulted in Nobel Prize for Sanger in 1959. The two commonly used animal insulins were bovine and porcine. Porcine insulin is very similar to human insulin, differing only in single amino acid difference in polypeptide chain. Bovine insulin is most similar to feline insulin.

Animal insulin became the first to be available insulin to treat diabetes. The disadvantages were insulin reactions, antibody formation, allergies, and sacrificing a large number of animals for extracting the insulin from their pancreas.

In the 1980s, biosynthetic insulins were produced, with human DNA using biotechnology and were made available commercially. Figure 1 depicts the timelines in the development of insulin.

**Recombinant DNA Technology and Human Insulin**

The recombinant DNA (rDNA) technique was the advancement we all were waiting for and this ensured a uniform and continuous supply of insulin for the days to come. This technique involves inserting the human insulin gene and the promoter gene in the plasmids of either "Escherichia coli or yeast (Saccharomyces cerevisiae)." The genes for insulin A and B chains are isolated and then inserted as separate entity in the plasmid of two different E. coli cultures. The E. coli cells are then incubated and allowed to grow in a medium containing lactose, which induces the synthesis of chain A & B separately. The insulin chains so obtained can be isolated, purified, and joined together to give human insulin. This breakthrough provided the first opportunity to “mass-produce ‘human’ insulin using gene technology resulting in recombinant insulins.”
CHAPTER 47
Development of Insulin: 99 Years and Counting

Fig. 1: Timelines in insulin development
Types of Human Insulin

Human insulin is available in three forms:

- Normal regular insulin which is short acting.
- Insulin which is crystalized using fish protein protamine, named as "Isophane or NPH (Neutral Protamine Hagedorn)."
- Mixed insulin or premix insulin, where NPH insulin is present as suspension with regular insulin.

Short acting (regular) insulin starts to act about 30 minutes after injecting, and the peak action is reached between 2 and 3 hours of dosing. The duration is up to 10 hours. Intermediate acting insulin or NPH takes about 2–4 hours for onset of action with peak action happening at about 4–10 hours. The total duration of action can be up to 18 hours.

The main principle employed to enhance the time of action of insulin is to use protamine, which crystalizes the insulin and makes it insoluble, along with that zinc is employed to stabilize the insulin hexamers in solution. This protaminated insulin dissolves slowly, along with slow dissipation of zinc after subcutaneous injection destabilizes the hexamers resulting in slow release of insulin monomers, which readily gets absorbed. 10

Premix insulins are suspensions of short acting soluble insulin and insoluble protaminated long acting insulin. Due to this nature before ever dose “insulin vial should be rolled or repeatedly turned upside down,” this ensures the uniformity of dosing of each component whole injecting. The premix insulins are formulated generally in ratio of either 30:70 or 50:50, but other variations are also available. 10

Human recombinant insulins have some advantages over highly purified animal insulins, namely:

- Lower immunogenicity shown by lower titers of circulating antibodies to insulin;
- Few reactions at injection site;
- Better and more rapid absorption in circulation; and
- Low breakdown at the site of injection itself.

Insulin Analogue

Insulin analogs are formed by altering the amino acid sequence such that the receptor activity is preserved while providing other benefits. Genetic engineering is employed to modify or change the amino acids of the peptide chains resulting in changed absorption, distribution, metabolism, and excretion (ADME) characteristics. 10

These modifications are done to have better pharmacokinetic profile of the insulins in terms of their duration of action and metabolism. These are done to have two types of insulin analogs. One which are fast acting, faster than the regular human insulin and also those which provide a better basal coverage with long duration if action and no peak effect, better than what can be achieved by NPH insulin.

Basal Insulins

Glargine: First long acting basal insulin analogue which was formulated by adding two arginine residues to the C-terminus of the B-chain and the substitution of glycine for asparagine at position A21. These changes made it possible for glargine to be soluble at acidic pH (resulting in a clear insulin in the vial) and the solubility decreases once the pH becomes neutral or basic. This when injected in slightly basic environment of subcutaneous tissue forms micro-precipitates at the injection site. These micro precipitates take time to dissolve, and hence we get long duration of action.

Detemir: With insulin detemir, the threonine residue at position B30 was deleted and a myristic acid (fatty acid) side chain was added to the lysine residue at position B29. These modifications enable insulin detemir to bind reversibly to albumin with high affinity once injected. These modifications results in slow release of insulin from albumin binding thereby delaying both absorption and breakdown. This prolongs the duration of action but in few instances twice daily dosing is needed. The fatty acid side-chain not only enhances self-association of monomers in the subcutaneous depot, but also provides the added benefit of reduced glycemic variability. 11

Glargine U-300: An advanced formulation of glargine insulin. The glargine insulin polypeptide chain is unchanged in Glargine U300, only the concentration of glargine is changed to 300 units/mL. This increased concentration leads to the formation of more compact depots in the subcutaneous tissue once injected. This more compact depots decrease the surface area and dissolution rates, further leading to an increased subcutaneous half-life. The result is a better flatter insulin profile in circulation when compared to glargine U100. This concentrated formulation results in a good half-life of 18–19 hours with action up to 36 hours. 12

Table 1 gives action profile of basal insulins.
Degludec: In insulin degludec, the threonine residue at position B30 is deleted and the ε-amino group of LysB29 is acylated with a 16-carbon fatty acid side-chain via a γ-L-glutamic acid linker. In solution degludec is present in the form of stable dihexamers due to the presence of phenol. Once injected, phenol rapidly dissipates from the subcutaneous tissue and these dihexamers link up end to end to form large chains of multihexamer. These multihexamer chains increase the size and prevent the absorption of insulin, which can happen only when these multihexamers are converted to monomers. The process happens gradually with the removal of zinc from one end of these chains.

Rapid-Acting Insulin Analogs

“Rapid-acting insulin analogs” are designed to provide rapid onset of action which also terminate early in comparison to regular human insulin. Currently, three such insulins are available commercially: insulin aspart, insulin lispro, and insulin glulisine.13

Rapid acting insulin analogs are administered with the meals or shortly before starting the meal, as they are rapidly absorbed in systemic circulation from subcutaneous tissue. The peak action is reached in 1–2 hours of administration and it takes around 4–6 hours for their action to wear off completely. Rapid acting insulin analog therapy is directed to have a good postprandial glycemic control.

Rapid-acting insulins also found their use in insulin pumps, also known as “continuous subcutaneous insulin infusion (CSII) devices.” In CSII therapy, insulin is administered as a continuous infusion in the subcutaneous tissue. This continuous supply of rapid acting insulin works to provide both bolus and basal coverage as well as correctional doses.

Insulin lispro: Modifications done in insulin peptide chain include the reversal of amino acids at positions B28 (proline) and B29 (lysine). This makes it similar to the sequence seen in “insulin-like growth factor 1 (IGF-1).” This change makes the absorption faster with a definite advantage over regular human insulin.14

Insulin aspart: Modification to peptide chain includes replacing proline at B28 with another amino acid, that is, aspartic acid. This structural alteration results in increased monomer fraction.14

Insulin glulisine: Insulin glulisine is formed by “replacing glutamic acid for lysine at B29 and replacing asparagine with lysine at B3.” This has resulted in addition of extra charge to the peptide chain resulting in somewhat lower isoelectric point in comparison to regular human insulin; this enhances solubility of insulin glulisine at normal body pH.14 Table 2 delineates action profile of rapid acting insulins. Figure 2 shows action profile of different insulins.

**Inhaled (Technosphere) Insulin (AFREZZA)**

Technosphere insulin (Afrezza) was FDA approved in 2014. Its pulmonary absorption leads to a more rapid

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**TABLE 1** Action profile of basal insulins11-14

<table>
<thead>
<tr>
<th>Basal insulin</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH Insulin</td>
<td>1.5</td>
<td>4.0–10</td>
<td>10–16 hours</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Insulin degludec</td>
<td>1–2</td>
<td>Peak less</td>
<td>&gt;42 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Glargine U300</td>
<td>6</td>
<td>Peak less</td>
<td>Up to 36 hours</td>
<td>Once Daily</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>2–4</td>
<td>No peak</td>
<td>Up to 24 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>2</td>
<td>No peak</td>
<td>14–21 hours</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

**FIGURE 2** Action profile of different insulins.

**TABLE 2** Action profile of rapid acting insulins13-15

<table>
<thead>
<tr>
<th>Rapid Insulin</th>
<th>Onset (min)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular insulin</td>
<td>30</td>
<td>1.5–3.5</td>
<td>7–8</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>10–20</td>
<td>1–3</td>
<td>3–5</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>15</td>
<td>2.4</td>
<td>2–5</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>20</td>
<td>1</td>
<td>Not available</td>
</tr>
<tr>
<td>Faster aspart</td>
<td>5–10</td>
<td>1–2</td>
<td>3–5</td>
</tr>
<tr>
<td>Ultra-rapid lispro</td>
<td>5</td>
<td>1–3</td>
<td>3–5</td>
</tr>
</tbody>
</table>
absorption than currently available, subcutaneously administered rapid-acting insulin preparations but due to many side effects not preferred.14

**Ultrafast Acting Insulin**

Further development aimed at mimicking the natural physiological insulin release had resulted into the development of ultra-rapid acting insulins. Many approaches were used to make insulin act faster than available bolus insulin. Such as by increase of local blood flow, inhalation of a rapidly absorbed insulin, intradermal application or spreading the insulin into a wider area in the SC tissue (either mechanically or enzymatically), or adding excipients that promote monomerization of insulin molecules.15,16

Finally, after incremental research faster-acting insulin aspart was developed. Insulin Faster Aspart is a new formulation containing insulin aspart and two additional excipients (nicotinamide and arginine). Nicotinamide, commonly known as Vitamin B3, acts as an absorption enhancer in the subcutaneous tissue while arginine provides stability to insulin hexamers while in storage.14

Its onset of action is about 6 minutes earlier, the peak is 7 minutes earlier, and it gives 74% greater action during the first 30 minutes compared to traditional aspart.15

Another ultra-rapid acting insulin, currently in development is Insulin Ultra-Rapid Lispro (URLi). URLi is insulin lispro with added excipients—Treprostinil & Citrate. Treprostinil increases absorption by causing local vasodilation in sub-cutaneous tissue without any systemic exposure, while citrate increases vascular permeability at injection site. The onset of action is 11 minutes faster than insulin lispro.16

**Premix Insulin**

The pharmacokinetic and pharmacodynamic limitations of the premixed human insulin formulations have been largely overcome with the introduction of premixed insulin analogues containing a rapid-acting insulin analogue for postprandial glycemic control and an intermediate-acting insulin analogue that controls basal glycemic levels. Unlike premixed human insulin formulations, premixed insulin analogues can be administered within 15 minutes of a meal, a convenience for patients with irregular meal schedules that may increase adherence to treatment.

It consists of premix human insulin or premix insulin analogue in ratio of 30:70 and 50:50. Rapid/short-acting component (30% or 50%) covers mealtime glucose excursions, while intermediate/long-acting insulin (70% or 50%) augments background insulin levels. In clinical terms this gives the added benefit of controlling both fasting (FPG), prandial (PPG), and thereby also leading to better HbA1c, all with one injection only.17

There is evidence that premix may be used as an option in situations like primary care. The INITIATE study showed that addition of premix insulin to oral antidiabetic drugs
(OADs) was more effective, than adding basal insulin for treatment of type 2 diabetes. Rapid-acting insulin, Lispro, is combined with insoluble lispro protamine suspension in a 50:50 and 75:25 (75% protaminated lispro suspension and 25% insulin lispro) ratio. Insulin aspart combinations also are available as 70:30 mixtures (70% insoluble protamine aspart and 30% soluble insulin aspart).

**Insulin Degludec Aspart Co-Formulation (IDegAsp)**

IDegAsp is a co-formulation of two soluble insulins, consisting “70% of insulin degludec and 30% of insulin aspart.” It consists of insulin degludec, a long-acting insulin, and insulin aspart, a rapid-acting insulin both of which function as independently acting blood-glucose-lowering agents.

This co-formulation is made possible because insulin degludec, due to its unique properties, can be combined in a soluble solution with a mealtime insulin analogue without having any effect on the pharmacokinetics and pharmacodynamics of each other. Because of these unique and unprecedented formulation, it is termed as a co-formulation.

**Analog versus Human Insulin: Are there any Advantages?**

There has been a great deal of advancement in insulins over last 99 years but how this has translated into better clinical outcomes has been debated quite a number of times. In current clinical practice, though the adoption of analogue insulins has increased but a large number of patients are still using the good old human insulins. In terms of achieving the glycemic targets and lowering of HbA1c, both analogue and human insulin are many times considered similar. The difference lies in better safety with the newer analogue insulin preparations. Two aspects where the analogue insulins clearly win are:

- Type 1 diabetic patients where the basic requirement of 24 hours of insulin coverage can be best fulfilled by using basal and bolus analog insulins in combination.
- Patients who suffer from night time or overnight hypoglycemia in type 2 diabetes. It is helpful to prescribe a rapid-acting insulin analogue before dinner if the hypoglycemia occurs early in the night or a basal analogue insulin if it occurs toward morning.

Analog insulins provide better outcomes and increases convenience over human insulins. Advantages of using analogue insulins can be summarized as:

- Better mimicking of normal physiological insulin release
- Less rate and chances of hypoglycemia
- Better flexibility in timings of dosing
- Better response at lower dose
- Less immunogenicity

**The Future of Insulin**

Current innovations going on in insulin development, holds a good promise for the future. A great amount of research is going on to modify the pharmacokinetics and pharmacodynamics of insulins for the better.

**Insulin icodec:** A once weekly insulin, this will significantly reduce the burden of injections involved with insulin therapy. Icodec has recently finished phase 2 clinical trials with promising results.

**Oral insulin (ORMD-0801):** An oral insulin under development from Oramed has good results in a recently released results of a pilot study with good reduction of hepatic fats.

**Insulin Ultra-Rapid Lispro (URLi):** An ultra-rapid insulin from Lilly, it is formulated by adding Treprostinil and Citrate as excipients to insulin lispro. This given it an onset of action 11 minutes faster than the conventional insulin lispro. URLi is recently been approved in the European Union as an ultrafast acting insulin.

**BioChaperone lispro insulin:** Again a modification of insulin lispro, this is another ultrafast acting insulin, currently in phase 3 trials. To make this faster, citrate is added along with a novel excipient with a modified oligosaccharide chain, BC222.

**Cone snail insulin:** Another ultrafast acting insulin under development, where the insulin molecule remains in monomer state. It is being derived from the poison of certain cone snails.

Other than the above mentioned, there is a good research going on to modify the action of action of insulin. One such example is the ongoing development of Smart Insulin—“Glucose responsive insulin (GRI).” This next
generation under development insulin will work on the principle of demand and supply. If the blood glucose is more, more of insulin will get activated and show its effect, while if the blood sugar goes down, activated insulin supply will be cut off.\textsuperscript{22,23}

**Conclusion**

Even after 99 years of its discovery and use, insulin is still going strong. Different insulin formulations have been tried over a period of time, some are found to be quite good compared to their predecessor, others fared not so well. Some major milestones in the journey of insulin therapy include—development of NPH insulin, move from animal to human recombinant insulin, and the advent of analog insulin. Innovation is still on and what we can see in the future is a once weekly insulin or even an insulin which is glucose controlled. The future holds a lot of promise for insulin therapy. In terms of effective therapy for diabetes, insulin is sitting on the pedestal as a winner amongst all available options and will remain so for a long time to come.

**References**

Abstract

Insulin is the natural therapy for diabetes and its long journey had gone through various modifications and advancements so as to suit the physiological needs and enhance the adherence among patients. The time tested, most potent drug, Insulin is still a life saving agent and documented to improve quality of life of millions of diabetics. Once weekly basal insulin, Icodec, has promising results and is expected to bring a paradigm change in the management of diabetes. The future of insulin is bright as we discuss here about the newest insulins and various delivery devices and techniques that are in research pipeline.

Introduction

Ever since, Banting and Best’s novel discovery in 1921, Insulin remains the indispensable treatment in diabetes as it primarily regulates carbohydrate and fat metabolism.1 It’s the centenary celebration, this year since insulin has been described as a polypeptide hormone from the islets of Langerhans in the pancreas and yet the quest for the perfect physiological insulin remains. The increase in burden of diabetes and drawbacks in injectable insulins are leading researchers to pursue novel approaches in more effective insulin production, application and delivery. Accordingly, numerous drug candidates are being developed, evaluated and now progressing through the clinic. The development of a once-weekly basal insulin therapy that remained a dream for ages is now ready for Phase 3 trials.

Expanding Horizons with Weekly Basal Insulin—Icodec

The pursuit of the quest to develop weekly insulin remains challenging. In order to improve patient convenience and adherence without increasing hypo/hyperglycemia, a new longer acting once weekly novel insulin named icodec has been developed. It has completed three phase 2 clinical trials in March 2020 and is planned to initiate phase 3a program by the year end.

Molecular and Biological Properties of Insulin Icodec

Insulin icodec [icosaGreek numerical prefix representing 20; dec-derived from degludec] is an insulin analogue with a terminal elimination half-life of ~196 hours with a single subcutaneous injection. This insulin molecule was modified to achieve an albumin-bound circulating inactive depot which acts just as human insulin (HI) but is more slowly cleared. Strong but reversible albumin binding is ensured with the addition of C20 fatty diacid side chain at B29K via a hydrophilic linker. Three amino acid substitutions (A14E, B16H, and B25H) ensure reduced enzymatic degradation of icodec and contribute to attenuating insulin receptor (IR) binding and clearance, further prolonging the half-life (Fig. 1).
The affinity of icodec for the IGF-1 receptor was found to be proportionately lower than its binding to the IR resulting in relatively low IR affinity but full activity, allowing a gradual effect over an extended time period. A steady state is achieved that provides the full therapeutic effect after three to four once-weekly injections. Icodec, in functional assays elicited metabolic effects (like glucose uptake and lipogenesis in fat cells, and stimulation of glycogen synthesis in liver cells) like HI.

Formulation and Dosing
Icodec is formulated into a concentrated concentration as 700 units per mL (700 U/mL) to ensure that the injection dose and volume is not increased. Comparable to insulin NPH and degludec, it is also coformulated with standard pharmaceutical excipients: Zinc functions as a stabilizing agent, while phenol and m-cresol are preservatives.

Phase 1 Data: PK/PD Properties Support Once-Weekly Dosing with a Good Safety and Tolerability Profile
Fifty patients with T2D enrolled for phase I trial to evaluate the PK/PD parameters and safety of insulin icodec at three escalating fixed doses over a 5-week period (Fig. 2). The median Tmax was 16 hours and the geometric mean T1/2 was 196 hours, with no systematic differences between dose levels. As depicted in Figure 3, there was relatively even distribution of glucose-lowering effect over the 7 days, irrespective of dose. The maximum effect was achieved at days 2 and 3 after administration. By day 7, the level was close to the maximum. Adverse event rates were not dose dependent. During the trial, no serious AEs or serious hypoglycemic episodes recorded.

Phase 2 Data: Insulin Icodec Provides Similar Efficacy and Safety to Once Daily Glargine
This pivotal phase 2, 26-week treat-to-target trial with a randomized, double-blinded, double-dummy design evaluated the efficacy and safety of once-weekly icodec versus once-daily insulin glargine U100 (IGlar U100) in 247 insulin-naïve patients with T2D inadequately controlled (A1C 7.0–9.5%) with metformin ± DPP-4i. At end of trial period, estimated mean A1C were 6.69% and 6.87% for icodec and IGlar U100, respectively (mean change from baseline: –1.33% for icodec and –1.15% for IGlar) (Fig. 4). So, no statistically significant treatment difference for change in A1C from baseline to week 26 (–0.18%, 95% CI, –0.38; 0.02) noted. Total dose of insulin glargine was
significantly higher than the dose of insulin icodex in order to achieve similar effect. No new safety issues were identified. Observed rates of level 2 & 3 hypoglycemia were low (60.55 and 52.36 events per 100 patient years of exposure for icodex and IGlar U100, respectively). There was no increase in the rate of level 2 or 3 hypoglycemia compared with insulin glargine ($p = 0.85$).

To summarize, after promising results from Phase 1 & 2 clinical trials, a comprehensive phase 3 program will be conducted for icodex. Fewer injections, more convenience
and simplicity with insulin icodec, will overcome clinical inertia and more patients will accept initiation and continuation on insulin therapy more readily.

**Newer Dimensions in Insulin Research**

**Newer Ultra Rapid Acting Insulins**

Normally insulin glargine cannot be combined with insulin lispro as the pH required to combine them both is not viable. To overcome this challenge, a polyanionic amphiphilic polymer, BioChaperone (BC147) has been devised. With the help of this, glargine can be solubilized at neutral pH enabling it to be combined in a stable formulation with insulin lispro. A combination of 25% of insulin lispro and 75% of insulin glargine known as BioChaperone Lispro or BCLIS has demonstrated a higher significant reduction in postprandial pharmacokinetic exposure leading to significant decrease in both 1 hour and 2 hours PPG levels when compared to Insulin Lispro.4,5 BCLIS elicited a superior earlier PPG control both against LisproMix and to Insulin Glargine, and Insulin Lispro administered separately. BCLIS also demonstrated lower hypoglycemic episodes when compared to Insulin LisproMix.4

Insulin is always present in the hexameric state. This state is required to help stabilize the insulin outside the human body. Once insulin is injected, it is broken down into monomers, which then act in the body. It is essentially this which hinders the insulin to act fast enough to mimic the human physiology. In the most recent developments, an Ultra-Fast-Absorbing-insulin-Lispro (UFAL) has been developed. Insulin when presents as monomers cause aggregation into amyloid fibrils. A unique acrylamide carrier/dopant copolymer excipient has been developed which helps prevent the aggregation of insulin monomers. Insulin being in the monomeric form takes a lot lesser time for absorption once inside the body.6 Preclinical studies have already shown the molecule to be stable for a period of 25 hours in stressed conditions along with a peak action of 9 minutes. Such exciting trials make the molecule more promising in creating a breakthrough in the future treatment of diabetes.6

**Inhaled Insulin**

Technosphere technology has enabled the development of pulmonary routes of insulin drug delivery and presently, rDNA originated inhaled HIs are being reviewed by the FDA for approval.7 Pre-metered unit doses of insulin in
breath activated inhaler devices dissipates into liquid form once exposed to the neutral pH of the alveolar epithelium. Gastrointestinal peptidases that break down insulin in the GI tract are absent in pulmonary route, hence these insulin delivery bypasses the first-pass metabolism system.8

**Oral Insulin**

Oral route supposed to mimic physiological secretion to the portal vein will definitely improve convenience and compliance. Nanoparticle-based approach improved the bioavailability by protecting insulin from proteolytic enzymes and harsh gastrointestinal environment. Anionic natural polymer blocks the release of insulin into the stomach to prevent its degradation. There occurs cellular uptake of nanoparticles or paracellular transport across tight junctions, which enhance paracellular insulin absorption.9–11 An oral insulin formulation (ORMD-0801) elicited clinically significant reductions in HbA1c in poorly controlled T2DM (mean HbA1c levels >8%) patients on standard therapies, without increasing hypoglycemia rates or weight. Preliminary observations from a trial on oral insulin [ORMD-0801] suggested a palliative effect of on non-alcoholic steatohepatitis in T2DM patients by reducing in liver fat content and chronic hepatitis.12,13

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**Fig. 5:** Schematic of regulating the glucose-transport activity with insulin analog (IA; in this study, i-insulin serves as a model analog). Insulin analog can bind to Glut in a glucose-responsive manner. Upon injection and in normoglycemia, insulin analog achieves a regular blood glucose clearance rate, and an insulin analog–Glut complex reservoir is formed. Upon a glucose challenge, increased blood glucose levels result in the release of insulin analog from the insulin analog–Glut complex, which subsequently binds to IR to trigger the translocation of Gluts to cell membranes. With dissociation of insulin analog, glucose-inaccessible insulin analog-bound Glut becomes free Glut, enhancing excess blood glucose clearance. Upon an excess insulin analog injection (i.e., overdose), the formation of the insulin analog–Glut complex attenuates the glucose transport activity of Glut, therefore mitigating hypoglycemia risk.14
Recently, researchers have also explored the use of liposomes, biliosomes, and proliposomes for insulin delivery, which will encapsulate the insulin using the appropriate phospholipid/cholesterol ratio and prevent degradation and enhance bioavailability of oral insulins.

**Glucose-responsive “Smart” Insulins**

A form of smart insulin, named as \(i\)-insulin, which comprises an insulin analogue attached to a glucose transporter [Glut] inhibitor is developed by bioengineers at the University of California. Endogenous Glut associated delivery reservoir of insulin that is capable of modulating glucose metabolism in a blood glucose-dependent manner could be achieved by Insulin facilitated Glut inhibitor conjugate—a long-acting insulin analogue.

Plasma and tissue glucose levels modulate its binding affinity to Glut. The in situ—generated insulin analogue—Glut complex will dissociate in states of hyperglycemia and will release insulin analogue and glucose-accessible Glut to restore normal blood glucose levels in Figure 5. In situations of hyperinsulinemia, glucose uptake will be reduced due to enhanced binding of insulin analogue to Glut that will suppress the glucose transport activity of Glut. Thus, it prevents over-uptake of glucose into cells when there is dip in blood glucose level. When an extra dose of \(i\)-insulin was administered in diabetic mice, the modified insulin kept blood glucose levels within the normal range longer and protected them from hypoglycemia.

**Transdermal Patch**

With the advent of techniques like iontophoresis, sono-phoresis, or phonophoresis, transdermal administration is considered to be an encouraging approach for insulin delivery in near future (Figs. 6A and B).

**Stem Cell Therapy**

Stem cell therapy that aims to ameliorate insulin resistance, improve pancreatic islet \(\beta\) cells regeneration and protect pancreatic islets from apoptosis is looked upon as cure for diabetes. Programmed stem cells (especially, Mesenchymal Stem Cells or MSCs) differentiating into insulin-producing cells (IPCs), evolves as an alternative to islet cell transplant as it also promises to create an optimal environment by secretion of paracrine factors.

**Bioresponsive Insulin Delivery System**

An artificial beta cell with a glucose-sensitive hydrogel membrane that traps glucose-oxidase enzymes in a hydrogel polymer is integrated in this system. This membrane reduces the pH of the membrane and increases the permeability of the hydrogel membrane to insulin. Thus, the system works to accelerate the release of insulin with increasing levels of glucose to ensure feedback-controlled delivery of insulin. The development of closed-loop systems for real-time glucose sensing and controlled insulin release will aim at achieving near-physiological precision in glucose control.

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**Figs. 6A and B:** Transdermal application of insulin
Conclusion

Insulin therapy because of being injectable and risk of hypoglycemia is delayed inordinately even though it is considered as cornerstone of managing diabetes. It has been recommended by every guideline based upon data from several landmark trials. Once-a-week icodec may result in a major paradigm shift in patients’ acceptance of insulin. Promising results have been reported from phase 2 trial demonstrating similar efficacy and hypoglycemia risk with icodec versus once daily glargine. However, search for ultimate therapy for managing hyperglycemia remains among the spectrum of new concepts of insulins and delivery systems that remains further down the road to see the light of clinical reality.

References

CHAPTER 49

Blood Pressure Variability in Diabetes: Its Role in Development of Diabetes Complications

KK Pareek, Girish Mathur, GD Ramchandani, Ashutosh Chaturvedi

Abstract

Recently, blood pressure variability (BPV) has gained focus owing to its role in predicting cardiovascular (CV) outcomes. Additionally, alterations in BPV contribute to the progression of end organ damage and trigger vascular events in hypertensive patients. Therefore, amelioration of BPV is considered a potentially important target and different classes of drugs are used to achieve the desired blood pressure (BP) goal. Based on several studies and clinical trials, treatments with CCB such as amlodipine have been found to be most effective in the management of BPV in hypertensive patients with diabetes. Growing evidence substantiates the role of amlodipine in significant reduction of BPV, thus, lowering the risk of diabetes-related complications. This review sheds light on the importance of BPV reduction and the effectiveness of amlodipine in preventing cardiovascular morbidity and mortality in hypertensive patients with diabetes. Reduced arterial compliance in patients with diabetes mellitus has been shown in several studies, but it has not been significantly associated with either atherosclerosis or vessel wall thickness. BP variability is still poorly explored in diabetic patients. The aim of this study was to compare BP variability and arterial compliance in patients with type 2 diabetes mellitus and controls matched for sex, age, and weight.

Introduction

The coexistence of diabetes and hypertension is greatly linked to the causation of several entities, viz., cardiovascular events, microvascular complications, retinopathy, nephropathy, and increased contribution to all-cause mortality. Blood pressure variability (BPV) is now considered an important risk factor responsible for various complications occurring in hypertensive and diabetic patients. Although physiological blood pressure (BP) variations are commonly seen in most individuals, but when these variations exceed the acceptable range, they acquire pathological significance. Normal circadian BP rhythm is retained during the initial phase of development of hypertension but variability tends to increase when the target organ damage alters the regulatory mechanism of B.P. These findings become of greater importance in case of diabetic patients who are already at a significantly higher risk of development of cardiovascular (CV) events as compared with non-diabetic individuals.

Type 2 diabetes (T2D) patients usually have autonomic dysregulation of cardiovascular functions which increases BPV. In several studies it has been seen that intensification directed at multiple risk factors which are responsible for development of complications in T2D patients, have beneficial effects in respect of macro and microvascular complications.

Blood Pressure Variability

BPV, in very simple terms, can be defined as the variations in BP over time. B.P fluctuations are initiated by a complex interplay between multiple cardiovascular control mechanisms or during change between day to day
life, behavior and triggered by changed environmental situations. These variations increase in patients who are having disordered cardiovascular control mechanisms. Typical examples of routine fluctuations are like BP rise after physical activity or psychological stress and BP reduction when person is in sleep or relaxation. Research has shown that increased BPV values are a strong predictor of CV mortality and morbidity.

In addition to diabetes and hypertension, many studies have shown that like glucose variability visit-to-visit BPV is a great risk factor for macro- and microvascular complications in T2DM patients.

BP measurements undergo automatic variations due to multiple reasons. Short-term variations (within 24 hours) may be due to day-night changes. Likewise long-term variations can be due to differences between days, months, and seasons. Also, systolic BP increases with age and diastolic BP also exhibits an age-related biphasic change; management of such patients with antihypertensive therapy might help to obtain normal BP control with optimal CV protection. This may be valuable in understanding the basic concepts of BPV.

Types of BPV

BPV can be classified into the following four different types:
- Short-term (24-hour BPV)
- Very short-term
- Mid-term
- Long-term
These four types are depicted in Figure 1.

Short-term or 24-hour BPV

Twenty-four-hour BPV is due to many factors, like physical activity, emotional stimuli, and sleep. Day and night changes can be under the influence of signals initiated by the brain. BPV can also be because of mechanical forces generated by ventilation and due to humoral and local vasomotor phenomena. Night time BP (sleep) is on an average 10–20% lower as compared to daytime (waking hours). However, in hypertensive patients, the 24-hour BPV patterns may remain different. Some show >20% or <10% decrease in BP at night, and some may even show a rise in night time BP as compared with day time BP values.

Fig. 1: Various types of BPV, their determinants, and prognostic relevance for cardiovascular and renal outcomes
TABLE 1 Salient features of morning BP surge or morning hypertension

<table>
<thead>
<tr>
<th>Morning hypertension (surge)</th>
<th>Early morning BP ≥ 135/85 mm Hg (HBP/ABP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patterns of morning HT</strong></td>
<td><strong>Clinical outcomes</strong></td>
</tr>
<tr>
<td>• Extension of nocturnal HT</td>
<td>• ↑ Cardiovascular risk</td>
</tr>
<tr>
<td>• ↑ BP variability over 24-hr</td>
<td>• ↑ Occurrence of events</td>
</tr>
<tr>
<td>• Morning surge (rapid BP rise)</td>
<td>• Target organ damage</td>
</tr>
<tr>
<td><strong>Factors influencing morning hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>• Physiological BP surge</td>
<td>• ↑ Sympathetic, neuroendocrine activities</td>
</tr>
<tr>
<td>• Associated conditions</td>
<td>• Stress, OSA, drinking, cold, old age</td>
</tr>
<tr>
<td>• Inadequate 24-hr control</td>
<td>• Loss of drug efficacy at night/over 24-hr</td>
</tr>
</tbody>
</table>

Depending on their SBP values patients can be categorized as extreme dippers (night-day BP ratio ≤ 0.8), dippers (0.8 < ratio ≤ 0.9), nondippers (0.9 < ratio ≤ 1.0), and reverse dippers or risers (ratio > 1.0).

Reverse dippers have worse outcomes as compared to dippers, and the reasons for this rise in BP at night may be because of:
- Nocturnal autonomic dysfunction
- Disturbed baroreflex sensitivity
- Sleep apnea
- Abnormal sodium handling
- Nocturnal volume overload

Table 1 outlines the salient features of morning BP surge or morning hypertension.

**Mid-term or Day-to-day BPV**

Day-to-day variations in BP can be defined as mid-term BP variations. These mostly occur because of inappropriate, non-titration, and poor adherence of patients to antihypertensive therapy. Many a times errors in BP measurement by the clinicians can also lead to such variations. Other factors which can influence mid-term BPV are:
- Advanced age
- Increased arterial stiffness
- Female gender
- Excessive alcohol intake
- Cigarette smoking
- History of peripheral artery disease, cardiovascular disease, diabetes mellitus, and diabetic nephropathy

**Long-term BPV**

Long-term BPVs are seasonal variations, day-to-day variations, and also visit-to-visit (VVV) variations. Behavioral characteristics play an important role in the development of long-term BPV as seen by the clear-cut differences seen in ambulatory BP (ABP) values measured during weekdays and weekends. Insufficient antihypertensive treatment due to non compliance of BP treatment or improper dosing/titration of medications by the physician might also influence long-term BPV. In VVV BPVs, the errors in BP measurement play an important role. Also BP variations between summer and winter indicate the influence of temperature and day light hours due to changes in seasons.

Very Short-Term BPV

It can be defined as beat-to-beat variability.

**Mechanism of BPV**

The association of BPV and all-cause mortality in patients suffering from diabetes (where this is not “dampened” by BP lowering medication) may be because of increased arterial stiffness. So, BPV may be a marker of age-related changes in arterial morphology resulting in arterial stiffness. Thus, an association between BPV and all-cause mortality in patients with diabetes but (not on BP lowering drugs) may be because of accelerated vascular aging. An increased BPV in persons with diabetes is a sign of autonomic dysfunction, in the form of impaired baroreflex sensitivity. Cardiovascular autonomic neuropathy is an important complication of diabetes, and increases mortality risk in patients where it is present. Longer duration of diabetes and evidence of target organ damage can be considered its predictors. The beat-to-beat BP changes occur due to interaction between several CV regulatory systems, such as the baroreceptor reflex, renin-angiotensin system, vascular myogenic response, and release of nitric oxide from the endothelium. But definitive evidence is lacking for the exact underlying mechanism.

**Oxidative Stress**

Oxidative stress itself is an independent predictor of increased LV mass and correlates with abnormal glucose and BPV. In short-term diabetic patients having optimal
metabolic control but impaired GV and BPV risk are associated with endothelial and cardiovascular damage. Not only HbA1c, high SBP, and high DBP but also glucose and BPV are significant in the clinical management of patients suffering from T2DM and hypertension.

**Arterial Compliance**

Many studies have shown that in T2DM patients, that hyperglycemia may affect the compliance of the vascular system, which results in large BP fluctuations. This indicates the need to control glycemic status, high BPV and reduced arterial compliance of patients to prevent increase end-organ damage.

Figure 2 outlines the mechanisms of BPV in patients with diabetes.

**Methods of BPV Measurement**

Various methods for BPV measurements are available:
- Continuous beat-to-beat BP recordings
- Repeated office BP measurement (OBPM)
- 24-hour ambulatory BP monitoring (ABPM)
- Home BP monitoring (HBPM) for long periods

The key index of short-term BPV is standard deviation (SD) of 24-hour average ABP measurements. Since night time decrease in BP interferes with accurate BPV measurements, it has been suggested that 24-hour SD can be a useful guide for the correct assessment of BPV. Day-to-day BPV can be assessed by ABPM for over 48 hours, which may not be a convenient modality for most of the patients. The alternative to ABPM assessment of BPV is use of HBPM that can gather data over many days. The availability of day-to-day BPV may be useful to our physicians in streamlining the management much earlier. Visit-to-visit BPV can be assessed by ABPM or OBPM. However, OBPM is not a correct modality to assess VVV BPV since it might not reflect the BP burden during the patient’s normal activities and also requires multiple visits to the physician’s office. As ABPM cannot be measured frequently, it may not be a good modality to measure VVV BPV. On the other hand, HBPM looks to be an ideal tool for the assessment of VVV BPV under fairly constant conditions without the “white coat effect”.

But it is also true that ambulatory BP monitoring not only provides information regarding BP level, but also indicates changes in BP. As BPV is a multifaceted phenomenon which includes short-term as well as long-term components, the same can be estimated by the SD of the BP values over a defined period of the day or the night-to-day BP ratio, respectively. In T2DM patients, dysregulation of the autonomic control of cardiovascular functions can increase BPV.

**Night Time BPV**

For night time BPV in diabetic patients, it has been shown that ABP measurement is much better modality as compared to clinic BP measurement as it can also confirm the role of abnormal circadian BP variations in predicting future CV events. The SDs of sleep SBP and DBP were independent predictors for CVD risk but the SD of awake BP was not. These finding are in consonance with a study of isolated systolic hypertension which showed that increased night time SBP variability was an independent risk factor for development of stroke.

In a study in diabetic population, neither an abnormal dipping pattern nor the morning BP surge was a predictor of CVD events, whereas the night time BPV appeared to be a strong predictor of CVD risk, independent of ABP level, and other traditional risk factors. These results
diabetes autonomic neuropathy, may be important for the prediction of cardiovascular events in future.

**BPV—Causal or Casual?**

Visit-to-visit variability of BP is associated with risk of developing stroke and CAD, independently of mean BP in office visits. It is possible that this association may be causal and that BPV may be an important and significant factor especially in presence of higher autonomic imbalance as it occurs in diabetes patients. This is supported by many studies that visit-visit BPV is not only an independent predictor of macrovascular and microvascular complications in patients with T2D patients, but all-cause mortality.

The observational study—“Retrospective Epidemiological Study to Investigate Outcome and Mortality with Glucose Lowering treatment in Primary Care setting” (ROSE) on 9,855 diabetic patients included the main analysis of associations between BPV and all cause mortality. It indicated that although BPV may result in little improvements in mortality prediction, but may not translate into clinical usefulness for risk prediction above and beyond that of other routinely measured predictors of BP. It was found that mean BP level is better predictor of CVD and all-cause mortality than BPV.

Recent studies have shown that BPV persisting across several clinic visits (i.e., long-term BPV) is associated with the risk of stroke, CAD and all-cause mortality. Short-term BPV measured over 24 hours by ambulatory BP monitoring is also associated with increased CVD events but many studies have shown that within-visit BPV is associated with metabolic syndrome score, target organ damage (left ventricular hypertrophy and albuminuria), and the risk of stroke, but not with overall CV events or all-cause mortality.

**Clinical Significance of BPV in Diabetes**

- In a study of 8,811 patients with T2D in the ADVANCE trial it was concluded that VVV of SBP was significantly associated with the incidence of major micro- and macro-vascular events and all-cause mortality.
- A retrospective cohort study which evaluated the effect of VVV of SBP on CVD and all cause mortality among 124,105 Chinese patients with T2DM identified a positive linear relationship between the VVV of SBP and the first incidence of CVD and all-cause mortality over a median follow-up time of 39.5 months. Further, the patients with SD of SBP <5 mm Hg had the lowest risk of CVD and all-cause mortality, and those with SD of SBP ≥10 mm Hg had significantly higher risk.
- Study conducted on 2,161 T2D patients over 5.5 years, VVV BPV significantly predicted all-cause mortality, irrespective of mean BP values.
- Ushigome et al. evaluated in 858 Japanese patients with T2D for 14 consecutive days the relationship between day-to-day variability and to macro albuminuria by HBPM. After adjusting for several factors, the analysis showed that CoVs of morning SBP and DBP as well as those of evening SBP were independently linked with the algorithm of urinary albumin excretion (UAE), so coefficient of variations of HBPM can be a novel factor which correlates with macro albuminuria after accounting for known risk factors in patients with T2D.

**Table 2** depicts some of the salient studies of BPV in diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population characteristics (n)</th>
<th>BPV index</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilpatrick et al. (2010)</td>
<td>T1DM patients (1,441)</td>
<td>Visit-to-visit BPV</td>
<td>High risk of nephropathy</td>
</tr>
<tr>
<td>Ozawa et al. (2009)</td>
<td>Hypertensive diabetic patients (72)</td>
<td>Night time Systolic blood pressure variability</td>
<td>Increased risk of coronary heart disease</td>
</tr>
<tr>
<td>Ushigome et al. (2011)</td>
<td>Patients with T2D (858)</td>
<td>Day-to-day BPV</td>
<td>Increased risk of macro albuminuria</td>
</tr>
<tr>
<td>Hsieh et al. (2012)</td>
<td>Patients with T2DM (2,161)</td>
<td>Visit-to-visit SBP and DBP</td>
<td>High risk of all-cause mortality</td>
</tr>
</tbody>
</table>
Within-Visit BPV is Associated with Prediabetes and Diabetes

This study included 17,795 individuals aged 40–74 years who underwent health check-ups in Japan and completed two BP measurements. Associations between within-visit BPV and risks for cardiovascular events were investigated.

It was concluded that high within-visit BPV is significantly associated with the prevalence of prediabetes and diabetes, independent of mean SBP, in a large general population. Therefore, it was considered that blood sugar parameters should be monitored in patients with high-BPV as BPV can be assessed in a single visit and may prove to be a useful modality to diagnose patients at greater risk of impaired glycemic control.

BPV Management: Protection Provided by Antihypertensive Drugs

BPV is known to decrease with decrease in BP induced by antihypertensive management. But effect of different antihypertensive classes compared to one another is yet not known. Long acting dihydropyridine calcium channel blocker are undoubtedly the most promising drugs in the management of BPV. Many clinical studies have consistently found the advantage of these drugs in reducing ambulatory, home, and clinic BPV. In fact, the smoothness index (an index that includes information on the homogeneity of antihypertensive drug effects over 24 hours) correlates with both a reduction in 24 hour BPV and the regression of organ damage in hypertension with the use of long acting antihypertensive drugs. Apart from the use of specific drugs, drugs which cause iatrogenic increase in BPV (like the use of short acting antihypertensive treatment) should be avoided.

A study on hypertensive patients with diabetic nephropathy has shown that treatment with ARBs or ACE inhibitors could improve ambulatory short-term BPV. After 12 weeks of treatment 24-hours, daytime, and night-time short-term BPV were significantly decreased. Evidence is also available that some classes of oral anti-diabetic drugs, that is, thiazolidinediones, may not only have a beneficial effect on 24-hour BP levels but also improve day-night BP profile in diabetic subjects.

Conclusion

The concept of BPV has been there for last many years but did not get the attention and importance in routine clinical day-to-day practice. BPV has been identified as a risk factor for various hypertension-related complications, more so in diabetes patients. SD is the easiest way to calculate BPV. Mobile app can be helpful to the clinicians to calculate SD immediately. Various modalities such as ABPM, HBPM, and OBPM can be used to measure BPV depending on the availability and feasibility. The treatment of any patient of BPV and also of diabetes should be individualized accordingly. It has been shown to be beneficial if we adhere to the night time dose regimen of antihypertensive drugs. Based on several evidences the association between BPV and various complications like CV events, all-cause mortality, diabetic and renal complications, etc., it may be useful to include BPV in the diagnostic pool of hypertension management and there is a need for further research for determining the affect of BPV on CV complications and target organ damage in a patient of T2DM and hypertension.

Subjects with higher night time than day time BPV had a higher risk of death. However, reverse dippers on antihypertensive drugs were older and usually had a history of diabetes mellitus or previous CV events.

References


Abstract

Ectopic fat is defined by excess adipose tissue in locations not classically associated with adipose tissue storage or contains only small amounts of fat, such as the liver, skeletal muscle, heart, and pancreas. Ectopic fat can interfere with cellular functions and hence organ functions and is associated with insulin resistance. Adipose tissue consists of adipocytes and the vascular fraction that contains blood vessels. Adipose tissue has the unique capacity to store large amounts of energy in the form of triglycerides. For a long time, it has been presumed that energy storage was the only function of adipose tissue. However, adipose tissue acts as an endocrine organ by secreting various hormones and cytokines known as adipokines. These adipokines have effects on glucose and lipid metabolism and energy homeostasis. It now appears that adipose tissue dysfunction plays a role in developing insulin resistance. Adipose tissue dysfunction is characterized by large adipocytes and secretion of adipokines with a proinflammatory profile. The aim of this article is to discuss the pathophysiology of ectopic fat and its effect on insulin resistance. We will elaborate on the effect of ectopic fat deposition on the cellular level as well as on the various organ level involved in the pathogenesis of insulin-resistant. Genetic, environmental, and behavioral factors are involved in excess energy intake and decreased physical activity leading to ectopic fat deposition. Physiologic versus pathologic fat accumulation also plays an important role in its dysfunction. Human adipocytes can grow up to ~20 fold in diameter and several thousand-fold in volume. Too large adipocytes will release stress signals in response to hypoxia when vascularization is inadequate for the expanded adipose tissue and endoplasmic reticulum stress which is induced by hypoxia or nutrient excess. Consequences of ectopic fat accumulation depends upon the specific organ although cellular mechanisms remain same but Visceral fat accumulation is linked to higher level of insulin resistance. We have also discussed the issue in reference to diagnosis and its prevention with diet and lifestyle intervention.

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial disease with complex interplay of genetic, environmental, and lifestyle factors contributing to insulin resistance and impaired insulin secretion, which leads to a state of chronic hyperglycemia and its attendant complications. A dramatic rise in the number of people with obesity has been witnessed in the last few decades, with doubling of individuals with body mass index (BMI) >30 kg/m² in the last 30 years. Obesity predisposes to the development of insulin resistance, T2DM, metabolic syndrome, cardiovascular disease, and cancer. Interestingly people with metabolic syndrome present a fivefold higher risk of developing T2DM. It is expected that incidence of diabetes will double by 2025, and in 2030 diabetes will be the seventh cause of death in the world. Insulin resistance is an excellent predictor for the clinical onset of T2DM and precedes occurrence of the
Diabetes Mellitus

Dysfunction of Adipose Tissue

In obese subjects that develop insulin resistance, adipose tissue dysfunction plays a major role. Adipose tissue dysfunction is characterized by large adipocytes formation and secretion of adipokines with a proinflammatory profile ultimately leading to ectopic fat deposition. Ectopic fat is defined as storage of TG in tissues other than adipose tissue, that normally contain only small amounts of fat, such as the liver, skeletal muscle, heart, and pancreas. Ectopic fat can interfere with cellular functions, and hence organ function and is associated with insulin resistance.

Mechanism of Ectopic Fat-induced Organ Dysfunction

The consequences of ectopic fat accumulation depend on the specific organ involved. Firstly, it has to be noted that lipids can be dispersed intercellularly or accumulate intracellularly. Deposition of lipids in intercellular space might impair organ function via paracrine effects of the released adipokines. However, it is the intracellular lipid accumulation that is associated with decreased insulin sensitivity (Fig. 1).

It appears that it is not the FFAs themselves, but metabolites like long-chain acyl-CoA (LC-CoA), diacylglycerol (DAG), and ceramides, which are deleterious for the cell. These fatty acid metabolites induce a sustained activation of serine/threonine kinases such as protein kinase C (PKC) isoforms, IKB-kinase-β, and Jun N-terminal kinase, which phosphorylate insulin-receptor substrates (IRS) on serine residues. The subsequent defects in insulin signaling lead to a decrease in cellular function that depends on the cell type.

![Fig. 1: Pathophysiology of ectopic fat deposition](image)
FFAs are taken up by the skeletal muscle cell mainly by protein-mediated membrane transport, fatty acid transport protein (FATP), along with passive diffusional uptake. After uptake in muscle metabolites of these fatty acids induce a sustained activation of serine/threonine kinases leading to phosphorylation of insulin-receptor substrate (IRS1) on serine residues. Serine-phosphorylated forms of IRS1 cannot associate with and activate phosphatidylinositol3-kinase (PI3K), resulting in a decreased glucose transporter 4 (GLUT4) regulated glucose transport over the cell membrane.

The mechanism behind hepatic TG accumulation and the development of hepatic insulin resistance are much similar to that described for skeletal muscle.

**Fatty Liver a Cause or Consequence of Hepatic Insulin Resistance?**

Accumulation of TG in hepatocytes reflects an imbalance between hepatic TG synthesis and its utilization. Utilization includes mitochondrial beta-oxidation, production of ketone bodies, and secretion of TG in very-low-density lipoprotein (VLDL) particles.

Histologically, the fatty liver can be classified as micro- or macrovesicular. Causes of microvesicular steatosis, such as fatty liver during pregnancy, Reye’s syndrome, and certain drugs and toxins, are thought to share a common mechanistic feature—impairment of mitochondrial beta-oxidation. Microvesicular steatosis is often accompanied by severe hepatic dysfunction. The causes of macrovesicular steatosis include alcohol, non-alcoholic fatty liver disease (NAFLD) associated with features of insulin resistance, total parenteral nutrition, protein-calorie malnutrition, and jejunoileal bypass. NAFLD is a term describing a large spectrum of conditions ranging from fat alone to fat plus inflammation, fat plus ballooning degeneration, and non-alcoholic steatohepatitis (NASH).

**Endogenous or Exogenous Factors that Affect Ectopic Fat, Liver and Muscle IR**

Gender differences have been linked to ectopic fat accumulation and IR and these could partly be related to differences in body fat distribution in men and in women. Generally, women have a higher percentage of subcutaneous adipose tissue (SAT) as compared to BMI-matched men, who generally have more visceral adipose tissue (VAT). The expandability of SAT also could be a critical factor in the development of insulin resistance.

Lipids may be predominantly stored in SAT before marked VAT expansion occurs. VAT has been linked to higher levels of inflammatory markers, insulin resistance, and other cardiometabolic complications. Moreover, in general women accumulate more adipose tissue in the gluteal-femoral regions as compared to the abdominal fat deposition. Abdominal obesity is associated with an increased risk of developing T2DM and cardiovascular diseases.

Furthermore, although not completely elucidated, the metabolic differences between men and women are, also partly, a consequence of differences in hormonal status. Estrogen has been shown to reduce intrahepatocellular lipid (IHCL) accumulation and IR in both sexes. Until menopause, women have a lower risk for developing fatty liver, whereas postmenopausal women have a similar risk compared to age-matched males.

Age also seems to be a very relevant factor in the etiology and pathophysiology of IR, and seems to be positively related to ectopic fat accumulation.

**Imaging and Measurement of Ectopic Fat**

Magnetic resonance imaging (MRI) examination which allows noninvasive assessment of lipid infiltration in various organs may become an ideal tool or gold standard imaging technique that can help to quantify and illustrate the effects of obesity. MRI will allow early detection of reversible metabolic changes as well as their further monitoring. It is believed that in the future, the method could also be used as a biomarker for indicating the development of prediabetes insulin resistance.

**Effect of Macronutrients on Ectopic Fat in Distinct IR Phenotypes**

There has been a debate on different dietary approaches in the prevention of T2DM and tackling insulin resistance. One of the approaches is the Mediterranean diet, rich in olive oil, which may provide cardiovascular benefits. Secondly, diets low in fat and high in complex carbohydrates with increased fiber content along with lifestyle interventions may decrease the cumulative incidence of diabetes by more than 50% over next 3–6 years.
Available evidence clearly indicates that there is great potential to optimize the effectiveness of dietary interventions on glucose homeostasis by, for example, targeting liver- and muscle-IR phenotypes. A first step toward the development of more personalized nutrition could be to investigate the role of tissue specific IR and related ectopic fat content in the effectiveness of dietary interventions, in particular when studying the effect of manipulation of the macronutrient composition of the diet.

**Conclusion**

Ectopic fat accumulation in insulin-sensitive tissues is associated with insulin resistance independent of overall obesity. However, our understanding of the causes and mechanisms underlying fat accumulation in skeletal muscle and the liver are limited. Identifying why some individuals store fat in insulin-sensitive tissues, but others do not, may be of great importance for the development of new insulin-sensitizing agents and for optimal use of current therapies.

Diet and exercise are powerful tools in improving both ectopic fat deposition and the function of the organ in which the ectopic fat is deposited. Diet and lifestyle intervention, therefore, deserve more attention, both as preventive measure for obesity and T2DM as well as for the treatment of insulin resistance and T2DM.

**References**

Abstract

Acute increase in plasma glucose causes acute metabolic complications leading higher occurrence of morbidity and mortality in patients with diabetes. This can easily be prevented by early identification and aggressive treatment. Insulin insufficiency is coupled with rise in level of counter regulatory hormones which is usually precipitated by prolonged fasting, dehydration, pregnancy, physical stress, infection apart from missing exogenous insulin dose, and very high insulin resistance. Poor carbohydrate utilization prepares the ground of deriving energy from alternative fuel resources causing ketosis, acidosis and dehydration which is further aggravated by osmotic diuresis along with hyperglycemia and superadded electrolyte loss. Best strategy for prevention is early detection and identification of precipitating factors so they can be treated before causing acute metabolic diseases. Youngsters especially type 1 diabetes are more prone for diabetic ketoacidosis. Contrary to this, elderly individuals, especially with newly detected diabetes have higher risk for hyperglycemic hyperosmotic state, mostly in females. Raising awareness at community level is significant intervention for prevention. Treatment should be targeted to correct dehydration by restoring extracellular and intracellular fluid volume together with treating electrolytes imbalances, hyperglycemia, and acidosis.

Introduction

Diabetes mellitus (DM) is a chronic endocrine disorder, which occurs of pancreatic insufficiency to make insulin or to impaired action or both causing hyperglycemia. Acute rise in plasma glucose may lead to acute metabolic complications like diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar nonketotic coma (HHNK), lactic acidosis (LA), and hypoglycemia. These complications lead to increased mortality and morbidity, which can only be prevented by early identification and aggressive management.1

Pathogenesis

Underlying pathology includes raised blood sugar, metabolic acidosis, electrolyte abnormalities, hyperketosis and water deficit for all acute metabolic complications except hypoglycemia. Mostly it is because of relative insulin insufficiency together with excess of counter regulatory hormones like glucagon, catecholamines, cortisol, and growth hormone.2 Relative insulin insufficiency not only caused by β-cells failure but also due to abrupt deprivation caused by missing exogenous insulin and high resistance to insulin. Various precipitating factors, like prolonged fasting, dehydration, physical stress, infection, play a significant role in presence of excess of counterproductive hormones.3,4 Poor carbohydrates utilization is further worsened by synthesis of ketones causing acidosis and dehydration. Dehydration increases further by osmotic diuresis due to glycosuria and excretion of neutralized ketoacids by kidney. In addition there is an increased load of amino acid influx from muscles for metabolism together with saturation of hepatic functioning with gluconeogenic precursors thereby leading to higher
pyruvate and lactate synthesis. Unavailability of insulin begins utilization of amino acids and triglycerides as energy source. Unregulated lipolysis gives rise to increased levels of glyceral and free fatty acids. In state of insulin deficiency, glucagon in excess converts free fatty acids to ketones and produces glyceral and alanine while causing gluconeogenesis in liver. The culprit ketoacids that result in metabolic acidosis are acetoacetic acid and beta-hydroxybutyric acid. Acetoacetic acid converts to acetone, which is difficult to clear by respiration when accumulated. Uncontrolled hyperglycemia causes marked osmotic diuresis along with superadded loss of electrolytes under effect of ketones. Despite being actually in deficit, potassium levels are initially seen normal due to shift of potassium extracellularly with regards to acidosis. However, these levels further decline with insulin treatment and thus periodic K+ check is needed to avoid hypokalemia.

Including poor compliance of insulin treatment, infection, infarction, ischemia, intoxication with alcohol or drug abuse are five important stressors to increase secretion of stress hormones, glucagon, cortisol, and adrenaline causing hyperglycemia, which may end up with DKA in invariably in type 1 DM but sometimes in type 2 DM with insulin resistance along with erratic medication and poor diet plan. On the other hand the pathogenesis of hyperglycemic hyperosmolar state (HHS) differs from that of DKA as it occurs with more severe dehydration due to osmotic diuresis without significant ketosis/ketonemia. A higher concentration of circulating hepatic insulin may keep it free from ketosis. Patients presenting with HHNKC have lower level of free fatty acids, cortisol, growth hormone, and glucagon than patients with DKA. Patients with HHNKC may have mild metabolic acidosis due to compromised kidney functions and dehydration (Fig. 1).

Reactive oxygen species (ROS) play an important role in synthesis of advanced glycation end products (AGEs), increased activity of protein kinase C (PKC), stimulation of hexosamine pathway together with higher contribution from the polyol pathway actually underlies the whole pathobiological process. LA is an elevation of lactic acid beyond 5.0 mEq/L with acidosis (pH <7.3). Ketones are absent or very low. It accounts for 1.2% of all hospitalizations with diabetes in decade of 2001–2010 and is showing consistently rising trend from earlier data 0.6% in 1989–1991. Similar rising trend from 0.3% to 1% is noticed among non-diabetics. Hypoglycemia has also been identified as an underlying cause among 5.4% of total hospitalization with diabetes during 2001–2010. Severe hypoglycemia are increasing among patients aiming lower glycosylated hemoglobin (A1c) without enough prior education and support.
by sulfonylureas is more prolonged and hazardous in comparison to that caused by insulin.10

**Predictors and Precipitating Factors**

DKA occurs more commonly in younger age with established type 1 DM. Younger age can be taken as risk factor as children below 2 years of age have three times more risk than older kids.12 It increases with age in females but not in males. It is commoner in ethnic minorities.13 Apart from this lower socioeconomic status including low income and poor educational status and lower level of awareness of family members play an important role in causation of DKA.12 Family history of diabetes, particularly the presence of a first degree relative of type 1 DM plays a protective role. Medications like steroids, antipsychotics like clozapine or olanzapine, diazoxide, cocaine, and lithium can precipitate DKA especially in newly diagnosed patients with diabetes. Missing dose of insulin, pump failure, or treatment error like inadequate insulin therapy during acute illness, infection, myocardial infarction, or surgery may also lead to DKA.10,14 Ketoacidosis with normal or near normal plasma glucose level may occur during fasting, pregnancy, very young or partially treated patients, which is called Euglycemic Ketoacidosis.15 It is also reported in modern days patients being treated with newer molecules like SGLT-2 inhibitors.16 Contrary to DKA, elderly individuals, especially with newly detected diabetes have higher risk for HHS with female preponderance. Most of HHNKC episodes are precipitated by an infection followed by cerebrovascular accident, alcohol abuse, pancreatitis, myocardial infarction, trauma, and medications affecting carbohydrate metabolism like steroids, thiazides, and sympathomimetic agents like dobutamine and terbutaline.10,17

La is a medical emergency most commonly results from oxygen deprivation in the body's tissues, impaired liver function, respiratory failure, or cardiovascular disease. Other conditions poor oxygenation like hypoxemia, shock, sepsis, carbon monoxide poisoning, and some medications like phenformin and metformin, especially when they are used in patients with renal failure. Alcohol abuse also commonly causes LA in diabetic patients.18 Modifiable predictors of severe hypoglycemia include intensive insulin treatment with the intention of low HbA1c using higher dose of insulin. Patients keeping HbA1c levels below 7.0% (<53 mmol/mol), especially in patients with age of 75 years or more, with serum creatinine level more than 2.0 mg/dL or having cognitive impairment or dementia had shown higher occurrence of overtreatment translating into hypoglycemia.13

**Prevention and Treatment**

Best strategy for prevention of DKA is early detection of type 1 DM before the occurrence of DKA. Removal of precipitating factors after identifying them well should be the next. Raising awareness at community level is significant intervention for prevention. Treatment should be targeted to correct dehydration by restoring extracellular and intracellular fluid volume together with treating electrolytes imbalances, hyperglycemia, and acidosis. If there is no cardiac compromise, isotonic saline should be infused at a rate of 15–20 mL/kg/h, which must not be less than 1–1.5 L at least in the 1st hour. After that fluid replacement should be given on the basis of hemodynamic status, serum electrolyte levels, and urinary output. For hyperglycemia correction insulin treatment should be given in initial bolus dose of regular insulin intravenously at the rate of 0.1 units per kg followed by the infusion of 0.1 units/kg/h. A prospective randomized study has shown that a bolus dose of insulin can be avoided if hourly insulin infusion is given at the rate of 0.14 units/kg body weight.2 As per ADA recommendations criteria for resolution of DKA is blood glucose less than 200 mg/dL with any two of the three including

- Bicarbonate ≥15
- pH >7.3
- Anion gap ≤12.

Patients with HHNKC should be hospitalized and treated in similar way with goals of correcting volume deficits, reducing plasma hyperosmolality to normal. Hyperglycemia will be corrected with insulin while providing intravenous rehydration to resolve HHNKC promptly. After doing early fluid replacement with 1 liter of normal saline in first hour, fluids should be given intravenously as per patient’s hemodynamic and electrolyte status maintaining hourly infusion between 250 and 500 mL/h. Patients with normal or high corrected sodium can be shifted to half normal saline after 1 hour. Dextrose of 5% or 10% to be added after plasma glucose level approaches 250 mg/dL. Total body potassium deficit should be replaced after urine output is adequate. Between 20–30 mmol (20–30 mEq) potassium in each
the dose of insulin knowingly or unknowingly, infections, acute illness, inadequate insulin treatment, or other treatment errors have caused not only higher occurrence of DKA but also HHNKC. LA has emerged as more frequent acute complication than earlier due to higher use of biguanides like metformin in patients with renal failure. Rising alcohol abuse has also posed a challenge of LA among people having diabetes. Intention of maintaining lowest possible HbA1c has caused an increase in hypoglycemia. Increasing use of self-monitoring of blood glucose (SMBG) devices and sensor technology has made it possible to detect and document hypoglycemia at every level. Undoubtedly it adds up the protection of patient when we can easily know overnight and early morning hypoglycemia but obviously it is affecting statistics of hypoglycemia. Sensible use of advanced technology in newer medications, insulin analogues, delivery devices, and sensors can reduce overall acute complications in diabetes. Increasing awareness among patients and their relatives is the most important step to begin.

References


CHAPTER 52

Environmental Endocrine Disruptors and Diabetes: Novel Insights from Nallampatti

Krishnan Swaminathan

Abstract

There has been a huge explosion of diabetes over the last decade, especially in lower and middle income countries. While traditional risk factors like diet, lifestyle, urbanization, fast food culture, and less physical activity are extremely important risk factors, we believe that these factors alone do not explain the huge increase in diabetes in India. Our work in Nallampatti showcases the effects of endocrine disruptors, especially pesticides and heavy metals in the prevalence of diabetes and atherosclerosis. While in no way this study is confirmatory of the association, our work does highlight important unexplored aspects of diabetes pathophysiology in India that needs further large scale studies.

Introduction

South Asia, particularly India, home to around 18% of the world’s population, is currently in the midst of an epidemiological transition from infectious and nutritional illness to non-communicable diseases (NCDs), especially cardiovascular disease, predominantly driven by a cluster of “traditional risk factors” like diabetes, prediabetes, obesity, diet & lifestyle, hypertension, hyperlipidemia, and atherosclerosis. Individually, each of the above risk factor has huge health care, economical, and societal implications. Collectively, this “Axis of evil” is a disaster in the making for India and a “ticking time bomb” that will wreak the nation’s health.

Diabetes is a “vascular disease” and not a metabolic disorder alone. India leads the world in the numbers of patients with diabetes and has the infamous tag of being referred to as the “Diabetes Capital of the world.” Currently, it would not be an exaggeration to practically define diabetes as a state of premature cardiovascular death associated with chronic hyperglycemia and in the absence of effective treatment to control glucose levels, will lead to blindness, kidney failure, and foot amputation.

In fact, there is good evidence for terming diabetes as a "coronary risk equivalent." Studies have shown that diabetic patients without a previous heart attack have the same high risk of getting a heart attack as someone without diabetes who already had a previous heart attack. Poorly controlled diabetes is a major risk factor for end stage kidney disease (ESRD) needing dialysis and renal transplants in India. More than 1 lakh patients enter the renal replacement therapy annually in India, but due to extremely scarce resources, only 10% of this population receives renal replacement therapy. Poorly controlled diabetes is a leading cause of foot amputations in India. Foot ulcerations occur in 25% of patients with diabetes and approximately 15% of such foot ulcerations result in amputations. With this background, we are now witnessing a huge explosion in diabetes epidemic that can have potentially catastrophic consequences for the health care of our nation. One hospital admission with a diabetes-related complication will drain the family of all their resources, especially from the, lower socioeconomic backgrounds, as 70% of Indian urban and rural households visit only private sector providers over public services.
Prediabetes is the prelude to diabetes. Colloquially, this is termed as “borderline diabetes.” Intuitively, one would underestimate prediabetes, as this is not yet full-blown diabetes. However, even many physicians are unaware that prediabetes is also associated with the same set of comorbidities like heart attacks and strokes, very similar to diabetes. Indians also have one of the highest conversion rates from prediabetes to diabetes. Data from follow-up of patients over 10 years from the Chennai Urban Study (CURES Study) indicates a conversion rate of prediabetes to diabetes in the order of 60%. Taken together based on the above discussions, Indians have one of the highest incidence rates for diabetes with rapid conversion from prediabetes to diabetes. The pressing need of the hour is to slow down and reverse this epidemic in our population.

The concern for all health-care professionals and policymakers is the fact that the transition in both the risk factors and diabetes prevalence in India has occurred over a relatively short period of time. To compound this, India is a “Nation within a Nation,” where many states have populations close to that of countries in Europe! Therefore, there will be huge regional variations in diseases and risk factors that will have a bearing on how scanty resources can be utilized to optimize health care. Our concern is primarily centered toward rural Indian population where the triple burden of lack of awareness, health care costs, and poor health care facilities add significantly to morbidity and mortality from non-communicable diseases. The progression of this NCD epidemic, especially in rural areas, is characterized by a multitude of factors including rapid urbanization, reversal of socioeconomic gradients, fast food culture, less intake of fruits and vegetables, tobacco and alcohol use/abuse, less access to health care in the poorer socioeconomic strata of the society, and much more. Efforts to understand the pathophysiology of this transition have been traditionally focused on the above factors. However, there is growing body of evidence for the role of non-traditional risk factors, especially pesticides and heavy metals in fertilizers, in the development of diabetes, prediabetes, hypertension, atherosclerosis, and cardiovascular disease. Our aim was to adopt and explore the burden of NCDs in a traditional rural farming village in our area, do a longitudinal follow-up, and assess the role of both traditional as well as non-traditional risk factors like pesticide and heavy metal use in this population.

**Material and Methods**

**KMCH: Nallampatti Non-communicable Disease-I (KMCH-NNCD-I) Study**

Nallampatti is a typical farming village in Tamil Nadu, South India (Latitude: 11°21’2.39” N; Longitude: 77°32’4.79” E) (Fig. 1) with a population of around 3,000. This study, named the “Nallampatti non-communicable disease study-I—2015 (NNCD-I, 2015),” was conducted on every Sunday during a period of 4 weeks (15 March–05 April, 2015). Advertisements were given through pamphlets, word of mouth, and through administrative heads like the Panchayat President. The study design and protocol were approved by KMCH Ethics Committee, Kovai Medical Center and Hospital Limited, Coimbatore (Approval No. EC/AP/02/2015, dated 16 Feb, 2015), and informed written consent was obtained from all participants prior to participation and followed the principles of Declaration of Helsinki.

A total of 865 participants were screened with a questionnaire, bloods including HbA1c, non-fasting lipid profile, creatinine, carotid intima thickness (CIMT) using carotid ultrasound transported to the venue along with urine for heavy metals and serum pesticides. Methodology for all the above along with definitions for diabetes and prediabetes have been published. All subjects native to the village aged more than 20 years were invited for the study. Urine heavy metals and serum pesticides were stored at -80°C and transported to IIT Madras for analysis by ICP-MS and GC-MS, respectively.

**Results**

The topline results from our study showed a diabetes prevalence of 16.2%, prediabetes of 42%, hypertension 39%, hypercholesterolemia in 33%, and atherosclerosis in 10.3%. This was much higher than the ICMR-INDIAB prevalence (Table 1), even though comparing both studies may be analogous to comparing apples and oranges! Allowing for the methodological variations and confounding factors, the double-digit prevalence of diabetes was very consistent with our clinical experience and other studies done by our study group in rural Madurai & Theni districts of Tamil Nadu.

On multiple logistic regression analysis, diabetes in our rural population was surprisingly not associated with traditional risk factors except for age (Table 2). Generally,
**Fig. 1:** Geographic location of the study village (Nallampatti)\(^{33}\)

**TABLE 1** Differences in prevalence of NCDs between ICMR-INDIAB study and our study: Are we seriously underestimating the risk?\(^{33}\)

<table>
<thead>
<tr>
<th>Factors</th>
<th>ICMR-INDIAB study</th>
<th>Tamil Nadu (Rural)</th>
<th>KMCH-NNCD study</th>
<th>Tamil Nadu (Rural—Nallampatti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,480</td>
<td>4.1</td>
<td>865</td>
<td>9.1</td>
</tr>
<tr>
<td>Known diabetes (%)</td>
<td>IFG + IGT</td>
<td>3.8</td>
<td>HbA1c ≥ 6.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Newly detected diabetes (%)</td>
<td></td>
<td>1:0.9</td>
<td>1:0.78</td>
<td></td>
</tr>
<tr>
<td>Ratio of KD:NDD</td>
<td></td>
<td>7.8</td>
<td>16.2</td>
<td></td>
</tr>
<tr>
<td>Total diabetes (%)</td>
<td></td>
<td>7.1</td>
<td>5.7–6.4</td>
<td>42</td>
</tr>
<tr>
<td>Prediabetes (%)</td>
<td>IFG or IGT or both(^{1})</td>
<td>7.1</td>
<td>HbA1c 5.7–6.4</td>
<td></td>
</tr>
</tbody>
</table>

*Contd...*
Environmental Endocrine Disruptors and Diabetes: Novel Insights from Nallampatti

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TABLE 2

Multiple logistic regression with diabetes as dependent variable: non association of traditional risk factors with diabetes

<table>
<thead>
<tr>
<th>Factors</th>
<th>KMCH-NNCD study</th>
<th>Definitions</th>
<th>Tamil Nadu (Rural)</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>p-Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>19.9 (8.55–46.5)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>1.13 (0.63–2.01)</td>
<td>0.672</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking (daily smokers)</td>
<td>0.71 (0.15–3.47)</td>
<td>0.676</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol (daily drinkers)</td>
<td>1.92 (0.389–9.504)</td>
<td>0.422</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized obesity</td>
<td>1.295 (545–2356)</td>
<td>0.996</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.50 (0.98–2.30)</td>
<td>0.060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High LDL-cholesterol</td>
<td>0.83 (0.51–1.35)</td>
<td>0.449</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, Carotid Intima Media Thickness; DBP, diastolic blood pressure; HDL, high density lipoprotein; KD, known diabetes; KMCH-NNCD, Kovai Medical Center Hospital-Nallampatti Non communicable disease study; LDL, low density lipoprotein; NDD, newly detected diabetes; SBP, systolic blood pressure.

Contd...

Factors

one would intuitively expect diabetes to be associated with other traditional risk factors like smoking, obesity, hypertension, and hypercholesterolemia. The absence of such an association in our study raised a hypothesis generating question as to whether there may be non-traditional risk factors involved in the huge burden of NCDs in rural areas, especially in farming populations.

Urine Heavy Metals and Diabetes

Fertilizers are a big source of heavy metals especially arsenic. Arsenic has been implicated in diabetes by various mechanisms including beta cell toxicity and interference with insulin signaling. Increased level of these urinary metals, especially arsenic and zinc, were noted among the diabetic subjects in comparison with non-diabetic subjects (Table 3). On correlation and regression analyses of the urinary metals with cardiometabolic risk factors (HbA1c, systolic and diastolic blood pressure, BMI, total cholesterol, CIMT-left, CIMT-right, and cystatin-c), only HbA1c, and CIMT showed significant correlation with the metals.

Pesticides and Diabetes

We noticed a significant positive correlation between all the organophosphate residue levels and HbA1c (Table 4) indicating the role of insecticides in glucose homeostasis. Based on detection of insecticide residue level, the population was categorized as “detected below limits of detection (LOD)” and “detected above LOD.” On multivariate regression analysis between these two groups, significant odds ratio was obtained for monocrotophos, methyl parathion, malathion, chlorpyrifos, and profenofos for prediabetes, while for diabetes, all the above except profenofos showed significant association.
### TABLE 3  
Odds ratio (95% CI) of diabetes associated with quartile of urinary metals\(^{35}\)

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds ratio (95% CI)</th>
<th>(P_{\text{trend}})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quartile 1</td>
<td>Quartile 2</td>
</tr>
<tr>
<td>Cd</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
<tr>
<td>As</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
<tr>
<td>Pb</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
<tr>
<td>Cr</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
<tr>
<td>Al</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
<tr>
<td>Zn</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
<tr>
<td>Cu</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
<tr>
<td>Ni</td>
<td>Unadjusted</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Adjusted*</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### TABLE 4  
Association of serum pesticides and diabetes\(^{36}\)

<table>
<thead>
<tr>
<th>Total no. of samples above LOD (%)</th>
<th>Samples above LOD</th>
<th>Samples below LOD</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of diabetes</td>
<td>Percentage of diabetes</td>
<td>No. of diabetes</td>
</tr>
<tr>
<td>Dichlorvos</td>
<td>274 (38%)</td>
<td>25</td>
<td>9.1</td>
</tr>
<tr>
<td>Acephate</td>
<td>339 (47%)</td>
<td>62</td>
<td>18.3</td>
</tr>
<tr>
<td>Monocrotophos</td>
<td>563 (78%)</td>
<td>125</td>
<td>18.4</td>
</tr>
<tr>
<td>Phorate</td>
<td>312 (41%)</td>
<td>58</td>
<td>18.5</td>
</tr>
<tr>
<td>Dimethoate</td>
<td>469 (65%)</td>
<td>88</td>
<td>15.6</td>
</tr>
<tr>
<td>Methyl parathion</td>
<td>491 (68%)</td>
<td>112</td>
<td>19.1</td>
</tr>
<tr>
<td>Malathion</td>
<td>548 (76%)</td>
<td>135</td>
<td>20.4</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td>527 (73%)</td>
<td>124</td>
<td>19.7</td>
</tr>
<tr>
<td>Quinalphos</td>
<td>259 (36%)</td>
<td>45</td>
<td>12.8</td>
</tr>
<tr>
<td>Profenofos</td>
<td>296 (41%)</td>
<td>45</td>
<td>15.2</td>
</tr>
</tbody>
</table>

LOD, limits of detection
Adjusted: For confounding factors (Age, sex, hypertension, cholesterol)
*p<0.05, **p<0.01, ***p<0.001
Conclusion

The work that depicted in this chapter highlights the burden of diabetes, prediabetes, and atherosclerosis in 865 subjects more than 20 years of age in a rural farming population. It also explores the role of non-traditional risk factors like heavy metals in fertilizers and pesticides on the health of the studied population.

In summary, we showed significant associations between heavy metals in urine and pesticides with prevalent diabetes in Nallampatti village. All subjects had heavy metal analysis done in their urine samples, which was then categorized into four increasing quartiles, quartile 1 the least and quartile 4 the most. Increasing urinary levels of arsenic and zinc was associated with diabetes in this study, even after adjustment for multiple confounding factors. The results of this study raise vital research questions on link between metals, especially arsenic used in fertilizers and diabetes & vascular disease.

All of our subjects had serum pesticides measured by GC-MS and the levels were categorized into above and below LOD. Monocrotophos, Methyl parathion, and Chlorpyrifos particularly showed a significant association with diabetes after adjustment for multiple confounding factors. We conclude by hypothesizing that pesticides seem to be an attractive non-traditional “diabetogenic link” for the society at large due to ubiquitous and unscrupulous use of pesticides in the everyday fruits and vegetables we consume, apart from being a risk factor for farmers spraying pesticides without personal protective equipment (PPE).

Doctors and scientists have predominantly focused on traditional risk factors in the etiology of diabetes and vascular disease. Our work is an attempt to focus on the role of non-traditional risk factors, especially agrochemicals in the development of diabetes and atherosclerosis. We envisage progress in the future in the following areas: more focus on occupational safety, especially use of PPEs by farmers, promotion of safer regulatory policies governing the use of pesticides and fertilizers by Governmental agencies, for example, ICAR (Indian Council of Agricultural research) and Agriculture Ministry, Point of care testing devices to assess the levels of pesticides and heavy metals in the blood or urine, (Animal) Work to understand the molecular mechanisms and the efficacy of medications used to treat diabetes and vascular disease in the presence of agrochemicals. Therapeutics targeted at detoxifying diabetic agrochemicals, development of more “metabolic friendly” pesticides, and fertilizers.

We genuinely hope that this chapter has made a meaningful contribution to the health of our rural population. With more efforts, we believe that this work will be translational to make lives of millions of our rural population better.

References

**Abstract**

It is estimated that 415 million people are living with diabetes in the world, which is estimated to be 9.9% of the world’s adult population (9.9%). Forty-six percent of people with diabetes remain undiagnosed till complications ensue. The problem is more grave in our country since our diet contains more carbohydrates than protein, chemical fertilizers, pesticides use is rampant. India will be Diabetes Capital by 2030 is a true and stark reality. As they say “Early Bird catches the worm”, we should target the people with pre-clinical diabetes and people with clinical diabetes with alteration in food habits, enhanced nutrition (quality wise), encouraging people to do aerobic exercises, stopping of tobacco, alcohol moderation, good-healthy sexual life. We should guide people to adopt yoga, meditation, relaxation techniques to make their life happier and healthier. Remember, happiness comes through good quality of life. Happiness Index is directly proportional to good quality of life. Adopt these Top Ten measures for a wholesome improvement in quality of life.

**Introduction**

Type 2 diabetes mellitus (T2DM) is a global non-communicable lifestyle disease (NCD) prevalent all over the world. The unfortunate part of this disease is its ever increasing incidence in all socioeconomic groups of population. As per estimate of WHO, incidence of non-insulin-dependent diabetes mellitus (NIDDM) is 10% of population, the world over. Whereas in India, the incidence is 11–14%. It is manifested by a chronic hyperglycemic state in conjunction with other metabolic derangements. If left untreated or treated poorly, it leads to complications like end stage renal failure, heart failure, coronary artery disease (CAD), peripheral artery disease (PAD), strokes, retinopathy, erectile dysfunction, and many others. This leads to increased morbidity and mortality in general population.

T2DM is primarily due to either insulin deficiency or insulin resistance or both. Both the states result in increased hepatic glucose output, reduced utilization of glucose by various organs, increased renal reabsorption of glucose, reduced incretin hormones and increased production of glucagon among others.

Currently there is no known cure for the disease but can be controlled enabling the individual to have an improved quality of life. The main aim of management is directed at reducing acute and chronic complications, that is, microvascular and macrovascular.

**Epidemiology: Prevalence in India and World**

*India:* There are estimated 72.96 million cases of diabetes in adult population of India. The prevalence in urban areas ranges between 10.9% and 14.2% and prevalence in rural India was 3.0–7.8% among population aged 20 years and above with a much higher prevalence among individuals aged over 50 years (INDIAB Study). Kerala has the largest number of diabetes patients followed by Tamil Nadu and Punjab.
World: It is estimated that 415 million people are living with diabetes in the world, which is estimated to be 1 in 11 of the world’s adult population (9.9%). Forty-six percent of people with diabetes remain undiagnosed till complications ensue. The figure is expected to rise to 20% worldwide by 2040. China, followed by India has the highest incidence of T2DM. Lithuania, Sweden, Estonia, Ireland, and 35 more nations have the lowest incidence.

Though, there is no sex preponderance in incidence of DM in males or females. Both are equally affected. Genetic effects, epigenetic mechanisms, nutritional factors, pregnancy and sedentary lifestyle affect the risk and complications differently in both sexes. However, obesity, psychological stress, higher incidence of myocardial infarctions are more prevalent in females.

Of concern, is the population above 18 years of age who are unaware of their diabetic status (52% of diabetics). The percentage of undiagnosed diabetes is highest among the Malays (53%) followed by the Chinese (49%) and the Indians (42%). In terms of diabetes control, only 23.8% of patients in primary care and 12.7% in tertiary institutions were able to achieve their specified glycemic targets.

Risk Factors

- **Biological risk factors:** Body mass index (BMI); body fat distribution; Brown adipose tissue (BAT); metabolic syndrome (MetS); adipokines; imbalance of sex hormones; gestational diabetes mellitus (GDM), insulin resistance (metabolic syndrome).
- **Health related:** Smoking; alcoholism; lifestyle disorders including sedentary life; excessive intake sugar sweetened beverages.
- **Psychological:** Stress; economic status; sleep deprivation; drugs abuse.
- Pharmacological drug induced like steroids, etc.
- Genetics.

Management

T2DM is basically a combination of lifestyle disorder with genetic predisposition superimposed by pollution and other environmental factors. Obesity or metabolic syndrome further compounds the problem. Non-pharmacological measures are the most important faculties in managing diabetes. Next step is to add OHAs-Insulins. Surgery esp. in diabesity or stem cell or pancreatic transplantation is the other option, but reserved for highly morbid conditions. I hereby, postulate ten Commandants for the management of T2DM (Box 1).

**Nutrition Therapy (i.e., Diet)**

Medical nutrition therapy (MNT) has a great role in preventing or delaying the onset of T2DM specifically with obesity. The basic idea is to control the calories intake as appropriate for the body weight of the individual. Calorie intake depends on work style, BMI, place of work, gender and ethnicity (decides muscle mass of the body). However, the calorie composition should be: Carbohydrates: Normal=60% (Diabesity=40–50%); Proteins: Normal=25–30% (Diabesity=30%, not to exceed 1 gm/kg body weight); Fats: Normal=25–30% (Diabesity≤30% of which MUFA=10–20%; PUFA<7–10%; Saturated 7–10%) (Table 1).

In weight reducing diets, a calorie reduction of 500–1,000 cal are planned with simultaneous increase in expenditure of 500–1,000 cal in the form of exercise. ADA, DCCT, RSSDI, Diabetes India recommend the healthy

---

**Table 1**

<table>
<thead>
<tr>
<th>Component</th>
<th>Energy intake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates (Sucrose should be &lt;10%)</td>
<td>40–50%</td>
</tr>
<tr>
<td>Proteins</td>
<td>20–30% (not to exceed 1 gm/kg body weight)</td>
</tr>
<tr>
<td>Fats</td>
<td>20–30%</td>
</tr>
<tr>
<td>n-6 PUFA</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>n-3 PUFA</td>
<td>&lt;2% Oily fish is the main source. Once a week</td>
</tr>
<tr>
<td>MUFA</td>
<td>10–20%</td>
</tr>
<tr>
<td>Saturated</td>
<td>7–10%</td>
</tr>
</tbody>
</table>
### BOX 2  Nutrition—broad guidelines

- Reduce saturated fats to about 10% of total fat intake
- Increase MUFA by 40% of balance fat intake
- Increase PUFA by 40% of balance fat intake
- Eliminate transfats totally
- Increase viscous fibers in diet to min. 50 g/day
- Increase vegetable to 6 servings per day
- Reduce refined carbohydrates. Use complex carbohydrates
- Take at least one fruit per day. Daily the color of fruit must change. Preferably use low glycemic fruits
- Add plant/marine sterols or nuts to the diet
- Consume high quality proteins like soy, cold water fish, organic lean meat and poultry
- Exercise 60 minutes daily with aerobics and resistance training
- Achieve ideal body weight, BMI, waist circumference and body fat composition

### BOX 3  Ideal meal plan

- Reduce carbohydrates in your diet by 20%
- Change eating pattern
- Take fruits with highly glycemic index before the meal as meal prevents surge of glycemia. Daily change the color of fruit. Different antioxidants and high fibers which slow the absorption of carbs
- Nuts and dried fruits should be taken daily. This supplements Vit E & Omega FAs
- Pulses provide micro nutrients. Must include them in diet.
- Increase protein in diet: 2 Eggs or 1 cup chicken, fish, soyabean, cheese, milk, tofu
- Substitute rice with brown rice or water drained rice
- Snacks in between meals: Should be made of less carbs, high proteins with some fat
- Curd must be taken daily as it keeps stomach healthy with probiotics
- Garlic-Ginger-Mint, Aloe Vera provide good antioxidants
- No Sugar/Jaggery/Palm Sugar—100% cut
- Refined flour—Replace with multigrain
- Increase high fiber veggies like beans, cabbage, spinach, etc.
- Sprouted beans, salads provide good working snacks
- Before deciding the Diet/Meal Plan, calculate your Calorie needs
  - 20 Cals/kg Wt (Sedentary), 30 Cals (Moderate), 35–40 Cals (Heavy)
  - Ideal Wt; Height in CMs-100 Maintain Proper BMI

choice of foods and good physical activity to decrease the risk of diabetes and prevention of CV morbidity and mortality. DASH, mediterranean, ketogenic diets are other concepts for control of diabesity (Box 2).

### Micronutrition Therapy

Although use of micronutrients as nutrition therapy is a cornerstone of the management of diabetes, but uncertainty prevails in its guidelines. Whether the micronutrients are causative agents of diabetes or its complications or just innocent bystanders.

Zinc, chromium, iron, vitamin D, alpha lipoic acid, carotenoids, vitamins E and C, selenium, and some of the B vitamins, notably folate, pyridoxine, and cyanocobalamin play an important role in managing diabetes.

Best source of micronutrients are: fruits, nuts, fresh vegetables, sprouts, seeds, sun-shine, fatty fish, egg, and supplements. Cooking oils, flours, rice, cereals, and juices are now being available in the market with fortified vitamin A, D, Calcium, etc. (Box 3).

### Exercise

Regular moderate exercise not only utilizes blood sugar but improves blood circulation removing oxidants from the body. It further reduces the development and progression of atherosclerosis; hence reduction in CVD related mortality. Exercise induces longevity by 1.1/2 years in moderate and 3.1/2 years in vigorous exercise individuals. The beneficial effects include reduction in HbA1c; blood sugar levels, triglycerides (TGs) (9.5%); LDL (13.7%), and increase HDL (9.6%). American College of Sports Medicine and AHA Current recommendation for exercise is:

- 30 minutes of moderate exercise (5–6 Scale*), that is, mild increase in HR and breathing—5 days a week.
- 20 minutes of vigorous exercise (7–8 Scale), that is, noticeable change in HR breathing—5 days a week.
- In addition resistance training (weight training × 10 minutes) daily. All major muscle groups should be involved using 8–10 repetitions.

*10-point scale: Sitting is 0 scale and all out effort is 10.

WHO recommends 10,000 steps per day for a healthy living. Those who cannot walk should do sitting exercise,
exercise on bicycle ergometer, swimming, pushups, weight training, upper/lower body exercises depending on the deformity. Aerobic exercise especially jogging/cycling/swimming are considered the best.

**Sweeteners**

Sweeteners are the ingredients that are added to food to bring sweetness, which can be sugar (nutritive) or sugar (non-nutritive) substitutes. Nutritive sweeteners are those sugars which contain carbohydrates and provide calories, whereas, non-nutritive sugars provide only sweetness for taste and no calories. These are:

- Monosaccharides—Sugar, jaggery, khaand, etc.
- Disaccharides—Fruit sugars
- Polysaccharides—Honey, polyols
- Non-nutritive sugars (artificial sweeteners)—Aspartame, sorbitole, stevia, tagatose, sucralose, etc.

**Which Sugar to Use in DM**

- **Naturals:** Polys or Polysaccharides, Disaccharides with low glycemic index
- **Artificial:** Plant product—Stevia or Sucralose (Min. side effects)

Fresh or dried fruits can be used as adjuvants without much rise in blood sugar levels. Additional benefit is that these fruits add vitamins, minerals, and antioxidants to diet. One type (color) of fruit must be taken at least once a day. Fruits with moderate or high-glycemic index should be taken before meals as it does not increase the blood sugar levels much.

**Tobacco: Chewing or Smoking**

Tobacco smoking and chewing are the leading causes of preventive mortality. The acute effects of tobacco smoking are sharp rise in blood pressure acutely and enhanced risk of renovascular, malignant, and masked hypertension. The effect is due to stimulation of sympathetic nervous system. Whereas chronic use promotes atherosclerosis with fall in HDL, rise in LDL-C, rise in PFFAs levels, thickening of arterial walls, especially the peripheral arteries, increased levels of carboxyhemoglobins with resultant coronary insufficiency, high platelets adhesiveness, high plasma fibrinogen levels, increased risk of subarachnoid hemorrhages. A study from Canada indicated that women who smoke are more at risk of preeclampsia and eclampsia.

Smoking in diabetes increases the risk of CV mortality and peripheral neuropathy.

**Alcohol**

Alcohol use has been a very debatable issue for a very long time. Safe limit, however, is no alcohol.

Mild level of alcohol intake lowers the risk of thrombosis due to decreased inflammation markers and increased HDL levels. Moderate to heavy drinking impairs insulin release and hyperglycemia with increase in CVD related mortality and liver failure and pancreatitis. Chronic and more than permissible alcohol intake is associated with increased LDL, TGs, increased inflammatory markers, insulin resistance, increased incidence of cardiomyopathy, vent, arrhythmias, and endothelial dysfunction. One standard drink is 10 gm of pure ethyl alcohol. This amounts to 375 mL of beer (5% alcohol); 150 mL of wine (12% alcohol), and 45 mL of whiskey (40% alcohol). This is considered safe limit in a day for men. For women it is 75% of above values. Red wine offers better protection due to presence of plant sterol—resveratrol. But wines and beers contain high levels of carbohydrates, hence calorie count is must while taking alcohol.

**Caution:** No alcohol is the best option.

**Sex**

Studies show that men with diabetes often have reduced testosterone levels, which can affect their sex drive. Moreover diabetes damages the blood vessels, which affect blood flow to the penis leading to erectile dysfunction. Intimacy is ageless. It makes you young, energetic and you live longer with good quality of life. Tips for better sex in diabetics are:

- Approach sex like exercise with full emotional support.
- Use a lubricant. If a woman with vaginal dryness, a vaginal lubricant can make sex feel better.
- Creativity is sexy watch erotica together. Explore different ways to climax.
- Limit alcohol. A little alcohol may boost your desire, but drinking can also make your blood sugar level drop quickly.
- Get help for emotional issues. Depression, anxiety, poor self-image, and other emotional concerns can hurt your sex life.
- Relax: Be confident, be relaxed, do not try to force yourself. Be active.
- Use sildenafil or tadalafil, if ED is the problem.
Psychological Stress
Yoga, Meditation, Positive Thoughts Therapy, Laughter Therapy, Music, and Dancing. Stress result in imbalance of hormones and catecholamines, which has deleterious effects on blood sugar levels and blood pressure. Stress act primarily on hypothalamus pituitary axis to produce more steroidal hormones, decrease insulin sensitivity and alter calcium-vitamin D metabolism, increased sympathetic stimulation and decreased parasympathetic system. A variety of measures have been suggested to overcome stress and improve lifestyle. Yoga, meditation, music therapy, dancing, and laughter therapy are very helpful in alleviating stress. Professional counselors also play a very important role in managing stress. Enjoying holidays, family vacations, going to movies or theatres, doing arts, paintings, etc. also help in stress management. UKPDS over 12 years, observed the beneficial effects of stress management.

Lifestyle Heart Trial: Pranayam, Surya namaskar, Vrijasan asans; Meditation, Group support sessions, Music therapy all lead to correction of Glycosylated HbA1c levels, dyslipidemias with reversal of atherosclerotic plaques.

Meditation, sound sleep for 6–7 hours, listening to music, dancing all lead to reduction of stress hormones, relaxation of mind and body. This results in improving good quality of life.

Environmental Pollution
- **Air Pollution**: PM 2.5—SO₂, CO₂ are the main culprits from Prali burning, vehicles, thermal plants, increased construction activity.
- **Water Pollution**: Contamination of underground water table with heavy metals like arsenic-mercury, etc.
- **Earth Pollution**: Overuse of pesticides, chemical fertilizers, etc.
- **Noise Pollution**: Affects catecholamine secretion, stress hormones like corticosteroids, dopamine.

Pollutions affect the general health leading to anemia, hypocalemia, Vit. D deficiency, and other micronutrients deficiency which alters sympathetic-parasympathetic axis dysfunction, and hence, poor control of T2DM. The pollutants increase stress levels also especially noise pollution. This leads to poor insulin secretion and efficacy.

Pharmacotherapy
It includes oral hypoglycemic drugs, incretins, insulins, surgery like bariatric surgery, duodenal mucosal resurfacing (DMR); islet cells and pancreatic transplants and genetic engineering to alter genes (Box 4).

Conclusion
Goals of therapy for T2DM patients include evaluation of diabetic status, BMI, work style (i.e., sedentary or hard worker), socioeconomic status, presence of comorbidities and patient’s willingness or compliance with the drugs management. Always start with lifestyle modification (LSM) followed by oral drugs with or without insulin, depending on the patient’s condition and parameters. Diet prescribed to the patient must confirm to his/her tastes, availability, and affordability. Diet should be a balanced diet, rich in proteins, must include seasonal fruits. Drugs used, should also be easily available, affordable, and the regime should be tailor-made to the patient. If socioeconomic status is not good, there is no fun of writing fancy, expensive medicines, which, patient will not take in long run. Patient counseling is must so that he/she understands the modality of treatment and the need of initiating insulin therapy or undergoing surgery. The ideal target of control of diabetes is HbA1c of 6.5–7.0% in Indian population. Though, it may be difficult to achieve in elderly, but tight control always gives benefit in terms of reducing complications, and hence enhanced morbidity and mortality.
Suggested Readings

Abstract

It’s a well-accepted fact that treatment of diabetic patients has some lacunas, which may range from non-compliant patient to a busy clinician. This chapter tries to encompass these gaps in the treatment of diabetes.

Traditionally the top three knowledge gaps in clinicians include:
- Type(s) of diabetes
- Insulinization: Too early/too late
- Complications of diabetes

Similarly the top three knowledge gaps in patients include:
- Diabetes: Remission OR Cure?
- Diet
- Social media prescriptions

Introduction

Top three knowledge gaps in diabetes can be divided into: 1,2
- Top three knowledge gaps in Clinicians
- Top three knowledge gaps in Patients

Top three Knowledge Gaps in Clinicians

Knowledge gaps in clinicians can be divided into:
- Type(s) of diabetes
- Insulinization: Too early/Too late
- Complications of diabetes

Clinician Knowledge Gap I

- Identifying types of diabetes: 1,2 Many a times, especially in the “gray-zone area patients,” for example, patients with newly diagnosed hyperglycemia and in the age group of 20–25 years, type of diabetes is not routinely attempted to be sought. This is very important as it dictates not only treatment but also prognostication. Some ready reckoners for the type of diabetes can be—
  - Young (15–25 year old) diabetic
  - Type I (GAD +, C Peptide +)
  - MODY (Young on OADs, Genetic link)
  - LADA (Type II, GAD -, C Peptide -)
  - Elderly Type I (GAD +, C Peptide -)

Type(s) of diabetes: 3,4
- Type 1 diabetes
- Type 2 diabetes
- Genetic defects of β-cell function—
  - Chromosome 12, HNF-1α (MODY 3)
  - Chromosome 7, glucokinase (MODY 2)
  - Chromosome 20, HNF-4α (MODY 1)
  - Chromosome 13, insulin promoter factor-1 (IPF-1; MODY 4)
— Chromosome 17, HNF-1β (MODY 5)
— Chromosome 2, NeuroD1 (MODY 6)
— Mitochondrial DNA

In some cases the diabetes is secondary to some other pathophysiological process, which if identified, will lead to better treatment protocols in the patient. For example—
- Syndromes of Extreme Insulin Resistance
- Transient Hyperglycemia
- Diseases of the exocrine pancreas
- Endocrinopathies
  - Acromegaly
  - Cushing’s syndrome
  - Glucagonoma
  - Pheochromocytoma
  - Hyperthyroidism
  - Somatostatinoma
  - Aldosteronoma

Certain medical conditions can lead to diabetes themselves, such as—
- Glucagonoma
- Chronic pancreatitis
- Cystic fibrosis
  
  Also, certain conditions linked with Type 1 DM, such as—
- Celiac disease
- Rheumatoid arthritis
- Addison’s disease
- Autoimmune thyroid disease
- Celiac disease
- Rheumatoid arthritis
- Addison’s disease
- Autoimmune thyroid disease

Similarly, certain conditions are linked with Type 2 DM, such as—
- Alzheimer’s disease
- Polycystic ovary syndrome (PCOS)
- Cushing’s syndrome
- Pancreatic cancer

If the “gaps” enumerated above in the etiopathogenesis/pathophysiological conditions are ascertained in all patient right at the time of diagnosis, it helps in better treatment outcomes.

**Clinician Knowledge Gap II**

- Insulinization: Too early/Too late
- Targeting the “Dirty Dozen”

*Insulinization: Too early/Too late*5,6

The following pie-charts demonstrate the overall blood sugar control in diabetics worldwide. As observed, the sugar control is not very optimal. Figure 1 demonstrates worldwide prevalence of glycaemic control.

Worldwide studies have repeatedly proven that insulin is by far the most effective drug for sugar control, as seen by the following bar chart.6,7 Figure 2 illustrates that early Insulanisation is the need of the hour for an effective glycaemic control.

In spite all of the above, there is a lot of inertia for initiation of insulin therapy and this inertia is from clinicians and patients alike, this “gap” in the management of diabetics need to change.

*Target the Dirty Dozen*7,8

ADA consensus statement of 2016 says, target the treatment of organ damage early on, irrespective of initial glucose levels. Most of the clinicians in routine busy out-patients practice tend to only observe and dictate therapy depending on the blood sugar reports. This ‘gap’ in the mind-set needs to change to allow routine assessment of ‘ominous octave’, to create a wholesome treatment for the patient.

**Clinician Knowledge Gap III**

*Complications of diabetes—*Complications of diabetes can be categorized in this scenario into complications due to “infections” and complications due to “vasculopathy.”

*Infections—*
It is very imperative to look for infections leading to & associated with diabetic ketoacidosis—

*For example—*
- Mucormycosis
- External otitis media
- Emphysematous pyelonephritis
- Well controlled diabetic on a OPD follow-up, acutely becomes uncontrolled—look for underlying infections (do not only control BS).

Many times, especially targeting only sugar management may cause a “gap” in the treatment of a critically ill diabetic leading to morbidity and or mortality.

*Vasculopathy*8,9

Clinicians should not forget to correlate between organ-specific vasculopathy:
For example—
- Retinopathy if present—look for nephropathy
- Microalbuminuria if present, retinopathy absent—look for causes beyond diabetes
- Erectile dysfunction if present—work up toward ischemic heart disease

Top three Knowledge Gaps in Patients

Knowledge gaps in patients can be classified as—
- Diabetes: Remission or Cure??
- Diet
- Social media prescriptions

Patient Knowledge Gap I

Diabetes: Remission or Cure??—Patients have to be clearly counseled that diabetes is a lifelong disease. Only remission is possible not cure!!, which in simple words means, a diabetic can go off drugs and can be controlled on
only lifestyle changes, but he does not become “Diabetes Free.” This “gap” in patient knowledge will ensure better follow-up compliance.

**Patient Knowledge Gap II**

*Diet*—Various diets such as intermittent fasting diet, crash diets, supplementary diet, etc. are advocated and are being followed. The “gaps” in knowledge of these diets are—
- **Diet** have to be under guidance—“no one single diet suits all.”
- **Sustainability**—the patient should be clearly made aware that most of the individuals fail to keep up the dietary restrictions lifelong.

**Patient Knowledge Gap III**

*Social Media Prescriptions*—This “gap” in knowledge encompasses Doctor-Patient prescriptions over social media platforms. Though this is a very “convenient” method, it has its own inherent risks such as not involving physical examination of the patient; some medical parameters may get omitted during such communications, etc. The patient has to be made very clear that online consultation does not replace a physical consult and should be sought only in certain scenarios, such as lockdowns, etc.

**Conclusion**

**Top three Knowledge Gaps in Clinicians:**
- Type(s) of Diabetes
- Insulinization: Too early/Too late
- Complications of diabetes

**Top three Knowledge Gaps in Patients:**
- Diabetes: Remission or Cure??
- Diet
- Social media prescriptions

**References**

Abstract

The prevalence of diabetes in India is enormous and remained at 11.8% in last 4 years. Approximately 77 million people are living with diabetes while nearly 43.9 million (57%) of the cases of diabetes are undiagnosed. Moreover, challenges such as malnutrition, poverty, and socioeconomic burden precipitated by communicable diseases strain the already burdened health-care system of India. Adding to this, the Indian public health infrastructure can be characterized as chronically underfinanced since 1999. The Indian health sector received only 1–1.5% of the total GDP annually and even less is allocated to public health, health promotion, and awareness campaigns. There is lack of cohesion amongst a plenty of unregulated private centers with varying level of quality, poor coordination and communication, weak referral mechanisms, poor record-keeping, negligible accountability, and transparency which promotes distrust in medical establishment. Therefore, there is large-scale inequity in terms of accessibility and quality of service provision between rich and poor. Potential solutions are private and public sectors, especially public-PCC, need to be strengthened. A strong political will and a robust, evidence-based translational research, a bridge between theory and reality, achieve this beyond the broad structural characteristics of system and make the journey worthwhile for all the stakeholders.

Introduction

Dr. Amartya Sen reflected, “Health equity cannot be concerned only with health seen in isolation. Rather, it must come to grip with the larger issues of fairness and justice in social arrangements, including economic allocations, paying appropriate attention to the role of health in human life and freedom.”

Equitable diabetes care means that the individuals have access to affordable, high quality culturally and linguistically appropriate care in timely manner. This includes regular preventive care, in addition to emergency care, as well as mental health support.

Inadequacies in Diabetes Care: Current Scenario in India

Diabetes is a complex, chronic disease recognized as an important cause of premature death and disability, and disproportionately affects socially and economically disadvantaged population, especially poor and young sub-populations of Third World Countries.

The prevalence of diabetes in India is enormous and remained at 11.8% in last 4 years. Approximately 77 million people are living with diabetes while nearly 43.9 million (57%) of the cases of diabetes are undiagnosed. To complicate the matters more, majority of the T2DM patients have uncontrolled diabetes with HbA1c around 9%. Moreover, challenges such as malnutrition, poverty and socioeconomic burden precipitated by communicable diseases strain the already burdened health-care system of India. Adding to this, the Indian public health infrastructure can be characterized as chronically underfinanced since 1999. The Indian health sector received only 1–1.5% of the total GDP annually and ranks 184th out of 191 in terms of GDP percent-spend on health care. Even less is allocated to public health, health
promotion, and awareness campaigns; consequently there is large-scale inequity in terms of accessibility and quality of service provision between rich and poor. The economic model suggests that an additional 1% in GDP spent on precisely defined proven health schemes would save 480 million healthy life years.

Fee for service health seeking prevails in India and public-private fragmentation of health system results in skewed distribution of human and financial resources. Additionally, with disparity in expenses, infrastructure and manpower, drug delivery, and training are ubiquitous in India. Annual health expenditure in India, 80% of which is spent in private facilities, amount to trillion Indian rupees—greatest of which is perceived by the households. Thus, those who cannot afford fee can only access services characterized by poor infrastructure, overworked, and yawning personnel. In other words, poor quality service provision is left for the unprosperous.

Along with these lines the inverse curve law states that "the availability of good medical care tends to vary inversely with the need of it in a population served," which holds true in low- and middle-income countries.

Also, direct specialist consultation is common in India and there is no obligation regarding continuity of care from either physician or patients. There is lack of cohesion amongst a plenty of unregulated private centers with varying level of quality, poor coordination and communication, and weak referral mechanisms. Poor record-keeping, negligible accountability and transparency present opportunities for unethical practice promoting distrust in medical establishment. There exist many functionally illiterate populations with consequent poor health literacy. Whatever the underlying causes, inadequate glycemic and comorbid risk factors manifest in seriously disabling and life-threatening complications.

Majority of resource constrained Indians are deprived of annual routine monitoring of health indicators, BP, BMI, eye and feet examination, serum cholesterol, serum creatinine, HbA1c, urinary albumins, smoking review, mental health evaluation, etc. which form the regular elements of diabetes care along with the access to specialist health-care professionals including opthalmologists, podiatrist, and dietitians.

However, the ambition is to achieve universal health coverage for successful diabetes care by making the health services accessible with the targets to provide essential medicines and diagnosis to at least three-fourths of the cases by 2025.

**Need and Awareness**

It is essential to have person with diabetes as caregivers and sustain a multitude of daily self-management decisions that include:

- Compliance with medications regarding correct dose, frequency, route, and protection against adverse effects.
- Lifestyle modification: Adequate physical activity and daily exercise with a healthy diet.
- Cessation of smoking and harmful use of alcohol.
- Self-monitoring of blood glucose.
- Foot care.

Diabetes Self-Management Education and Support (DSME/S) for educating the patient on diabetes self-care is an intrinsic and vital segment of continuous care model of primary care facilities, which is very fruitful in improving diabetes-related health outcomes.

The ADA has endorsed measuring and tracking key results of DMSE/S, comprising self-management, clinical outcomes, health status, and quality of life.

**Challenges in Provision of Diabetes Self-management Support through Public Sector Primary Care as Candid and Equitable Diabetes Care**

- Lack of readiness of Public sector—Primary Care Centre for diabetes self-management
- Lack of awareness and understanding among patients with diabetes
- Suboptimal prescription adherence and therapeutic inertia
- Poor diabetes clinical audits and prospective registries
- Lack of inclusion of mental health services with diabetes care
- Enablement of smoking and tobacco cessation
- Dearth of diabetes educator and dietitian at the point of care level
- Lack of private public partnership
- Lack of political will

**Potential Solutions**

Strengthening of public sector-PCC is the key. Diabetes care research should also focus on quality of care accorded in primary care facility, especially in resource constrained settings.
Feasibility of adherence, avoidance of clinical inertia, patient counseling, peer education, provision of uninterrupted drug supply through team based DSME/S for patients in primary care need high quality trained nurses, MPWs, and diabetes educators. A robust back up of laboratory investigations also help in maintaining the flow of patient care.\textsuperscript{11}

Depression plays an important barrier in achieving optimum patient adherence to treatment. It can be effectively managed by planned community outreach programs, by setting up of yoga or meditation centers for the patients, using a proper peer support system.\textsuperscript{11}

A valid and practical adherence assessment system is necessary to reduce clinical inertia to a certain extent. Proper and targeted training of health workers and adequate supply of insulin and insulin syringes to avoid out of pocket expenses is of paramount importance.\textsuperscript{11}

This surely would help to balance the economic burden on the society and cost effectiveness of diabetes therapy.

**Specific Models of Sustainable Health-care Delivery and Disease Prevention in Resource Constrained Environment**

Professor V Mohan et al. demonstrated in MDRF, Chennai, how framework of systemic research may be applied to diabetes in developing countries to address deficiencies in knowledge and inequities in care. The MDRF and its associated clinical facility provide a good example of this. It illustrates the value of structured research in laying a foundation of policy development through assessing burden and translating evidence into practical responsive interventions, as well as harnessing the benefits of interventional collaborations and information technology.\textsuperscript{9}

*Alternative form of financing* must be sought since the cost of health care is so burdensome in most developing countries draining family and societal resources. Charging fee relative to respective income may be feasible in a context of fee for service facilities which has been hugely successful for India’s Aravind Eye Hospital (AEH).\textsuperscript{16}

*Research Centre for Diabetes Hypertension and Obesity (R.C.D.H.O.),* established in 2002 in district of Samastipur, is focused on serving the impoverished population of North Bihar and around. The idea to set up a non-profit centre emerged from management of diabetes and related comorbidities with huge lapses in the follow-up due to complex interplay of poverty, lack of awareness and education, daily-wage loss, misinformation, and myths. Those resource-poor patients later landed in the same clinic with life threatening infections, CKD, heart failure stroke, or blindness.

The centre detects, treats, educates, and defines timely and necessary referral pattern, and undertakes clinical and epidemiological research in sustainable and equitable manner charging fee relative to respective income.\textsuperscript{17} The role of private sector in diabetes care also needs to be made more accessible to the general population.\textsuperscript{18}

**Role of Private Sectors in Equitable Diabetes Care**

As we aspire to grow to a 5 trillion US dollar economy by 2025, private sector has a crucial role to play not only in even-handed and objective diabetes care but also in universal health coverage (UHC). It is due to widely divided and dispersed health infrastructure the voice of private sector is muddled and often goes unnoticed. This needs to change and we need to align it to our national goals of a high quality, affordable, accessible, equitable health system made in India for India.\textsuperscript{18} Unfortunately the cost of private health care is still about four to six times greater than our country’s public health care. The public health services are hugely grant-aided and supported by Indian government through interest in free capitals, interest rate subsidy, free land, electricity, and a number of other rebates and grants, all of which make it difficult to compare the real efficiency and comparable cost of service deliveries. Thus, there is large private-public gap in logistics, capacity, and delivery of care.

**Conclusion**

Both private and public sectors, especially public-PCC, need to be strengthened. A strong political will and a robust, evidence-based translational research, a bridge between theory and reality, achieve this beyond the broad structural characteristics of system and demonstrate if the financial benefits are reproducible, have a fair distribution and are collaborative with hand in glove approach. All of it guarantees a minimum set of core services of equitable diabetes care backed by our unified...
Diabetes Mellitus

Contd...

common pool of national resources which make the journey worthwhile for all the stakeholders.

“Nothing is faced can be changed but nothing can be changed until it is faced.”

–James Baldwin

References

CHAPTER 56
Resistant Hyperglycemia—A Practical Approach

Raveendran AV

Abstract
Blood sugar level not responding to a reasonable dose of oral anti-diabetic medication or insulin or other injectable therapies is called resistant hyperglycemia which is common in clinical practice. We will briefly review the causes of resistant hyperglycemia and practical approach to tackle this issue.

Introduction
Hyperglycemia not responding to usual doses of oral anti-diabetic medication or insulin or other injectable therapies is a common clinical challenge. In type 2 diabetes mellitus (T2DM), most of the time its transient due to coexisting acute medical condition. Hyperglycemia not responding to usual doses of medication can be due to some rare conditions associated with severe insulin resistance.

Lots of people with diabetes are not achieving treatment targets and this contributes to increased risk of development of complications. Common factors contributing to worsening of diabetes control is given in Box 1.

In people with T2DM, failure to respond to oral hypoglycemic agent (OHA) is a common issue. Most of the time it shows the progression of the disease, with loss of beta cell function.

Oral Hypoglycemic Agent Failure
Failure to respond to OHA can be of two types: primary or secondary.  
- **Primary failure to OHA**: When a newly diagnosed patient initially classified as T2DM has little or no glycemic response to OHA, it is called Primary OHA failure.
- **Secondary failure to OHA**: In people with diabetes who have a fair glycemic control on oral medications initially, may subsequently fail to achieve glycemic targets. This is called secondary OHA failure. When sulphonylurea (SU) and metformin (MET), in appropriate doses and diet, lose its capacity to produce

<table>
<thead>
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<th>BOX 1 Factors that can contribute to worsening of glycemic control</th>
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<tbody>
<tr>
<td>- Decreased compliance with:</td>
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<tr>
<td>- Diet</td>
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<tr>
<td>- Exercise</td>
</tr>
<tr>
<td>- Medical regimen</td>
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<tr>
<td>- Weight gain</td>
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<tr>
<td>- An intercurrent illness</td>
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<tr>
<td>- The use of medicines causing:</td>
</tr>
<tr>
<td>- Increase insulin resistance</td>
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<tr>
<td>- Interfere with insulin release</td>
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<tr>
<td>- Increase hepatic glucose production</td>
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<tr>
<td>- Progression of the underlying disease process:</td>
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<tr>
<td>- Decreased insulin secretion</td>
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<tr>
<td>- Increased insulin resistance</td>
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<tr>
<td>- Undiagnosed type 1 diabetes with gradual destruction of the</td>
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<td>pancreatic beta cells:</td>
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<tr>
<td>- “Latent Autoimmune Diabetes in Adults” (LADA)</td>
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<tr>
<td>- Therapeutic inertia</td>
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a desired maximal therapeutic effect (FBG < 8.0 mmol/L or HBA1c < 7.0%) after administration in the absence of other conditions causing hyperglycemia, it is called secondary OHA failure. Factors contributing to secondary OHA failure are given in Box 2.

**Insulin Requirements and Insulin Resistance**

The average total daily insulin dose (TDID) requirement for patients with T1DM is around 0.3–0.8 U/kg/day, except in teenagers where it is 1.0–1.5 U/kg/day. Anyone with a TDID of <1.0 U/kg/day is considered as having normal insulin sensitivity. The average TDID for patients with T2DM is around 1.0–1.5 U/kg/day, but, it can be as high as 2.0 U/kg/day. Anyone with a TDID of 1.0–2.0 U/kg/day is considered to have insulin resistance in the range of typical T2DM.

Insulin resistance is characterized by an impaired response to insulin—either endogenous or exogenous. Insulin resistance is defined as “a state (of a cell, tissue, or organism) in which a greater than normal amount of insulin is required to elicit a quantitatively normal glycemic response.” According to TDID requirement, insulin resistance is divided into severe and extreme insulin resistance (Table 1).

**Insulin Resistance: Measurement**

Various methods to measure insulin resistance are briefly mentioned below:

- **Insulin level at fasting:** Fasting serum insulin levels is usually less than 20 μU/mL in normal individual whereas it is over 70 μU/mL in those with severe insulin resistance.

### BOX 2

Factors associated with secondary oral hypoglycemic agent (OHA) failure

- Genetics
- Chronic hyperglycemia: Glucotoxicity, Lipotoxicity
- Amyloid deposition in the β-cells
- GAD positive
- ICA positive
- Low body mass index (BMI)
- Duration of diabetes
- Type of OHA used

### BOX 3

Mechanisms of insulin resistance

- Defects in insulin receptors:
  - Genetic defect
  - Insulin receptor antibodies
- Interference with intracellular insulin action:
  - Excess of counter-regulatory hormones
  - Inflammatory cytokines
- Increased insulin clearance

### TABLE 1

<table>
<thead>
<tr>
<th>Insulin resistance classification</th>
<th>Total daily insulin dose (TDID) requirement (unit/kg/day)</th>
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</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Severe insulin resistance</td>
<td>≥2</td>
</tr>
<tr>
<td>Extreme insulin resistance</td>
<td>&gt;3</td>
</tr>
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</table>

- **Assessing the peak level of insulin achieved after oral glucose tolerance test (OGTT):** In normal individual peak post-OGTT insulin level is usually less than 150 μU/mL, but it is greater than 350 μU/mL in people with severe insulin resistance.

- **Measuring the index of insulin sensitivity (SI):** SI is the fractional clearance rate of glucose per unit change in the plasma insulin concentration. In normal individual SI is above 5 μU/mL/min × 10⁻⁶ whereas in people with severe insulin resistance SI is below 2 μU/mL/min × 10⁻⁶.

- **Gold standard technique is to measure insulin mediated glucose disposal, i.e., MMM rate by the euglycemic hyperinsulinemic clamp.** In normal individual it is above 6 mg/kg/min, whereas in people with severe insulin resistance, it is less than 2 mg/kg/min.

Frequently sampled intravenous glucose tolerance test (FSIVGTT) and Homeostatic model assessment (HOMA) are also used for assessing insulin resistance.

Insulin resistance can be due to inability of the insulin to act effectively or increased destruction of insulin (Box 3).

**Pseudoresistance**

Insulin resistance has to be differentiated from pseudo-resistance (Box 4). It can be ruled out by conducting a
modified insulin tolerance test. During such a test, patients are administered a witnessed dose of short-acting insulin in the clinic, and their blood glucose level is monitored every 30 minutes for a period of 4–8 hours.6

After ruling out pseudoresistance, in people with T2DM look for cause of unexplained hyperglycemia, and correct it in order to control blood sugar level (Box 5). Presence of antibodies to insulin and subcutaneous insulin resistance causes poor response to insulin (Tables 2 and 3).9,10

**Extreme Subcutaneous Insulin Resistance (SIR)**

It is characterized by severe resistance to subcutaneous insulin with normal or near normal response to intravenous insulin.11 Insulin degradation in subcutaneous adipose tissue and muscle result in extreme subcutaneous insulin resistance (Table 2).

**Gustatory Insulin Resistance**

Some people with diabetes who are not on diet control develop a special situation. They get into a vicious cycle of
unrestrained eating (hence the term gustatory), resulting in poor glycemic control, which leads to up titration of insulin dose, which in turn leads to further eating, and so on. Because of unrestrained eating results in all these consequences it is called gustatory insulin resistance. This results in progressive weight gain, poor glycemic control, and, ever increasing, large doses of, seemingly ineffective insulin.

Lot of conditions can cause severe insulin resistance, including rare syndromes (Box 6). Proper evaluation helps to find out the causes of resistant hyperglycemia.

**Conclusion**

Resistant hyperglycemia is a common clinical problem. Most of the time, it is due to severe insulin resistance. Modified insulin tolerance test helps to rule out pseudoresistance. In people with T2DM, any acute medical condition can precipitate resistant hyperglycemia. Severe hyperglycemia not responding to conventional therapy may be due to rare genetic condition associated with severe insulin resistance.

**References**

Hypertension is the major cause of cardiovascular mortality, and it forms a sinister alliance with diabetes, leading to catastrophic results. Besides achieving optimal glycemic goals, it is imperative to treat blood pressure to mitigate any complications. Various guidelines have been published in the recent past. There is a consensus that the threshold of initiating antihypertensive therapy is a blood pressure of 140/90 mm Hg. The goal of treatment is a blood pressure <130/80–85 mm Hg. Because of various reasons, Asians are more susceptible to cardiovascular risk as compared to Caucasians. While treating blood pressure to goals, individual characteristics and the total cardiovascular risk burden should be taken into account. However, the blood pressure should not be brought down to <120/70 mm Hg.
The study concluded that the risk of cardiac disease as per the coronary artery score appears as a stepwise increment right from a SBP of 90 mm Hg and gradually increases with rising systolic BP. These results further confirm that it is important to prevent rise in SBP even within the so-called normal levels of blood pressure, as there also occurs a similar graded increase in cardiac risk with rising SBP levels.6

Hypertension in Diabetes
The cardiovascular risk doubles with every 20/10 mm Hg increase in blood pressure.7 SBP is a stronger predictor of cardiovascular disease and diabetic kidney disease than diastolic blood pressure. In fact, Systolic hypertension is more common (about 65%) in patients with diabetes, and more difficult to control.8

Blood Pressure Guidelines: Various guidelines have been published in the last couple of years, by the European Society of Hypertension (ESH 2018), American Heart Association/American College of Cardiology (AHA/ACC 2017), and the International Society of Hypertension (ISH 2020). ISH 2020 and ESH 2018 guidelines categorize the grade 1 hypertension when SBP 140–159 mm Hg and/or DBP 90–99 mm Hg while AHA/ACC 2017 categorize the stage 1 hypertension when SBP 130–139 mm Hg and/or DBP 80–89 mm Hg. However, the Goal of blood pressure for patients with diabetes is same in all guidelines, that is, less than 130/80–85 mm Hg. All guidelines emphasize that in all patients with hypertension and associated diabetes, drug treatment should be initiated at a BP of 140/90 or higher, aiming at a goal of less than 130/80–85 mm Hg.

Cardiovascular Risk in Hypertension
The 2018 ESC & ESH Joint Guidelines for the management of arterial hypertension, published on 9th June, 2018, were the first international guidelines, which not only classified patients with diabetes (asymptomatic, without organ damage) as Stage 2 Risk & Symptomatic patients with diabetes and organ damage as Stage 3 (Highest Risk), but also for the first time classified Asians at a higher risk by 40% (multiplication factor of 1.4 for correction for cardiovascular risk). The ISH guidelines also emphasize the racial and ethnic differences attributed to genetic differences along with a major contribution from life-style factors, which confer a higher risk for Asians.10

CV Risk in Hypertension—Are Asians Different?
The association between HTN and CVD is stronger in Asians as compared to the Western population, and occurs at an earlier age. Stroke is more common than CAD in Asian people, whereas the reverse is true in Western population (2.8 times higher—HONEST Study).11 The slope of the association between rising BP levels and CV events is also steeper in Asians vis-à-vis the Western population.12 Moreover, Asians are more susceptible for developing high BP even with mild obesity.

Asians also have a genetic predisposition to salt sensitivity, compounded by a high dietary salt intake as well as a significant seasonal variation of BP, with a rise in BP during the winter season.

Asians are more likely to have morning surge and nocturnal hypertension leading to greater BP variability.14 The Mumbai/India cohort study showed a 16% rise in risk of deaths and cerebrovascular accidents when SBP was in range of 120–129, but jumped to 73% higher risk, when SBP was more than 130 mm Hg. Moreover, risk of ischemic heart disease rose to 16% & 19%, respectively.15 Hence, a SBP of less than 130 mm Hg would be more beneficial for Asians.

How Aggressive should be the Treatment of Hypertension in DM?
Overall benefits of intensive BP treatment less than 120 mm Hg were only seen in ACCORD BP study participants receiving standard glycemic control (hazard ratio, 0.71; 95%, 0.56–0.90; P=0.005). Episodes of severe hypoglycemia have interfered with the intensive lowering of BP and probably cancelled out potential benefits of lowering SBP <120 mm Hg in patients with both DM and hypertension.16

The participants with DM in the ADVANCE trial benefitted from more intensive BP treatment regardless of baseline BP and of 10-year estimated ASCVD risk. This is consistent with recent guidelines recommending a lower BP target than the previous target of 140/90 mm Hg.17

In the ACCORD BP and SPRINT trials, BP was measured using Automated Office Blood Pressure, whose values are generally lower than typical office blood pressure by approximately 5–10 mm Hg. This implies that if protocols of the ACCORD BP or SPRINT are applied to routine clinical practice, then a SBP target higher than 120 mm Hg is required.18
Moreover, lowering the blood pressure to less than 110/75 had excess of risk for mortality at 3.5 years.19

A meta-analysis of 49 trials, including 73,738 patients by Mattais Brunstrom et al., showed that antihypertensive treatment in patients with SBP >150 mm Hg, reduced risk of all-cause mortality by 11%, CV mortality by 25%, stroke by 23% and end stage renal disease by 18%. For patients with baseline SBP of 140–149, additional treatment reduced risk of all-cause mortality by 13%, MI by 16% and heart failure by 20%. However, if baseline SBP is less than 140, additional treatment increased risk of CV mortality by 15%, and likely an increased risk of all cause mortality by 5%.20 In another meta-analysis by Mueller et al., in patients with diabetes but without cardiovascular disease, patients with a SBP of 110–119 mm Hg had a lower risk of non-fatal MI by 24% and non-fatal stroke/CHD/total CHD by 15%, as compared to patients with SBP of 130–139 mm Hg. However, risk of heart failure was higher by 20% and all-cause death by 28% in the 110–119 group as compared to 130–139 group.21

This basically means that the baseline systolic BP <130 mm Hg conferred significantly lower risk for adverse CV events than did systolic BP 130–139 mm Hg—the current systolic BP treatment goal for this population. It also suggests the association between low baseline systolic BP and all-cause death is not due primarily to CV disease, but rather to concomitant disease or patient factors (not measured by this study) that lead to both low BP and excess risk.

### Is there a J-Curve?

J-curve implies a higher risk of cardiovascular risk in patients both with a higher BP >140/90, as well as a lower BP <120/70 mm Hg. It is thus evident that in diabetics with a higher cardiovascular risk, there is a significant and lasting risk of subclinical myocardial injury and myocardial infarction, even when extensive adjustments have been made for any underlying disease burden.22

Hence, the available evidence from various well conducted scientific studies suggest that in patients with preexisting CVD, specifically CHD, it is prudent not to lower SBP ≤130 mm Hg. However, for those at higher risk of stroke (such as black and Asian patients) who do not have preexisting CHD, it may be beneficial to reduce SBP ≤120 mm Hg if this can be done without any harm.23 The J-curve does exist, but only for patients with preexisting coronary artery disease.

### Key Points

The ideal SBP goal for all is less than 130 mm Hg, irrespective of the presence or absence of diabetes. Those having a SBP of 130–139 mm Hg should first be treated non-pharmacologically with intensive life-style modification, and for those with high cardiovascular risk drug therapy should be initiated if resources allow.24

However, in the majority, if the goal BP of less than 130/80 is not achieved after 6 months with intensive life style modification, drug therapy should be initiated, irrespective of their cardiovascular risk.

Younger patients less than 40 years of age with SBP of 120–129 mm Hg, and a strong family history of risk factors like hypertension, dyslipidemia or diabetes, drug therapy should be initiated if after 6 months of intensive life style modification, the goal BP of less than 120/80 is not achieved and they are able to tolerate such levels of BP.25

### Conclusion

It is time to move beyond conflicting evidences and guidelines, derived from clinical trials that have excluded many patients due to age, comorbidities, and various social factors to a more nuanced and individualized approach based on scientific evidence and ethical principles, that can be implemented in clinical practice.

We should be treating patients and not mm Hg!!

### References

Abstract

Based on the science and the clinical studies that have been done over the last 100 years on Keto Diet (KD), KD has made a demonstrable impact on type 2 diabetes management. Such dietary modification led to improvements in glycemic control and medication reduction/elimination in motivated volunteers with type 2 diabetes. While larger, longer-term studies are needed, the data gathered thus far make a strong case for incorporating KD into treatment guidelines for type 2 diabetes. The ADA has recognized that reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia. The ADA also notes that reducing overall carbohydrate intake with a low- or very low-carbohydrate eating pattern is a viable option for those patients who are not meeting their glycemic targets or for whom reducing glucose-lowering drugs is a priority. However, the ADA does recognize that low-carbohydrate plans can be hard for diabetics to sustain in the long term and thus recommends that clinicians work with their patients and reassess their nutritional status through the life course.

Introduction

Diabetes mellitus, as defined by the American Diabetes Association (ADA), is a metabolic disease of consistent hyperglycemia, caused by either a defect in insulin secretion, a defect in insulin response, or both. The ADA has provided criteria for diabetes diagnosis as follows:

- Symptoms of diabetes plus causal plasma glucose concentration more than or equal to 200 mg/dL (11.1 mmol/L). Causal is defined as any time of the day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
- Fasting plasma glucose more than or equal to 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
- Two-hour post-load glucose more than or equal to 200 mg/dL (11.1 mmol/L) during an oral glucose load test.

The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 gm anhydrous glucose dissolved in water.

The pathophysiology behind why diabetes occurs is complex. In type 1 diabetes, the primary cause is an absolute deficiency of insulin secretion. Individuals with type 1 diabetes have evidence of an autoimmune process in the pancreas, specifically the pancreatic beta cells. The specific markers of pancreatic beta cell destructions include islet cell autoantibodies as well as autoantibodies to insulin, glutamic acid decarboxylase (GAD65), and tyrosine phosphatases IA-2 and IA-2β. There are also genetic factors include mutations in the HLA DQA and DQB genes.

In type 2 diabetes, it is multifactorial: there is a combination of insulin resistance and inadequate insulin secretory response to combat signals that there is high blood glucose. The majority of these persons with type diabetes are obese, which in of itself is a metabolic
condition that can cause insulin resistance. Even in those not classified as obese, the extent of insulin resistance, when reaches a critical threshold, can lead to the beginning signs of disease.

The degree of hyperglycemia varies by the individual and can vary over time and with the circumstances. How a particular person goes from an asymptomatic state to one where there is multiple-organ involvement is moderated by both genetics and the environment. Especially with type 2 diabetes, continued elevations in blood glucose with inability to upregulate insulin secretion and insulin resistance can lead to deleterious consequences in the short- and long-terms (including macrovascular and microvascular complications).

To combat and ultimately reverse type 2 diabetes requires a multi-pronged approach customized to each individual’s physiology. Insulin resistance can be improved with a combination of pharmacologic treatment as well as weight reduction. Over the past decade, there have been significant advancements in diabetic pharmaceuticals with new medications specifically focused on getting more insulin responsiveness. There have also been significant improvements in bariatric surgical techniques with improved patient outcomes. While nutrition therapy (via low-carbohydrate diet) has been considered to be the tried-and-true method to modifying carbohydrate metabolism and endorsed by many professional medical societies around the globe, diligent adherence, and continued compliance to this diet regimen remain major obstacles.

Recently, the ketogenic diet (KD) has been proposed as a potential means to achieve euglycemia and reverse diabetes altogether. This diet was initially used to treat children with refractory epilepsy in the early 19th century. However, over the last 35 years, KD has been promoted in the diet world as a fast and easy way to lose weight. In this review, we will go through the pharmacology of ketogenesis and evaluate the origins of KD. We will also review the current evidence in humans demonstrating the effectiveness of KD in diabetes type 2 reversal as well as the potential complications. We will also review low carbohydrate high fat (LCHF) diets.

**Ketogenesis: The Basics**

Physiological ketosis means that the body is able to optimize its fat utilization, reducing lipogenesis, and increasing lipolysis and fat oxidation. By consuming below-average amounts of carbohydrates, the body starts to deplete its carbohydrate reserves (in the form of glycogen). Once those reserves have been exhausted, the body then starts to generate its own glucose (gluconeogenesis). After that route is exhausted, the body is put into a state of ketosis. As a result, there is a high concentration of free fatty acids (FFAs) in the bloodstream, which are directed to the liver. In the liver, these FFAs are oxidized into ketone bodies (KBs). The KBs generated include β-hydroxybutyrate (βHB), acetoacetate (AA), and acetone. The beta-oxidation of these KBs in conjunction with the FFAs can generate a large amount of energy compared to just carbohydrates alone. βHB (100 gm) can yield 10,500 gm of ATP (the main currency of energy in the body), whereas 100 gm of glucose can generate 8,700 gm of ATP. Moreover, 108 ATPs are produced per 16 carbon FAs, as compared to 32 ATPs per unit of glucose. This energy-efficient process makes KBs and FFAs a good substrate for cells, especially in low-oxygen environments. These KBs are also able to cross the blood-brain barrier and can serve as energy source for brain cells, providing up to approximately 70% of the brain’s energy requirements. KBs are stable chemical structures and can remain in circulation for years. FFAs are especially effective in exercise, enhancing the skeletal muscle’s ability to oxidize fat.

It should be noted that while a person can get sufficient calories from KD, it does not necessarily mean that the body is optimally using KBs and FAAs for fuel. The body has to be primed to exclusively use KBs and FAAs. Keto-adaptation is the term used to describe the changes the body has to make metabolically to be able to completely depend on KBs and FAAs as the primary energy source. For the body to be able to “keto-adapt” requires carbohydrate restriction for an extended period of time. The exact amount of time required to reach that point where multiple organs in the body have reached KB/FAA homeostasis is unclear. Goedecke et al. attempted to do a time-course of metabolic adaptations to KD among 16 elite cyclists and found that changes in glucose tolerance were identified in these cyclists between 5 and 10 days of starting the KD. Looking at keto-adapted among elite athletes in the long-term (between 9 and 36 months), Volek and colleagues found that those on the KD had twofold greater peak fat oxidation rate and a higher serum KBs (indicating upregulated ketogenesis and lipolysis) compared to those on the high-carbohydrate group.
The Origins of the Ketogenic Diet

KD is a eucaloric diet composed of high fat and low carbohydrates with normalized protein intake, resulting in the production of KBs. This process is able to keep the body in a continued state of KB production.

KD as a diet had not been fully formulated until the mid-1930s, but only after a series of discoveries had been made. Multiple clinicians in the early 1900s had observed that fasting their epileptic patients would eliminate the seizures altogether. This was formally introduced to professional medical society by H. Rawle Geyelin, an endocrinologist at New York Presbyterian Hospital. Dr. Woodyatt, another clinician from the same time period, had noted that βHB and acetone appeared in a normal subject by starvation or a diet containing too low a proportion of carbohydrate and too high a proportion of fat. It was Dr. Wilder at the Mayo Clinic who was able to put it all together: he hypothesized that a diet should be as effective as fasting for treating epileptic patients and could be maintained for a much longer period of time. Wilder conducted a small trial of patients treated with the ketone-producing diet at the Mayo Clinic and then called the diet the “ketogenic diet.”

There are many types of KDs currently in use around the world (including the popular Atkins diet). However, there is no uniform guideline or professional consensus on what specific ratios of fat to carbohydrate to protein constitutes a “true” KD.

The first physiologic study looking at the long-term metabolic effects of KD was by Phinney et al. in the early 1980s. This study consisted of cyclists who were given a eucaloric balanced diet for 1 week (which provided 35–50 kcal per kg per day and 1.75 gm of protein per kg per day, with the remaining calories provided as two-thirds carbohydrate-based calories and the remaining one-third fat-based). Then the cyclists were put on a eucaloric KD for 4 weeks. This diet provided less than 20 gm of carbohydrates per day but the protein was matched to the balanced diet (1.75 gm per kg per day) so that the reduction in carbohydrate-based calories was replaced with an increase in fat-based calories. The goal was to evaluate whether there was a change in maximal oxygen uptake and pedal efficiency with the KD in comparison to the balanced diet group. The study authors found that there was neither any clinical nor biochemical evidence of any hypoglycemic event occurring during the time the cyclists were on the KD, demonstrating that aerobic endurance was not compromised by 4 weeks of KD. Moreover, the there was an across-the-board reduction in blood glucose (by about 15%) as well as in glucose metabolism (by about 30%).

Today in most nutrition circles, a KD is a state of increased fat consumption, which leads to ketosis. In the average person, the upper limit of carbohydrate intake is approximately 50 gm per day and protein intake ranges anywhere from 1.2–2 gm per kg per day in order to maintain this ketotic state.

Effectiveness of KD in Diabetes Type 2 Reversal

The potential to utilize KD in the management of type 2 diabetes has been explored primarily in small clinical populations. Even with major medical and technological advancements, the greatest challenge has been trying to control post-prandial glycemia. Focusing on the type of carbohydrate consumed and how it is metabolized has been the driving force behind the pursuit of a carbohydrate-modified diet specifically suited for type 2 diabetics.

But to understand the impetus behind KD and diabetes type 2 management, one needs to review Dr. Atkinson’s work. Dr. Atkinson, a professor of Medicine at Eastern Virginia School of Medicine and Chief of the Division of Clinical Nutrition had written a series of papers and authored many books and book chapters from the late 1970s through the 1990s looking at the use of low and very low calorie diets which were low in overall calories, low in carbohydrates, and high in protein. While many of them were linked to fad diets, the science behind a diet more in-line with a traditional KD had gained traction in the diabetic research community and the principles have been utilized to create targeted interventions focused on glycemic control.

There have been multiple studies looking at variations of KD and impact on hyperglycemia in type 2 diabetics.

To determine whether obese type 2 diabetics would achieve better glycemic control on a high-ketogenic very-low-energy diet (VLED) versus a low-ketogenic VLED, Gumbiner et al. conducted a small study among 13 patients over 6 weeks. Gumbiner and his study colleagues enrolled seven patients and put them on the high-ketogenic VLED for 3 weeks and compared them with six patients treated with a low-ketogenic VLED. The patients were then
crossed over and treated with the alternate diet for another 3 weeks. The study authors ensured that the caloric intakes for both diets were the same, but compared to a normal diet, the protein amounts were 55% higher. Both these diets created ketogenic states, but the low-ketogenic VLED (which had more carbohydrates) reduced ketosis by about 60% compared to the high-ketogenic VLED. After dieting, the amount of weight loss was not different between the groups but fasting and oral glucose tolerance test glycemia among those on the high-ketogenic VLED were lower than those on low-ketogenic VLED.

To evaluate how a low-carbohydrate KD could be effective way to improve glycemia and ultimately reduce the number of medications in type 2 diabetics, Yancy and associates conducted the following study: 28 patients from an outpatient clinic were selected to be part of a 16-week single-arm pilot diet intervention trial. The low-carbohydrate KD had a target carbohydrate amount of 20 gm per day or less. Twenty-one of the 28 participants who were enrolled completed the study. Twenty participants were men; 13 were white, 8 were African-American. The mean age was 42.2 years (BMI was 56.0). Hemoglobin A1c decreased by from an average of 7.5 to an average of 6.3 ± 1.4% to 6.3 from baseline to week 16. Diabetes medications were discontinued in 7 out of the 21 participants, reduced in 10 out of the 21 participants, and unchanged in 4 out of the 21 participants. The end results: glycemic control in patients with type 2 diabetes was optimized for the majority of the patients enrolled. However, given the rapid changes in hyperglycemia, patients on diabetes medication who use this diet were advised that they should be under close medical supervision to ensure that there were no major complications.

To be able to identify if a diet lower in carbohydrate would lead to greater improvement in glycemic control in patients with obesity and type 2 diabetes mellitus over the course of 6 months, Westman and associates recruited 84 community volunteers with obesity and type 2 diabetes from the outpatient setting. These individuals were randomized to either a low-carbohydrate KD (defined as 20 gm or less of carbohydrate daily) or a low-glycemic, reduced-calorie diet (500 kcal/day deficit from weight maintenance diet). The main outcome was glycemic control (as measured by hemoglobin A1c). Out of the initial 84, 49 completed the study. While both interventions led to improvements in hemoglobin A1c, fasting glucose, fasting insulin, and weight loss, the low-carbohydrate KD group had more significant results. The low-carbohydrate KD group had an average of 1.5% reduction in Hemoglobin A1c (compared to 0.5% in the low-glycemic group), an average weight loss of 11.1 kg (compared to 6.9 in the low-glycemic group, and reduction/elimination of diabetes medications in 95.2% of the low-carbohydrate KD group (compared to 62% in the low-glycemic group). LCHF diets had become a contentious area of nutrition, especially as it pertains to diabetes and diabetes reversal.

An LCHF diet is defined as one that restricts carbohydrate intake to 130 gm per day or less whereas a very LCHF (ketogenic) diet restricts carbohydrate intake to between 20 and 50 gm per day. There have been recent studies looking at LCHF in the management and potential reversal of diabetes type 2.

In one trial, 363 overweight and obese patients were allowed to choose either a ketogenic LCHF diet or a "low calorie, high nutritional value" diet and were on their respective diets for 24 weeks. About 220 (59 men and 161 women) were on the ketogenic LCHF diet and 143 (27 men and 116 women) were on a low-calorie diet, with 102 of the participants had established type 2 diabetes. After 24 weeks, HbA1c and fasting blood glucose concentrations decreased significantly more with the LCHF diet (down from an average of 7.7 mg/dL to an average of 6.7 mg/dL, a 1-point drop in HbA1c).

A randomized trial enrolled 34 prediabetic or type 2 diabetic patients to a calorie-restricted diet consistent with ADA guidelines or very LCHF diet. The very LCHF group showed a significant reduction (6.6–6.0%) in HbA1c values compared with unchanged values (6.9% at baseline and follow-up) in the ADA group. A significant number of more participants in the very low LCHF group decreased their use of diabetic medications as compared to the ADA group. The very low LCHF group also lost more weight (−5.5 kg) as compared to the ADA group (−2.6 kg).

Tay and colleagues randomized 115 obese type 2 diabetics to adults to either LCHF or LFHC diets for 1 year. The outcomes measured included: HbA1c, fasting blood glucose, glycemic variability assessed with use of 48-hour continuous glucose monitoring, diabetes medication, weight, blood pressure, and lipids assessed at baseline, 24, and 52 weeks. While there were no differences in HbA1c and blood glucose levels among the groups, the LCHF-diet group achieved greater mean reductions in the diabetes medication score, and there was less glycemic variability.
Conclusion

Based on the science and the clinical studies that have been done over the last 100 years on KD, KD has made a demonstrable impact on type 2 diabetes management. Such dietary modification led to improvements in glycemic control and medication reduction/elimination in motivated volunteers with type 2 diabetes. While larger, longer-term studies incorporating more people of color (including African-Americans and Hispanic-Americans, who are disproportionately affected by type 2 diabetes as compared to other racial/ethnic groups) are needed, the data gathered thus far make a strong case for incorporating KD into treatment guidelines for type 2 diabetes. The ADA has recognized that reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia. The ADA also notes that reducing overall carbohydrate intake with a low- or very-low-carbohydrate eating pattern is a viable option for those patients who are not meeting their glycemic targets or for whom reducing glucose-lowering drugs is a priority. However, the ADA does recognize that low-carbohydrate plans can be hard for diabetics to sustain in the long-term and thus recommends that clinicians work with their patients and reassess their nutritional status through the life course.

References

Abstract

Metformin is the drug of choice for type 2 DM as recommended by most of scientific society dealing in diabetes. Although being one of oldest hypoglycaemic agents, the mechanism of action is still to be revealed completely, currently it is best correlated with AMPK activation and altering redox state to reduce hepatic gluconeogenesis. Recent implication of metformin in meta inflammation has opened a big vista for its use not just as a hypoglycemic agent but in other states such as dementia by decreasing effect of MPTP, in cancer by inhibiting mitochondrial respiratory chain complex 1, anti ageing by inhibiting mTORC 1, in chronic infection like mycobacterium tuberculosis by inhibiting the mammalian target of rapamycin targets p70S6K and 4EBP1, in PCOS by increasing SHBP, by reducing pulmonary fibrosis via down regulating TGFβ1-mediated fibrogenesis and most important its cardiovascular modulating actions in CHF, DCMP, cardiac fibrosis, and hypertrophy. And the story does not commence here without mentioning its noble effect on thyroid health, obesity, and osteoporosis too. Below is a concise narrative of metformin and its expanded scope in medicine.

Introduction

Metformin is the preferred first-line oral blood glucose lowering agent to manage type 2 diabetes mellitus (T2DM) by almost all diabetic and cardiological societies all over the world either ADA or ECS. Galega officinalis (also known as goat’s rue), a traditional herbal medicine in Europe was found rich in guanidine. Metformin was introduced in 1920s, but came into US market in 1960s and gradually became one of the first-line oral antihyperglycemic drugs.

Pharmacokinetics and Pharmacogenetics

Drug is administered orally. It has low bioavailability 40–60%. Absorption predominantly occurs in the small intestine. Drug is not metabolized and excreted unchanged in the urine. After a dose of 500 mg it gets distributed systemically within 6 hours. Peak plasma concentration occurs after 3 hours. Half-life is 4–9 hours.

Mechanism of Metformin and Hepatic Glucose Regulation

Liver is the centrally acting body in glucose lowering effect of metformin.

Metformin-induced AMPK Activation

AMPK (5-AMP activated protein kinase) is a regulator of energy homeostasis. Metformin lowers hepatic gluconeogenesis through activation of AMPK. Due to metformin the ratio of ADP/ATP; AMP/ATP increases as a result of AMPK activation. Lack of energy inhibits gluconeogenesis.

Alterations of Redox State

Metformin also decreases hepatic gluconeogenesis independently of AMPK mediated and energy charge mediated effects through direct inhibition of
mitochondrial glycerol 3 phosphate dehydrogenase (G3PDH). Inhibition of this shuttle decreases the glucose production from reduced substrates but not from already oxidized substrates.

**What Makes Metformin the Oldest, Most Trustful, and Still an Enigma?**

**Metformin and Meta Inflammation**

Chronic low-grade inflammation associated with obesity is known as meta inflammation. It leads to insulin resistance, impaired lipid, and glucose homeostasis in metabolic syndrome and metformin have all potentials to reduce this meta inflammation.

**Metformin Action in Intestine**

*Gut is the primary target of metformin.* It inhibits glucose absorption from intestine along with increased glucose utilization by enterocytes by the upregulation of GLUT-2 and SGLT-1. Decrease glucose absorption in upper small intestine makes more glucose available in ileum, which further leads to more release of glucagon like peptide 1 (GLP-1). Fineman et al. showed primary action of metformin is in human gut. They demonstrated delayed release metformin which releases drug until pH was 6.5 in small intestine or beyond where the systemic absorption of metformin is low, resulted in more blood glucose lowering as compared to immediate releasing composition. Metformin also possess action on *gut-brain-neuronal axis.* It results in more release of GLP-1, which acts on GLP receptor on vagal afferent nerves innervating gut mucosa and augments the glucose lowering effect. Metformin plays role in modulating the *gut microbiota.* It causes increase in Escherichia species, lactobacillus and decrease in intestinibacter species, Bacteroides fragilis. Studies showed that altering the gut microbiota may contribute to glucose lowering effect of metformin. Metformin is also effective in type 1 diabetes as evidenced by REMOVAL TRIAL.

**Metformin Therapeutic Repurposing**

**Neurodegenerative Diseases**

The search for treatments for neurodegenerative diseases is a major concern in light of today’s aging population and an increasing burden on individuals, families, and societies. Therapeutic factor might be how metformin is able to balance *survival and death signaling in cells* through pathways that are commonly associated with neurodegenerative diseases. Metformin has the potential to interfere with neuronal longevity mechanisms. Insulin resistance and diabetes are increasingly recognized as a contributor to disease development especially in the field of dementias. Therefore, rationale for using metformin is its potential to slow aging processes. Most common dementia is AD (*Alzheimer’s dementia*). Neurofibrillary tangles and amyloid plaques (derived from amyloid precursor proteins (app)) are pathological hallmarks. Insulin signaling and glucose tolerance are altered in app in rat models. Diabetic rats showed increased levels of app, a-beta, phosphorylated tau. Metformin has shown to reduce tau phosphorylation, improves memory, and cognition. Metformin *reduces the damaging effect of MPTP* (methyl phenyl tetrahydropyridine) on dopaminergic neurons shown by tyrosine hydroxylase staining (a marker of dopaminergic neurons) in the substantia nigra, pars compacta, striatum or both. ALS (Amyotrophic Lateral Sclerosis) is characterized by degeneration of first and second order motor neurons resulting in spasticity and muscle atrophy. Neurochemical imbalance and genetic mutations are known to cause ALS. A protective role of diabetes in elderly and increased risk of developing ALS in young with diabetes has been described.

**Cancer**

Various evidences have provided that metformin has utility in cancer prevention and/or treatment. It has the potential for *inhibition of tumorigenesis* as it inhibits mitochondrial respiratory chain complex. In recent years, epidemiological data have shown that diabetes increases the risk of breast cancer, colorectal cancer, pancreatic cancer, endometrial cancer, and other malignant tumors. Metformin likely has an inhibitory effect on tumor progression in patients with T2DM, which can reduce the risk of tumor and tumor-related mortality of patients, improving their survival rate. *ISPY trial* is aiming that metformin hydrochloride may prevent or lower risk of breast cancer and decrease cancer cells, lower risk of cancer spreading. Metformin may also cause eradication of cancer stem cells, induction of cell cycle arrest, and inhibition of unfolded protein response, which further aids in its anti-tumorigenesis property. Recent data
suggest that diabetic patients taking metformin have a lower incidence of certain cancer, including prostate carcinoma.

**Aging**

Metformin is likely to hold the three promises—Longevity, Rejuvenation, and Health Span. The Targeting Aging with Metformin (TAME) clinical trial was designed to investigate the effects of metformin on several age-related diseases in humans. As supportive evidence for the TAME trial, it was stated that “metformin modulates the biology of aging and health span in model organisms.” Caenorhabditis elegans showed a good evidence for metformin as a potential anti-ageing drug. Inhibition of mTORC1 via blockage of lysosomal ATPase (V-ATPase) was postulated as an anti-ageing mechanism of metformin. A megatrial, sponsored by the Veterans Administration (NCT02915198; VA-IMPACT), started on February 19, 2019. This trial plans to study 7,868 subjects with prediabetes and established atherosclerotic disease for 4.5 years in a double-blind fashion with metformin extended release versus placebo for a combined primary endpoint. Time-to-events for oncology-related diseases and diabetes are secondary endpoints.

**Mycobacterium Tuberculosis Infections**

Evidence has emerged that metformin significantly decreases mortality during treatment for *M. tuberculosis* infection, suggesting a role for the drug as a host-directed therapeutic adjuvant. Metformin has a range of potentially beneficial effects on cellular metabolism, immune functions, and gene transcription involved in innate host responses to tuberculosis. Metformin enhances in vitro cellular metabolism while inhibiting the mammalian target of rapamycin targets p70S6K and 4EBP1, with decreased cytokine production and cellular proliferation and increased phagocytosis activity. Metformin also induces shift in myeloid cells from classical to nonclassical monocytes.

**Polycystic Ovarian Disease**

There is excessive production of androgens that cause some of the most common clinical symptoms of hyperandrogenism (acne, hirsutism, and alopecia). It is often associated with obesity and the metabolic syndrome. Metformin decreases insulin resistance and hyperinsulinemia, improves dyslipidemia and meta-inflammation, decreases blood pressure, and exerts cardioprotective benefits through pleiotropic action on the vascular endothelium. In combination with lifestyle intervention, metformin treatment is also associated with a lower body weight and improved menstrual cyclicity and fertility potential in women with obesity and polycystic ovary syndrome (PCOD). Possible mechanism is increase in hepatic production of sex hormone binding globulin (SHBG), which decreases androgen levels. Alternatively, the drug directly inhibits androgen synthesis in theca cells, which decreases testosterone levels.

**Lung Fibrosis**

A study in 2018 found that therapeutic concentrations of metformin accelerated the resolution of established fibrosis in a mouse model of lung fibrosis by promoting AMPK activation and apoptosis in fibroblasts. Metformin induces lipogenic differentiation in myofibroblasts to reverse lung fibrosis. Metformin induces lipid accumulation in IPF lung fibroblasts, inhibits TGFβ1-mediated fibrogenesis in vitro.

**Premature Pubarche**

It refers to precocious appearance of pubic hair without other signs of puberty in girls less than 8 years, boys less than 9 years. In a study done at Ibanez et al., metformin showed to have favorable effects on abdominal adiposity, androgen levels, and insulin resistance.

**Cardiovascular Effect**

**Role in Cardiac Fibrosis**

Metformin decreases cardiac fibrosis by AMPK activation and decreasing TGF beta. It inhibits myofibroblasts differentiation by suppressing reactive oxygen production by inhibition of NADPH oxidase.

**Role in CHF**

It decreases oxidative stress induced cardiomyocyte apoptosis, improvement in insulin resistance, and left ventricular end diastolic pressures. To date metformin is the only anti-diabetic drug which has shown to decrease the macrovascular complications by reducing the risk for MI.
Majority of ATP for cardiomyocytes is derived from fatty acids. Normally fatty acids are oxidized as it inhibits glucose catabolism via Randle cycle. In DM heart loses this regulation and leads to development of DCMP. Metformin acts to channelize the ATP coming from fatty acids and glucose in appropriate proportion and prevents or decreases the morbidity and mortality resulting from DCMP.  

Role in Cardiac Hypertrophy

Anti-hypertrophic action of metformin is due to AMPK activation. It leads to negative regulation of
- protein synthesis via Motor inhibition
- gene transcription including mitogen activated protein kinase and calcineurin nuclear factor of activated T cell pathways.

Non-alcoholic Fatty Liver Disease (NASH)

Non-alcoholic fatty liver disease (NAFLD) related to insulin resistance (IR) is a growing global health concern. Metformin inhibits lipogenesis, increases fatty acid oxidation in liver and adipose tissue. Metformin improves liver function, HOMA-IR and BMI to some extent, but not histological response in NAFLD patients. Studies have indicated that metformin could improve IR and may be beneficial in the treatment of NAFLD.

Thyroid and Metformin

Individuals with hyperinsulinemia have larger thyroid gland and a higher prevalence of thyroid nodules and cancer. Accordingly, patients treated with metformin have a smaller thyroid volume and a lower risk of incident goiter, thyroid nodule. Metformin can inhibit thyroid dysfunction irrespective of thyroxine replacement and presence of thyroid autoimmunity. Perhaps, metformin has central action.

Obesity

It reduces the body weight independent of dosage. The mean body weight lost is in the range of 1–5 kg or 1–3% in both diabetic and non-diabetic patients. Metformin also helps to counteract the weight gain caused by sulfonylurea (SU), thiazolidinediones, and insulin.
Abstract

Diabetes mellitus is a worldwide serious health issue and an economic burden, rising in epidemic proportions over the last few decades. Although several treatment options are available, only half of the global diabetic population achieves the recommended or individualized glycemic targets. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetic agents with a novel insulin-independent action. SGLT2 is a transporter found in the proximal renal tubules, responsible for the reabsorption of most of the glucose filtered by the kidney. Inhibition of SGLT2 lowers the blood glucose level by promoting the urinary excretion of excess glucose. Due to their insulin-independent action, SGLT2 inhibitors can be used with any degree of beta-cell dysfunction or insulin resistance, related to a very low risk of hypoglycemia. In addition to improving glycemic control, SGLT2 inhibitors have been associated with a reduction in weight and blood pressure when used as monotherapy or in combination with other antidiabetic agents in patients with type 2 diabetes mellitus (T2DM). Treatment with SGLT2 inhibitors is usually well tolerated; however, they have been associated with an increased incidence of urinary tract and genital infections, although these infections are usually mild and easy to treat. SGLT2 inhibitors are a promising new option in the armamentarium of drugs for patients with T2DM.

Introduction

Diabetes is a growing epidemic due to population growth, ageing, urbanization, and westernization. Hereby, the burden of diabetes translates into substantial social and economic problems. The alleviation of hyperglycemia, often by oral antidiabetic drugs, leads to improvement of insulin sensitivity, b-cell function, and reduction of microvascular complication such as retinopathy, neuropathy, and nephropathy. The standard antihyperglycemic treatments do not necessarily confer full protection against coronary artery disease (CAD), stroke, and peripheral vascular disease as shown in several large, long-term outcome studies, partially explained by the risk at hypoglycemic events. Furthermore, in order to effectively reduce cardiovascular (CV) events in diabetic patients, comorbidities such as obesity, hypertension, and hypercholesterolemia must be cotargeted, in conjunction to the maintenance of glycemic control. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are approved for glucose lowering in patients with type 2 diabetes mellitus (T2DM) since 2012. These agents have shown benefit in cardiovascular as well as renal outcomes in T2DM patients, which make them an excellent therapeutic option and have opened a vast area of research.

Mechanism of Action

Glucose reabsorption is mainly mediated by the SGLT2 transporter. The SGLT2i reduce blood glucose by blocking its reabsorption in the proximal convoluted tubules of kidneys leading to glucose excretion via the urine. Apart
from the above it also causes reduction in SBP of 4–6 mm Hg and DBP of 2–4 mm Hg. Osmotic diuresis reduced renin-angiotensin-aldosterone system (RAAS):
- Reduction in body weight 1–5 kg: calorie loss in urine, dehydration in short term, fat mass loss and lesser insulin requirement
- Increase in hematocrit: dehydration, increased erythropoietin
- Lower urate concentration
- Lower triglycerides: calorie loss, glucosuria

**Currently Available SGLT2i**
The currently available SGLT2i are discussed in **Table 1**.

**Natural History of Diabetes**
Onset of macrovascular complications occurs early in metabolic dysregulation (Fig. 1 and Flowchart 1).

**Mechanisms of Cardiovascular Benefits with SGLT2i**
Mechanisms of cardiovascular benefits with SGLT2i have been discussed in **Table 2**.

**Cardiovascular Benefits of SGLT2i—Evidence**
- The EMPA-REG outcomes trial was the first to show not only non-inferiority but also superiority over

---

**TABLE 1** Currently available SGLT2i

<table>
<thead>
<tr>
<th>Name</th>
<th>Empagliflozin</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available doses</td>
<td>10 mg, 25 mg</td>
<td>100 mg, 300 mg</td>
<td>5 mg, 10 mg</td>
</tr>
<tr>
<td>Daily dosing</td>
<td>Od before breakfast</td>
<td>Od before breakfast</td>
<td>Od before breakfast</td>
</tr>
<tr>
<td>Food interaction</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Renal dose adjustment**</td>
<td>EGFR&gt;45: no dose adjustment EGFR&lt;45: NR EGFR&lt; 30 : C/I</td>
<td>EGFR&gt; 45: no dose adjustment EGFR 45–60: canagliflozin 100 mg eGFR&lt; 45: NR EGFR&lt; 30: C/I</td>
<td>EGFR&gt; 60: no dose adjustment EGFR&lt; 60: NR EGFR&lt; 30: C/I</td>
</tr>
</tbody>
</table>

Other agents approved in India: Remogliflozin

Other agents: Ertugliflozin (FDA approved, EMA authorized) sotagliflozin (SGLT2, 1 dual blockade FDA CRL, EMA authorized)

Approved in Japan: Tofogliflozin, luseogliflozin, ipragliflozin

---

![Fig. 1: Natural history of diabetes](image-url)
Flowchart 1: Metabolic adaptations following SGLT2i therapy

TABLE 2  Potential mechanisms of cardiovascular benefits with SGLT2i

<table>
<thead>
<tr>
<th>Hemodynamic effects</th>
<th>Metabolic alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmotic diuresis and reduced preload</td>
<td>Glycemic control</td>
</tr>
<tr>
<td>Bp reduction</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Local (renal) and systemic raaS activity inhibition</td>
<td>Ketone body generation and energy efficient utilization of ketone bodies over glucose by a failing myocardium—the &quot;thrifty fuel&quot; hypothesis</td>
</tr>
<tr>
<td>Neprilisyn inhibition</td>
<td>Uricosuria</td>
</tr>
<tr>
<td>Alternation in intra and extracellular Na⁺ distribution by inhibition of Na⁺h exchanger in cardiomyocytes (sodium hypothesis)</td>
<td>Increased erythropoietin production due to reduced glycemic exposure of macula dense improved hematocrit and O₂ carrying capacity</td>
</tr>
<tr>
<td>Decreased sympathetic nervous system activity</td>
<td></td>
</tr>
<tr>
<td>Improved arterial relaxation and decreased after load</td>
<td></td>
</tr>
</tbody>
</table>

placebo in CV outcomes in patients with T2DM receiving either doses of empagliflozin (10 mg or 25 mg).

- The primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke was reduced by 14% with empagliflozin. Interestingly, this was driven mainly by a significant decrease in CV death.³
- There was a non-significant reduction in nonfatal MI but a slight increase in nonfatal stroke with empagliflozin.
- There was also significant reduction in all-cause mortality by 32% and hospitalization due to heart failure by 35%.
- The CANVAS program integrated data from two trials—CANVAS and CANVAS-R patients with T2DM
on standards therapy at high cardiovascular risk were randomized to receive either canagliflozin (100 mg or 300 mg) or placebo.9

- Around one-third patients had high risk for CV disease while 65.8% of patients had already established CV disease.
- In the canagliflozin group, the relative risk of the primary composite outcome (3-p mace) significant decreased by 14%. There was however no significant difference in CV death, nonfatal MI, or nonfatal stroke.
- In the DECLARE-TIMI 58 trial, which was CVOT designed to satisfy the US FDA criteria of safety for dapagliflozin, 40.6% with atherosclerotic CV disease and 59.4% with risk factor for atherosclerotic CV disease.
- Though the trial showed the non-inferiority of dapagliflozin in 3-p mace but dapagliflozin did not result in a lower rate of mace than placebo in contrast to was seen in EMPA-REG and CANVAS trials.10

Comparison of Landmark CVOTS with SGLT2i

Comparison of landmark CVOTS with SGLT2i has been discussed in Table 3.

Renal Benefits with SGLT2i—Mechanisms

The mechanisms for renal benefits with SGLT2i could be multifactorial including both direct renal vascular and hemodynamic effects (Table 4).

Renal Benefits—Evidence

- The EMPA-REG outcome also investigated renal outcomes in patients with T2DM, established CV disease, and an estimated glomerular filtration rate (eGFR) 30 mL/min/1.73 m². In spite of an initial decline in eGFR in the first 4 weeks of empagliflozin treatment, overall, there were a 39% reduction in the relative risk of worsening nephropathy, a 38% reduction in the progression of macroalbuminuria, 44% reduction in the doubling of serum creatinine, and a 55% reduction in the initial of the renal-replacement therapy.
- CANVAS-R trial was predominantly aimed to study renal outcomes with canagliflozin treatment. It showed significant reduction in the risk of progression of albuminuria, requirement for renal-replacement therapy, or renal death by 23% and 40% respectively.11
- Credence trial, the primary outcomes, which was a composite of ESRD, doubling of serum creatinine or

### Table 3
Comparison of the landmark CVOTs with SGLT2i

<table>
<thead>
<tr>
<th>Trial</th>
<th>EMPA-REG outcome</th>
<th>Canvas program</th>
<th>DECLARE – TIMI 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>Doses analyzed</td>
<td>10 mg, 25 mg</td>
<td>100 mg, 300 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Median follow-up (yrs)</td>
<td>3.1</td>
<td>2.4</td>
<td>4.2</td>
</tr>
<tr>
<td>No of participants</td>
<td>7020</td>
<td>10142</td>
<td>17160</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>63.1</td>
<td>63.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Patients with established CV disease (%)</td>
<td>100</td>
<td>65.6</td>
<td>40.6</td>
</tr>
<tr>
<td>Patients with heart failure (%)</td>
<td>10.1</td>
<td>14.4</td>
<td>10</td>
</tr>
<tr>
<td>Patients with eGFR &lt;60 mL/min/1.73 m³</td>
<td>25.9</td>
<td>20.1</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Reduction in 3-p mace (HR with 95% cl)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients with atherosclerotic CVD</td>
<td>0.86 (0.74-0.99)</td>
<td>0.82 (0.72-0.99)</td>
<td>0.9 (0.79-1.02)</td>
</tr>
<tr>
<td>In patients with multiple risk factors for ASCVD</td>
<td>0.98 (0.74-1.30)</td>
<td>1.01 (0.86-1.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Reduction in CVD/HHF (HR with 95% cl)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients with atherosclerotic CVD</td>
<td>0.66 (0.55-0.76)</td>
<td>0.77 (0.65-0.92)</td>
<td>0.83 n(0.71-0.98)</td>
</tr>
<tr>
<td>In patients with multiple risk factors for ASCVD</td>
<td>0.83 (0.58-1.19)</td>
<td>0.84(0.67-1.04)</td>
<td></td>
</tr>
<tr>
<td>AMI/CVD</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Stroke</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Hospitalization due to heart failure</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
death from renal/CV diseases was reduced by 30% with canagliflozin in patients meeting the inclusion criteria two of which were the presence of macroalbuminuria and an eGFR as low as 30 mL/min/1.73 m². The best results were seen in those with eGFR 45–60 and those with baseline urine ACR >1,000 mg.

- Overall, canagliflozin has shown renoprotective effect in T2DM patients, especially those at high CV risk.
- Declare-trial with dapagliflozin, the renal composite outcome (40% decrease in eGFR to <60 mL/min/1.73 m², ESRD, or death from renal or cardiovascular cause) significantly favored dapagliflozin with an incidence of 4.3% in the dapagliflozin group and 5.6% in the placebo group.
- Remogliflozin—the robust developmental program conducted globally for remogliflozin till its first approval in India (Table 5).

### SGLT2i and CV Outcomes—Real World Evidence

- Real world evidence is captured in natural, uncontrolled settings and can provide date on effectiveness and safety during routine care and complement date from RCTS.
CVD real: compared the rates of hospitalization due to heart failure (HF) in individuals with T2DM who newly initiated on SGLT2i (canagliflozin, dapagliflozin, or empagliflozin) versus other oral hypoglycemic agents. Data for 160,033 people on SGLT2i and 1,226,221 on other agents were available from six different countries (US, UK and Nordic countries). Canagliflozin was used in 53% of the population, 37% received dapagliflozin and 10% received empagliflozin. Results favored SGLT2i over other agents for HF or death by any cause.

CVD real looked at CV and mortality outcomes from an additional six countries (four from Asia pacific, plus Canada and Israel). Up to 75% received dapagliflozin. Results were similar to CVD-real, with a lower incidence of the composite of HF or death by any cause.

Embrace—real world effectiveness and tolerability of remogliflozin.

Remogliflozin
Remogliflozin is an intensively researched molecule in 26 clinical studies conducted globally.

The phase III pivotal registration trial in India has demonstrated non-inferiority of remogliflozin 100 and 250 mg BID to dapagliflozin 10 mg OD. The reduction in HbA1c at 24 weeks in RE 100 g vs. Dapa 10 mg was 0.72 vs. 0.58 (p <0.001) for non-inferiority.

The reduction in PPG was seen to be numerically higher (39.2 vs. 32.4 g/dL) at 24 weeks.

The reduction in FBG was comparable at 24 weeks.

The reduction in non-glycemic parameters was seen comparable to dapagliflozin.

The adverse event profile was comparable to dapagliflozin 10 mg. Remogliflozin is demonstrated to be well tolerated.

Remogliflozin has equivalent PD (assessed by UGE), glycemic efficacy and real world clinical effectiveness as with other SGLT2i.

The economical costing of remogliflozin empowers for larger access to Indian T2DM patients.

The real world experiences from large scale utilization are/would be presented in various scientific forums, which underscore the efficacy and safety profile in real clinical practice.

The ongoing and future studies are expected to be generated to further strength the evidence exclusively in Indian patients.

The phase III pivotal registration trial in India has demonstrated non-inferiority of remogliflozin to dapagliflozin, with comparable result in all glycemic and non-glycemic parameters.

The adverse event profile of remogliflozin was comparable to dapagliflozin and is well-tolerated by patients.

Cardio-renal benefits are consistently seen with all agents of this class, and explained by mechanistic hypothesis of effective SGLT2 inhibition.

Efficient SGLT2 receptor blockage would potentially provide these benefits observed with this class of drugs.

Remogliflozin is equivalent but economical SGLT2i that would offer access to clinical benefits of SGLT2 inhibition to larger set of Indian patients.

Safety Concern around SGLT2i
Safety concern around SGLT2i has been discussed in Table 6.

Place of SGLT2i in current guidelines: as per the 2020 guidelines, apart from affordability issues, there is possibly no reason why agents other than SGLT2i or GLP-1RA should be preferred over these two agents as the second drug of choice after metformin (Figs. 2 to 4, Flowchart 2).

<table>
<thead>
<tr>
<th>TABLE 6</th>
<th>Safety concern with SGLT2i—results from landmark CVOTs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event studied</strong></td>
<td><strong>Higher rates than placebo?</strong></td>
</tr>
<tr>
<td>Major hypoglycemias</td>
<td>No</td>
</tr>
<tr>
<td>Euglycemic diabetic ketoacidosis</td>
<td>No, most events in patients with autoimmune diabetes</td>
</tr>
<tr>
<td>Genital mycotic infection</td>
<td>Yes, all agents</td>
</tr>
<tr>
<td>Urinary tract infection, pyelonephritis</td>
<td>No</td>
</tr>
<tr>
<td>Lower limb amputation</td>
<td>With canagliflozin</td>
</tr>
<tr>
<td>Fractures</td>
<td>With canagliflozin</td>
</tr>
<tr>
<td>Strokes</td>
<td>With empagliflozin</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>No</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>No</td>
</tr>
<tr>
<td>Cancers (bladder, renal cell, breasts)</td>
<td>No</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>No</td>
</tr>
</tbody>
</table>
CHAPTER 60
SGLT2 Inhibitors—Where to Use? Where not to Use?

Fig. 2: Algorithm for T2DM management from ADA 2020 guidelines.

LVH, left ventricular hypertrophy; HFrEF, heart failure reduced ejection fraction; UACR, urine albumin-to-creatinine ratio; LVEF, left ventricular ejection fraction.

1. Lowered ejection fraction (EF)
2. Clinical trial evidence showing decreased cardiovascular death and hospitalization for heart failure with SGLT2 inhibitors
3. Significant risk factors for heart failure, such as diabetes duration, heart failure history, and hypertension
4. Albuminuria or proteinuria
5. Estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m²
6. Selection of SGLT2 inhibitors based on the patient's preference and adherence
7. Consideration of body weight and BMI
8. Monitor for adverse effects, such as volume depletion and hypoglycemia

LVEF ≤40% with heart failure symptoms
LVH with or without heart failure symptoms
High-risk patients with diabetes mellitus
Diabetic nephropathy or microalbuminuria
The above criteria are not mutually exclusive, and patients may benefit from a combination of SGLT2 inhibitors and other medications.
Fig. 3: Algorithm for T2DM management from ACC 2020 guidelines

1. Order of medications represents a suggested hierarchy of usage. Length of line reflects strength of recommendation.
2. If goal not reached in 3 months proceed to next level therapy.
3. DPP-4i may be added to first-line therapy if patient weight remains unchanged.
4. Use of GLP-1RA may be considered as monotherapy in patients with reduced glomerular filtration rate (GFR < 60 ml/min/1.73 m²).

LEGEND:
- △: Use with caution: Few adverse events and or possible benefits
- ○: Use without caution: Few adverse events

PROGRESSION OF DISEASE
CHAPTER 60
SGLT2 Inhibitors—Where to Use? Where not to Use?

Fig. 4: Algorithm for T2DM management from EASD 2020 guidelines

LVH, left ventricular Hypertrophy; HFrEF, heart Failure reduce ejection fraction; UACR, urine albumin-to-creatinine ratio;
LVEF, left ventricular ejection fraction
**Flowchart 2:** Algorithm for T2DM management from ESC 2020 guidelines

**TABLE 7** SGLT2i—ongoing trials

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Drug</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertis – CV</td>
<td>Ertugliflozin 5 mg, 15 mg vs placebo</td>
<td>To assess CV safety of ertugliflozin in T2DM</td>
</tr>
<tr>
<td>Dapa-CKD</td>
<td>Dapagliflozin 10 mg, or 5 mg vs placebo</td>
<td>To assess the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease</td>
</tr>
<tr>
<td>Emperor preserved</td>
<td>Empagliflozin 10 mg vs placebo</td>
<td>To assess the risk of CV death and heart failure related hospitalization in patients with heart failure with preserved ejection fraction, with and without diabetes</td>
</tr>
<tr>
<td>Scored</td>
<td>Sotagliflozin vs placebo</td>
<td>CVOT of sotagliflozin</td>
</tr>
<tr>
<td>EMPA kindey</td>
<td>Empagliflozin vs placebo</td>
<td>To assess renal disease progression and CV death in diabetics and non-diabetics with eGFR&gt; 20-45 or eGFR&gt; 45 + urine ACR &gt; 200 mg/g</td>
</tr>
</tbody>
</table>
SGLT2 Inhibitors—Where to Use? Where not to Use?

SGLT2i—The Future

See Table 7.

Where to Use SGLT2i

- Type 2 diabetic patients with good renal function.
- Diabetic patients with hypertension.
- Overweight and obese type 2 diabetic patients.
- Type 2 diabetic patients with recurrent hypoglycemic episodes.
- Type 2 diabetic patients experiencing therapy related limiting adverse events. For example GI side effects with GLP-1 analogs or with AGI use. Type 2 diabetic patient with poor glycemic control while on monotherapy or combination therapy.18

Conclusion

- SGLT2i are one of the most attractive therapeutic options in T2DM management with reasonably acceptable safety profile.
- SGLT2i offer a very second-line option following metformin monotherapy especially in individuals with established renal or CV disease or at high risk for the latter. The most common side effect is genitourinary infection, which is however easily treated.
- Canagliflozin reduced the burden of the first and total HHF events by 39% and 36% respectively in patients with T2DM and CKD.
- SGLT2i recommended as monotherapy if metformin is contraindicated or not tolerated in T2DM with unmet needs of glycemic control with metformin monotherapy.
- SGLT2i as monotherapy/add-on to metformin effectively reduce A1c, FPG, body weight and BP in patients with T2DM.
- SGLT2i significantly reduce the risk of CV morbidity and mortality; and associated with reno-protective effects—viz. slower progression to kidney disease and progression of albuminuria, and reduction of eGFR.
- SGLT2i—potential benefits on β-cell function and reduction of insulin resistance may be more useful in Indian T2DM patients.
- Insulin independent action, hence greater durability of glycemic control.
- Efficacious in all stages of T2DM.
- Additional benefits of weight loss, BP reduction.
- Beneficial for combating multiple comorbid diseases associated with T2DM.
- Requires appropriate patient selection and adequate counseling.

References

Abstract
The journey of SGLT2 inhibitors is unimaginable. As new trials keep surfacing, tremendous potential of SGLT2 inhibitors becomes obvious. Not only unmet needs in diabetes therapy, but also indications in non-diabetic conditions have come to light. Use in non-diabetic heart failure has given new hope. We have now evidence to prevent new onset diabetes, lowering gout risk, and new modality for NALFD/NASH treatment. It has also become a new ray of hope for cardio-renal protection. In type 1 diabetic patients, taking SGLT2 inhibitors with insulin act as insulin dose modifier. Many other new indications might be visible in the coming days. The ever changing untold science of SGLT2 inhibitors has posed challenges for learned societies to make clear guidelines. Clearly, a diabetologist’s drug group is becoming favorite of cardiologists and nephrologists.

Introduction
Sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i) are perhaps the most exciting newer anti-diabetics, which now have garnered attention even beyond its traditional indication for type-2 diabetes mellitus (T2DM). The clinical dimension of SGLT2i is increasing apart from frontline metabolic, cardiovascular, and renal therapeutics. A plethora of extra cardiac and renal effects are on the horizon and has not been told. Some of these untold stories related to beyond glycemic lowering need serious considerations after they have been found to have some unique features and indications in some landmark trials (Tables 1 and 2).

Historical Perspective
SGLT2i has a remarkable history dating back more than 150 years. It was first isolated from the root bark of apple tree as a substance called Phlorizin as early as 1835. The first clue about how kidneys reabsorb glucose came in 1980s. The first SGLT2i, which was approved by FDA was canagliflozin in year 2013. Later dapagliflozin and empagliflozin were approved by FDA in January 2014 and August 2014, respectively. Ertugliflozin got approved by FDA in 2017. Remogliflozin is approved by health regulatory authority in India in 2019. Today SGLT2i are being successfully being used to treat diabetes by harnessing the kidneys. This journey of SGLT2i is going through an unimaginable curve showing tremendous benefits to meeting the multitudes of unmet needs of diabetic patients.

New Exciting Indications
Prevention of Diabetes
First evidence emerges by DAPA-HF trial with 32% reduction in new onset diabetes shown by Dr Inzucchi’s new analysis. In non-diabetic subjects dapagliflozin reduced the risk of developing new onset type 2 diabetes. Remarkably it was 32% reduction in comparison to
Prevention of Non-diabetic HF

EMPA-REG OUTCOME trial, CANVAS trial, and DECLARE-TIMI 58 trial have brought new ray of hope in diabetes management. These trials brought a historic change and led to change in guidelines. Today diabetologist are saying goodbye to glucocentric concept. Needless to say, we give top priority to cardiovascular and renal protection. We want reduction in hospitalization for heart failure. In 2019 DAPA-HF trial results amazed the scientific community. It showed 26% relative risk reduction in primary end point, which was composite of cardiovascular death, hospitalization to heart failure or urgent heart failure visit in patients with. It also showed 30% relative reduction in worsening heart failure. Cardiovascular death reduction was 18%. It is worth to note that DAPA-HF constituted 55% non-diabetic cohort. Both diabetics and non-diabetics cohorts got benefitted in equal proportion. It clearly tells that dapagliflozin efficacy was not related to glycemic reduction. Even the all cause death reduction was 17%. The message is clear and loud. Dapagliflozin can be used as a novel therapeutic drug to treat heart failure with reduced ejection fraction (HFrEF), irrespective of the presence of diabetes. It is a great news for heart failure patients (both diabetic & non-diabetic population). Latest Canadian guidelines have already included this benefit and extended use of dapagliflozin in non-diabetics.1

Emerging as Nephrologist’s Favorite to Treat Diabetic Kidney Disease

The evidence has emerged from unique RCTs and meta-analyses. In a patient with full blown kidney disease and base line eGFR up to 30 mL/min/1.73m², renoprotective...
and cardioprotective effects of SGLT2i are maintained. Scientific societies have moved to recommend the preferential use of SGLT2i in patients with DKD. It is expected that regulatory authorities will increase the range of eGFR at which SGLT2i can be used, as well as modify the indications to include nephron protection (Fig. 1). 4

**Lowering Gout Risk by SGLT2i**

A meta-analysis of 62 studies, comprising 34,941 patients shows that any of the SGLT2i significantly decreased serum uric acid levels compared to control. When compared with GLP-1 RA, clear benefits of SGLT2i have been found. It was 4.9 events per 1,000 person-years in SGLT2i group and 7.8 events per 1,000 person-years in GLP-1 RA group. [HR of 0.64, 95% CI, 0.57–0.72]. Empagliflozin resulted in superior reduction. SGLT2i might be beneficial for diabetic patients with hyperuricemia as per this meta-analysis. 5

**Abdominal Obesity**

Now it is well known that SGLT2i reduces body weight and visceral opacity. They also reduce ectopic fat deposition. Thus, they improve adipose tissue function. We have today an evidence-based therapeutic option for management of overweight and obese patients having type 2 diabetes (Flowchart 1). 6

**Evidence in Hypertension**

SGLT2i can bring modest reduction in blood pressure. Most of studies point that 5–6 mm Hg reduction in systolic blood pressure occurs. The diastolic blood pressure reduction has been found 1–2 mm Hg. This reduction is not dependent on blood sugar control. Initial reduction is due to diuretic mechanisms. Improvement of vascular stiffness could be another mechanism later on. Interestingly SGLT2i could be beneficial in difficult to control hypertension. Non-dipping resistant hypertension is a very difficult situation in day-to-day practice. Now, SGLT2i have been found to module such cases. It is worth to note that SGLT2i mediates osmotic diuresis. It leads to more electrolyte-free water clearance. Thus, more prominent fluid loss from interstitial spaces ensues. 7,8 No sympathetic nervous system activation occurs while reducing blood pressure by SGLT2i. This is in contrast to GLP-1 RA, which cause increase in heart rate. Reduction in preload and afterload is unique to SGLT2i. It is thus beneficial in reducing cardiac work load and also myocardial oxygen demand. Nevertheless, BP reduction is unlikely to explain all cardiovascular benefit. 9

**Use in NASH/NAFLD**

SGLT2i are showing promising results in non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease.
disease (NAFLD). Various studies have already shown that SGLT2i improve serum level of liver enzymes, decrease liver fat, and fibrosis. And also, improvement in various metabolic parameters in type 2 diabetes patients with NAFLD. Many more studies are on the way in this aspect and indicate that SGLT2i should be used for all NASH, NAFLD cases at least in diabetics. We have to watch for more studies, research in cases of non-diabetics as well (Flowchart 2).10

**SGLT-2i in Type 1 Diabetes**

At present SGLT2i are being used as off label drug in type 1 diabetes although some recent trials like DEPICT 1,2. EASE 1,2,3, and in-Tandem 1,2,3 clearly head to new indication to use SGLT2i with insulin in type 1 diabetes. In future SGLT2i may be included in guidelines to enable people with type 1 diabetes to achieve their glycemic goals. Dapagliflozin has credit to being the first SGLT2i to be approved in Europe. It has got approval from NICE (National Institute for Health and Care Excellence, UK) and SMC (Scottish Medicines Consortium) as an adjunct to insulin for people with T1DM if glucose levels are not adequately controlled with insulin alone. SGLT2i should be avoided if high risk of DKA is suspected. It should be used with utmost care if patient has difficulty in adhering to insulin regimen or having difficulty understanding and following treatment instructions.11 European Medicines Agency (EMA) approved dapagliflozin for use in some patients of type 1 diabetes but FDA has not approved it in the USA. Ipragliflozin has been approved in Japan for use together with insulin in adult with type 1 diabetes. The dual SGLT2i, sotagliflozin has shown improvements in HbA1C, weight loss and systolic blood pressure and reduction in insulin dose when added to insulin therapy.

**Primary Prevention of Cardiorenal Complications in T2DM**

It is now a proven fact that SGLT2i have a great affect in reduction to hospitalizations due to heart failure. DECLARE-TIMI58 trial data has thrown light that dapagliflozin has tremendous benefits in primary prevention. Taken together, cardiovascular death and hospitalization due to heart failure (HHF), we have now exciting data. The relative risk reduction in CV death was 17% and in HHF it was 27% in DECLARE-TIMI58 trial. ACC subgroup analysis further suggested and showed 16% reduction in MACE in subgroup analysis. Further, subgroup analysis of DECLARE-TIMI58 trial showed a reduction of 47% in renal outcomes. In nutshell, these drugs have shown a great promise in primary prevention of cardiorenal complications by dapagliflozin.12

**Use in HFrEF**

SGLT2i are yet to show proven benefits in HFrEF patients. Some important trials are on the way—DELIVER and...
DETERMINE-preserved trials with dapagliflozin and EMPEROR-preserved and EMPERIAL-preserved with empagliflozin. It shall be a landmark development and another big feather in cap of SGLT2i if these trials show positive trend.\textsuperscript{13}

**Some Emerging Indications**

- In cases of artificially-induced syndrome of inappropriate ADH secretion (SIADH), DIVE study has been done. It was done with empagliflozin. It gives an insight that SGLT2i can be used in diseases, which are associated with hyponatremia. It is so due to its effect on free water clearance.\textsuperscript{14}
- In polycystic ovarian syndrome (PCOS), use of SGLT2i resulted in weight loss and anthropometric parameters also improved. This was shown in a small study. When metabolic and hormonal outcomes were compared with metformin, no significant difference was seen.\textsuperscript{15}
- Now a very interesting data has emerged showing that empagliflozin can be very useful in reducing the requirement of insulin by 59%. This paper was presented at ADA virtual meeting 2020 (new-initiation of insulin, or >20% increase in insulin requirement in EMPA REG OUTCOME study). It appears SGLT2i are emerging as insulin dose modifier\textsuperscript{16}
- The risk of new onset obstructive sleep apnea can be reduced by SGLT2i. In EMPA REG OUTCOME study, this risk was reduced by 52%. This data was presented at ADA 2020 virtual meeting.\textsuperscript{5,17}
- In type 2 diabetes cases, dapagliflozin has been shown to reduce the risk of atrial fibrillation and flutter. In a new study it has been shown. Its effect remained consistent. There was not much effect on this regardless of previous history of atrial fibrillation, atherosclerotic cardiovascular disease or heart failure.\textsuperscript{18}

**Under-Prescription and Cost-Effective Issues**

In spite of being rated among as only anti-diabetic oral drugs capable of cardiorenal prevention and having potential for primary prevention, SGLT2i remains under-

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**TABLE 3**

<table>
<thead>
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<th>Why they have DARE-19</th>
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<tr>
<td>AstraZeneca and Saint Luke's Mid America Heart Insititue have initiated Phase II DARE-19 trial (completion date - December 2020) with Farxiga in COVID-19 patients</td>
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<td>An international, parallel-group, randomized, double-blind, placebo-controlled, investigator-sponsored phase III trial evaluating the efficacy and safety of Dapagliflozinin addition to background local standar of care therapy, on the riks of all-cause death or disease progression and complications in adults who are hospitalized with COVID-19</td>
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<td>They include 900 sickets patients of COVID with patient's history of at least one of the following:</td>
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<td>- Hypertension</td>
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<td>- T2DM</td>
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<td>- Atherosclerotic cardiovascular disease</td>
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<td>- HF and/or</td>
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<td>- CKD state 3 to 4 (*eGFR ≥25 mL/min/1.73 m)</td>
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<tr>
<td>There is a growing argument that dapaglifolzin, in particular, has shown to decrease lactic acidosis and thus has the potential to reverse acid-base balance inside the cells during hypoxi, which can prevent cell injury during the cytokine storm of COVID-19 illnes, in patients with diabetes</td>
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<tr>
<td>Both pre-clinical and clinical studies suggest that SGLT2i may favorably impact the underlying mechanisitic processes dysregulated in the setting of acute major illness (such as COVID-19) and include favorable effect on endothelial function, inflammation, oxidative stress, tissue hypoxia, energy metabolism, and autophagey</td>
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<tr>
<td></td>
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<tr>
<td>Some view it as a dangerous proposition as ketoacidosis in COVID-19 is associated with hypercoagubility</td>
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</table>
prescribed worldwide. In the USA in patients with diabetes and CVD only 9.3% were prescribed SGLT2i as per one study. As a matter of fact these are significantly cost-effective in long term by preventing cardiovascular and renal complications.

**Class Effect Dilemma, are all SGLT2i not Same?**

Much awaited VERTIS CV (ertugliflozin CVOT trial) was presented at ADA virtual meeting 2020 on 16th June. VERTIS CV trial did not superiority for MACE and cardiovascular death. Although the cohort population was almost similar to EMPA REG outcome trial.

There was a trend for lower HHF risk among ertugliflozin-versus placebo, with rates 2.5% versus 3.6%, but the difference was not statistically significant due to hierarchical testing sequence used. Still consistent class effect in HHF can be interpreted. It is worth to note that MACE reductions were only statistically significant only for empagliflozin and canagliflozin.

Now this trial gives suspicion that all SGLT2i are not the same. Many factors might be operating. No clear-cut answer exists. Some of debated factors are—a difference in patient population between trials, a true biological difference in drug efficacy or any other factor might be operating.

**DARE-19 Study with Dapagliflozin in COVID-19**

You can raise your eyebrow. While consensus today is to stop SGLT2i due of DKA in COVID-19, DARE-19 trial is daring to use SGLT2i in COVID-19.

Final results are expected in March or April 2021 (Table 3).

**Conclusion**

Usual indications of SGLT2i keep changing in light of latest clinical trials. Some stories are well known but immense potential has not been yet explored. SGLT2i which started its anti-diabetic journey with huge controversies has now emerged as an amazing weapon to fight not only in prevention of secondary cardiorenal complications but also in primary cardiorenal protection along with hosts of other metabolic disorders. Many new indications are emerging and these must be considered in clinical perspective (Fig. 2).

**References**

Abstract

Insulin was available for the treatment of diabetes for human use for almost 100 years after the discovery in 1921 by Prof. Macleod and Dr. Fredrick G. Banting with the help of Dr. Charles Best and Prof. J.B. Collip. The different types of insulins available today are the fruits of various innovations and modern state of art DNA recombinant technology. Evolution of insulin has been shown to start from crude animal extract insulins to the recent pure and precisely controlled formulations of insulin analogs. The modifications of the insulin formulation and of the insulin molecule have made it in such a way that approximate the natural endogenous insulin secretions. These modern designer insulins provide the peak less basal level of insulin or mimicking the spikes of meal insulin release. We have discussed in this review how pharmacokinetics and pharmacodynamics of old insulin molecules have been modified to be converted into modern new insulins. Hence, various insulin formulations like rapid-acting, short-acting, intermediate-acting, and long-acting insulins, as well as mixtures and concentrated formulations have been produced.

Introduction: Evolution of Insulin

The management of diabetes has changed significantly over the past century after the discovery of insulin around the year 1921. Insulin was invented by Frederick Banting, John Macleod, and Charles Best from animal pancreas. The earliest insulin preparations were largely animal-based, having either bovine or porcine origin. Eli Lilly was the major producer of animal-based insulin, which soon started falling short with the demands. To overcome this, insulin analogs gradually emerged in the picture. The main objective for developing analogs was to prolong the duration of action of insulin, which required several shots during the day. Achieving this, in the year 1983, the use of recombinant human insulin was approved, and insulin analogs were gradually developed.

Newer types of insulin or insulin analogs offer better replacement of insulin because of closer simulation to the human physiology. When compared with regular insulin, insulin analogs such as lispro, aspart, and glulisine have faster onset of action. Other analogs like glargine and degludec have longer duration of action. Both of these types have evidenced reduction in the risks of hypoglycemia. The most recent advancement in insulin has been the development of the insulin pen device, which allows better patient compliance and thereby corresponds with fewer side effects. It was developed in the year 1985 marking the era of better glycemic control for patients.

This chapter compares the old types of insulin with newer insulin formulations or insulin analogs. The discussion will be along the lines of safety and efficacy and will be supported by trial data and pharmacokinetic studies.

Old Insulin

Earliest preparations of human insulin were extracted from human cadaveric pancreas (refer to Figure 1 for its
structure) and its use was limited because of the risk of allergic reactions and lower availability. The first synthetic human insulin that was biologically equivalent to the hormone required significantly higher time and costs for production and also had lower rates of productivity (6–10%) thereby not offering higher success in terms of glycemic control of the patients. With subsequent productions, these drawbacks and side effects were gradually met.

Regular (rapid-acting), neutral protamine hagedorn (NPH) (intermediate-acting) and premixed insulin (long-acting) are human insulin preparations that are now also prepared by recombinant DNA technology. They have a slow onset of action (peak after 3 hours of dosage) and may also have variability in their effects resulting in a lower predictability of the clinical outcomes of the patient.

Human insulin formulations, particularly, intermediate-acting types like NPH (reaches a peak after 4–6 hours of administration) have a major limitation concerning the risk of hypoglycemia. Most particularly, nocturnal hypoglycemia is common in patients receiving this type of insulin. So, human insulins are not preferred for long-term use in patients for the stabilization of their HbA1c profiles. But, their combination with new insulin analogs supports better glycemic control in some patients and they are thus not completely obsolete.

**New Insulin**

Insulin analogs were formed with the help of recombinant DNA technology in the presence of either *Escherichia coli* or *Saccharomyces cerevisiae*. Analogs are produced with altered pharmacokinetic and absorptive properties through the modification of binding affinity for insulin and insulin-like growth factors to meet the drawbacks of human insulin such as slow onset and limited efficacy or duration of action.

**Rapid-acting Analogs**

Insulin analogs such as insulin lispro (Humalog), insulin aspart (Novolog), and insulin glulisine (Sanofi) function as rapid-acting agents having a faster onset of action (Figs. 2A to C).

When compared with regular insulin, rapid acting insulin had lesser risk of both postprandial hypoglycemia and nocturnal hypoglycemia thereby having a better safety profile. HypoAna trial of type 1 diabetic patients showed that treatment of patients with insulin detemir and aspart was associated with a 66% lower risk of nocturnal hypoglycemia.
hypoglycemia when compared with human insulin. Other than HypoAna, 17 other clinical trials conducted worldwide have evidenced this effect.

Findings from systematic review and meta-analysis intended to compare the safety and efficacy of rapid-acting insulin analogs with regular insulin have demonstrated similar results. Insulin analogs were found here to reduce 7% of total hypoglycemic episodes, 32% of severe hypoglycemic episodes, and they also reduced nocturnal hypoglycemia by 45%.

Other than reducing hypoglycemia, the use of rapid-acting insulin analogs over prolonged periods led to more stabilized blood sugar levels because of the capability of rapid-acting insulin to closely imitate the properties
of insulin hormone in its physiological state. Since postprandial fluctuation of blood glucose levels is primarily responsible for 50% of the hypoglycemic episodes and rapid-acting insulin prevents these episodes, it also results in better patient compliance to the treatment, which determines long-term glycemic control.

In a study comparing the rates of patient compliance, it was found that while only 7% of the patients adhered with the administration protocol of regular human insulin 30 minutes before their meals, for insulin lispro, the compliance rate was as high as 98% due to a more flexible protocol (0–15 minutes before meals). This is a significant advantage favoring better treatment efficacy with the use of insulin analogs (Table 1).

Indian data also depicts similar advantages of insulin lispro and other rapid-acting agents over regular human insulin. It confirms that the use of rapid-acting insulins more effectively manages postprandial spike in blood glucose levels and is thus associated with better glycemic control due to flexibility offered with both meals and insulin dosage.

### Long-acting Analogs

Glargine and degludec are soluble long-acting analogue, which have a long duration of action (24 hours or more) (Table 2). They are newer forms of insulin analogs and have also been labeled as second-generation insulin analogs (Fig. 3).

Because of a long duration of action, insulin glargine only needs to be administered once daily resulting in a much higher rate of patient compliance. Since it does not have a distinct peak of action, it also has a lower risk of hypoglycemia. When compared with human insulin formulations, insulin glargine has depicted lower risk of hypoglycemia in clinical studies. At similar HbA1c levels, patients receiving glargine were found to have fewer episodes of nocturnal hypoglycemia when compared with patients receiving NPH insulin because of its favorable pharmacodynamic and pharmacokinetic properties.

As per the findings of a meta-analysis report of 15 clinical trials, it was determined that insulin degludec was superior to insulin glargine. This can be attributed to its long-lasting basal insulin actions, which have twice more duration of effect than glargine, and much lower individual variability. Degludec can be administered at any time of the day without the risk of hypoglycemia in subjects, and can also be carefully combined with other types of insulin analogs such as aspart for managing the individual treatment needs of the patient. Further, it was stated that degludec resulted in lower rates of hypoglycemia in both type 1 and type 2 subjects.

The effectiveness of insulin analogs can also be judged through the results of clinical trials in insulin-naïve patients. CONFIRM trial, a large-scale non-interventional trial analyzing data from 4,056 patients depicted that the administration of degludec/glargine U300 significantly improved HbA1c profiles of adult type 2 diabetes patients (refer to Table 3 to understand the implications of diabetic control on the overall health status of the patient). Further, the administration of long-duration insulin analogs even lowered the risks and frequency of hypoglycemia as well as it minimized the possibility of treatment discontinuation, which is a common finding in insulin-naïve subjects.

Compared with IGIlar, IDeg is associated with equivalent glycemic control and a statistically significantly lower rate of nocturnal hypoglycemia in patients with T1DM and T2DM. In T2DM patients, IDeg also provides better results in terms of overall hypoglycemia.

### Critical View of Old Insulin versus New Insulin

Human insulin is considered to be less superior to newer insulin formulations in managing blood glucose levels of the patient as well as in reducing the risks of hypoglycemia,
Evolution of Insulin: Old Insulin versus Insulin Analogs

TABLE 3

<table>
<thead>
<tr>
<th>Risks</th>
<th>Risk reduction for each 1% reduction in HbA1c levels</th>
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</thead>
<tbody>
<tr>
<td>Death due to diabetes/diabetic complications</td>
<td>21%</td>
</tr>
<tr>
<td>Microvascular complications</td>
<td>37%</td>
</tr>
<tr>
<td>Risk of amputation due to diabetes or peripheral vascular disease</td>
<td>43%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>12%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14%</td>
</tr>
<tr>
<td>Stroke</td>
<td>12%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>16%</td>
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</table>

TABLE 3: Long-term effects of better HbA1c control on patients with type 2 diabetes

which is a major concern hindering the long-term management of diabetes. Despite this, a recent clinical trial involving 40 pediatric type 1 subjects affirmed that regular and NPH insulin showed similar efficacy to insulin glargine and aspart. In terms of glycemic control, it was noted that HbA1c levels were similar for both the groups of patients. While fasting blood glucose was better controlled for the group assigned to the glargine treatment, the result was not statistically significant implicating that human insulin could be as effective as newer insulin analogs. However, since this was a small-scale study involving only pediatric subjects and the risk of hypoglycemia was not evaluated at all, no derivations can be made in the favor of traditional insulin formulations over new insulin on the basis of this singular trial.

Because of this, it has been largely debated whether insulin analogs are better than regular or NPH insulin keeping in mind the clinical outcomes of the patient and their pre-existing awareness of old insulin. In this regard, greater evidence has been found in the favor of the use of insulin analogs when compared with regular or NPH insulin. This is because of its ability to reduce nocturnal hypoglycemia by 48% when compared with NPH, as well as severe hypoglycemic effects in patients compared with regular insulin. Both in type 1 and type 2 diabetes, detemir has proven to be better than NPH in several studies of 16–52 weeks of duration since it does not contribute to weight gain in patients.

Comparison among Insulin Analogs

Insulin degludec is an emerging treatment agent, which has is so far considered to be superior to human insulin
and analogue insulin. Findings from the multi-Centre, multi-national randomized controlled study BRIGHT trial are awaited to state with certainty that which of the insulin analogs is the most superior.

According to the large-scale blinded randomized control trial ORIGIN,\textsuperscript{14} optimal stabilization of fasting blood glucose levels of patients and a high rate of adherence to the treatment (85%) was found with the use of degludec. Furthermore, the previous claims of the risk of cancer and cardiovascular complications with the use of insulin analogs were largely refuted by this trial. However, the risk of hypoglycemia was higher in the glargine arm when compared with the placebo, which is a considerable risk for the patient.

Insulin degludec when used alone is associated with lower risk of hypoglycemia in both type 1 and type 2 subjects as per the findings of several phase 2 trials.\textsuperscript{15} It also has a low variability and thus is a safer alternative for individuals with blunted hypoglycemic awareness. Despite its benefits, one of the risks of insulin degludec is that it is an ultra long acting type and can be a potential risk for patients with renal or hepatic impairment. Overcoming this drawback, recent trial studies have demonstrated that the combination of degludec with rapid-acting insulin such as aspart results in significantly lesser hypoglycemia and can be regarded a safe alternative.

Pre-mixed formulations combining lispro and aspart have also been recently available, but their use is not recommended over other types of insulin.\textsuperscript{16} This is because of their highly rigid dosage structure, which interferes with the lifestyle activities of the patient and elevates their risk of hypoglycemia. It can only be administered in elderly patients or those with social problems where maintaining A1c levels less than 7.0% is not of utmost priority. Even in them, it must be used cautiously.

**Insulin Pen Devices**

According to the consensus guidelines of diabetic management experts in India, insulin pen devices have considerable advantages over the conventional vial and syringe methods because of better patient compliance and higher accuracy of administration achieved through its use. FlexPen offers lower injection force and dose force and is thereby associated with fewer side effects such as pain. On the other hand, NovoPen offers higher treatment accuracy. Regardless of the insulin delivery system used, pen devices, overall, facilitated about 2.1% higher reduction of hypoglycemia when compared with vials and syringes.\textsuperscript{17}

**Conclusion**

New insulin or analogue insulin including both rapid-acting and long-acting analogs are better than older insulin such as regular insulin or NPH. They correspond with better glycemic control (both HbA1c and fasting) and lower risk of hypoglycemic events, most particularly nocturnal or postprandial hypoglycemia. This concludes that insulin analogs have a higher safety and efficacy than old insulin and is also associated with better treatment compliance by the patient due to flexibility of treatment offered to them. Among insulin analogs, degludec is the most promising agent having a long duration of effect and no apparent peak. However, a combination of degludec and aspart is recommended in patients as a safer alternative.

**References**


CHAPTER 63

Insulin Regimens for Initiation in Type 2 Diabetes Mellitus

Sudhir Chandra Jha, Syed Yousuf Faisal, Gautam Kr Sandilya

Abstract

Type 2 diabetes mellitus (T2DM) has emerged as the global epidemic. It is a relentlessly progressive disease resulting in various dreadful complications. These complications, however, can be delayed/prevented by modifying risk factors and optimizing glycemic control. The optimization of glycemic control often requires using multiple pharmacological agents including oral antidiabetes drugs (OADs) and insulin. Insulin has the unmatched HbA1c lowering capacity. Therefore, in clinical situations where achieving HbA1c goal has not been possible despite using multiple OADs, insulin initiation seems logical. A basal regimen may be ideal to start with because of its simplicity and favorable impact on weight and lower risk of hypoglycemia. However, intensification of this regimen may be required later to maintain proper glycemic control.

Introduction

There is a tsunami of diabetes mellitus sweeping across the globe. In 2019, approximately 463 million adults (20–79 years) were living with diabetes. By 2045 this figure is likely to rise to 700 million. Type 2 diabetes Mellitus (T2DM) accounts for around 90% of cases. Nearly 1 million Indians die due to diabetes every year. T2DM has emerged as a major cause of blindness, stroke, heart attacks, kidney failure, and lower limb amputations. So T2DM is a chronic progressive disease associated with multiple complications that can be prevented or delayed by modifying risk factors and attaining proper glycemic control. UKPDS shows that at the time of diagnosis β-cell function is already markedly compromised by up to 50%, with β-cell function continuing to deteriorate in the years following diagnosis. So β-cell function progressively declines in T2DM, and there is increasing difficulty in maintaining glycemic control. In many patients, achieving HbA1c goal may not be possible despite using multiple OADs.

Due to unprecedented explosion in the number of cases of T2DM globally, diabetes-related complications are posing a major challenge both at the individual and social level. Insulin initiation early in the course of disease may be an important measure to meet this challenge. Unfortunately, clinical inertia exists and insulin is used quite late despite the benefits of timely glycemic control and guidelines encouraging earlier use of insulin. That is one important reason for increase in complications in T2DM. There are several barriers to initiation of insulin—both at the levels of the patient and the treating physician. At the level of patients, important factors are—fear of injections, risk of hypoglycemia, difficulties in managing insulin therapy. Physicians also contribute to clinical inertia by their concerns about potential side effects (particularly hypoglycemia), difficulties in training patients and absence of clear-cut guidelines. However, early institution of insulin therapy has shown beneficial effects on β-cell function and may cause remission in various studies.
Ryan et al. demonstrated in a study that if insulin is used early in the course of disease even for a short period of 2–3 weeks to achieve intensive glucose control, it may cut down glucotoxicity drastically. This may lead to improvement in β-cell function and high-remission rates even at the end of 1 year.5

In a landmark multicentric randomized study, Weng et al. compared the effects of short-term intensive control of blood glucose by multi-dose injections of insulin or CSII (continuous subcutaneous infusion of insulin) versus effects of multiple OADs. The insulin group showed marked improvement in β-cell function. In addition the insulin group also showed significantly higher remission rates even at the end of 1 year.6

In another important metaanalysis, Krammer et al. demonstrated that intensive insulin therapy for even a short period of 2–3 weeks had a positive impact on glycemic control, insulin resistance, and remission rates.7

Most patients with T2DM have inadequate glycemic control on one or more oral antidiabetes drugs (OADs). In these circumstances, it may be a vital decision to add another OAD or initiate insulin.

It is well known that insulin has the greatest and unparalleled glucose lowering effect. While OADs have limited capacity to decrease HbA1c by around 1–1.5% only. So patients with HbA1c of 8.5% or higher are good candidates for insulin initiation. Indian (RSSDI-ESI) guidelines suggest that insulin should be considered in those T2DM patients who have failed to achieve normal glycemic control despite using three OADs. These guidelines also recommend insulin initiation in significant hyperglycemia (fasting plasma glucose more than 270 mg/dL or HbA1c more than 9%) and patients having symptoms of polyuria, polydipsia, polyphagia, and loss of weight. RSSDI-ESI guidelines also advocate use of insulin in unstable states, severe infections, and ketosis. Patients put on insulin need to be monitored and titrated. In selected cases intensification of insulin regimen maybe done.8 One important thing to keep in mind is that OADs should not be suddenly stopped on initiating insulin therapy because of the risk of rebound hyperglycemia.9

Before discussing the different insulin regimens for T2DM, it may be worthwhile to know insulins, which are readily available in Indian market and their duration of action, onset, and peak of action (Table 1).

Analogues may be preferred because of less risk of hypoglycemia particularly during night. However, cost consideration is also very important in poor country like ours. Education/counseling about timing and monitoring of different insulins to the patient is very important.

**OADs During Initiation of Insulin**

Continuing OADs should be considered during initiation of insulin. Combination of therapies not only lowers daily insulin requirement but results in effective HbA1c reductions. Combination of most of OAD with insulin is usually safe and effective. In analysis of different studies—no increased risk of adverse effects was evident on combining insulin with OADs with few exceptions. When insulin is used with pioglitazone, there are more chances of fluid and water retention, edema, and weight gain.10 So one needs to be very careful and pioglitazone is better avoided. There is more chances of gastrointestinal disturbances if insulin is used with acarbose.11 Combination of insulin with sulfonylureas/secretogogues are better avoided because of the increased risk of hypoglycemia.12,13

However, it is known that glycemic and metabolic control can improve morbidity and mortality in T2DM, the impact of insulin and different regimens on cardiovascular outcomes remains unknown.

**Basal Insulin Regimen**

Adding once a day, long acting basal insulin to the OADs will help achieve not only optimum glycemic control but
also may prove to be easy for early facilitation to insulin in T2DM. Once a day basal insulin regimen is effective and safe in patients with T2DM with HbA1c of 8.5%. For this purpose, NPH insulin (once or twice a day) may be used. Alternatively a long acting analogue insulin—detemir, glargine, or a newer insulin like degludec or toujeo (high strength insulin glargine 300 U/mL) may be used. It has been found useful for symptom relief if tight control is not a major issue. Potentially there is less weight gain and less frequency of hypoglycemia. The starting dose may be 10 units/day or 0.1–0.2 U/kg/day and is titrated by 10–15% or 2–4 units to optimize fasting plasma glucose level.11

The advantages of long acting analogue insulins particularly degludec over NPH insulin are longer half-life, lesser glycemic variability and lower incidence of nocturnal hypoglycemia.14 Due to its flatter curve and lesser day-to-day variability, degludec promises to reduce risk of hypoglycemia as compared to other basal insulins. DEVOTE study demonstrated non-inferiority of degludec over glargine as far as cardiovascular outcome is concerned. At the same time there were significant reductions in the episodes of hypoglycemia particularly nocturnal ones in patients taking degludec.15

**Basal-plus Insulin Regime**

When a rapid acting bolus insulin is added before the main meal of the patient who is already on basal insulin regimen it is known as "basal-plus" strategy.15 This may be an effective step to insulin intensification before implementing the gold standard basal bolus regimen. Careful evaluation of the patient’s life style, eating habits, and self-monitoring of glucose are important for adopting this regimen.16

**Basal Bolus Regimen**

Basal bolus regimen is invaluable in uncontrolled severe hyperglycemia, and in life threatening or organ/limb threatening clinical situations. This regimen comes closest to normal physiological pattern of insulin secretion from a healthy pancreas. In this, long acting basal insulin takes care of the metabolism in the fasting state, whereas the rapid acting insulin prior to meals takes care of postprandial surge of glucose.17 Fifty percent of the total calculated insulin requirement is taken as basal insulin and rest 50% is distributed before major meals as bolus insulins. However, patients require education and counseling regarding self monitoring of blood glucose (SMBG), and carbohydrate insulin ratio and management of hypoglycemia.18

Insulin dose adjustment is done as shown in **Table 2**.

**Premix Insulin Regimen**

Premixed insulins are fixed premixed formulations of short-acting or rapid insulin and intermediate- or long-acting insulin for control of both fasting and postprandial glucose. These formulations may be a combination of short and long acting conventional human insulins or short and long acting insulin analogues. Premix insulin formulations are useful for those patients who have consistent lifestyle and find it difficult to count carbohydrates. They may be started as once or twice daily and intensified to three times a day in some cases. Premixed regimen has less complicated & less demanding glucose monitoring. Initiating with premix insulins offers improved efficacy and safety and offers the advantage of simplicity. Insulin analogues offer more predictable onset of action and lesser incidence of hypoglycemia. In some studies they have shown better glycemic control particularly postprandial glucose.19

**Conclusion**

T2DM is a chronic progressive disease associated with decline in β-cell function and multiple complications. Proper glycemic control is important to slow down or prevent the process. Insulin has shown maximum efficacy in reducing HbA1c and early insulin therapy can help reduce long-term complications. There are different insulin regimens to choose according to

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**TABLE 2 Insulin dose adjustment according to SMBG during insulin therapy**

<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Time of SMBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin</td>
<td>Fasting blood glucose before breakfast</td>
</tr>
<tr>
<td>Pre-breakfast bolus insulin</td>
<td>Blood glucose 2 hours after breakfast or before lunch</td>
</tr>
<tr>
<td>Pre-lunch bolus insulin</td>
<td>Blood glucose 2 hours after lunch or pre-dinner</td>
</tr>
<tr>
<td>Pre-dinner bolus insulin</td>
<td>Post-dinner or bedtime blood glucose</td>
</tr>
</tbody>
</table>

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the individual characteristics and factors of the patient. Basal insulin regimen is simple, effective, and easy as augmentation therapy with OADs. Later intensification may be required. Treatment needs to be individualized based on discussion with the patient and his family members on glucose control, cost, side effects, and QOL (quality of life) while choosing optimum insulins and regimens. Premix insulins have the advantage of simplicity in patients with routine life style and consistent eating pattern. Basal bolus regimen offers optimum flexibility in terms of diet and activity but it requires multiple insulin injections, is more complicated to support and teach and needs knowledge of carbohydrate counting. Problems of hypoglycemia and weight gain need to be kept in mind. So full patient motivation is required with regular monitoring of blood sugar.

References

1. IDF Diabetes Atlas, 9th edition, 2019 and other resources at www.diabetesatlas.org
Abstract

Until recently, the mainstay of blood glucose monitoring was mainly dependent on SMBG and HbA1c; however, both the modalities may not serve as a measure for glycemic variability. Intensified diabetes management requires accurate determination of blood glucose concentrations. Continuous glucose monitoring helps to detect trends and tracking patterns of glucose values, aids in detection of hypo- and hyperglycaemia, and help in minimizing glucose excursions, thus help in acute and long-term therapy adjustments.

Introduction

Blood glucose monitoring has entered a new era. The traditional methods of measuring glycemic control with glycated haemoglobin-HbA1c has been used for years and till date glycemic goals are defined by HbA1c, however HbA1c has many limitations. HbA1c though provides an average of blood glucose over a period of 8 to 12 weeks, it doesn’t provide an estimate of intraday and interday glycemic variations and excursions. Glycemic Excursions i.e hypoglycemia or hyperglycemia have been linked to both microvascular and macrovascular complications of diabetes. Continuous glucose monitoring (CGM) depends upon the measurement of the interstitial glucose levels and track glucose levels in real time.1

Limitations of HbA1c

Elevated HbA1c is associated with increased risk of microvascular and macrovascular complications of Diabetes Control and Complications Trial (DCCT). United Kingdom Prospective Diabetes Study (UKPDS) has emphasized the importance of good glycemic control in improving the health outcomes in patients living with diabetes. A target HbA1c of less than or equal to 7 is recommended by most of the global organizations; however, all the guidelines equivocally recommend that HbA1c goal should be individualized for every person living with diabetes according to age, duration of diabetes, comorbidities, and life expectancy. The HbA1c has several limitations like it only provides an average over 2–3 months and it does not provide any information on hypoglycemic or hyperglycemic events.2 HbA1c measurement may be unreliable in certain clinical settings like anemia, pregnancy, hemoglobinopathies, and iron deficiency. It does not provide data that can facilitate the decision to choose one drug over another. Studies have also reported variable glycation rates in people with different ethnic and racial backgrounds. HbA1c should be measured by a method certified by National Glycohemoglobin Standardization Program (NGSP). However, in spite of all the limitations, HbA1c remains an indispensable marker of glycemic control, a reliable marker for population health and a validated marker linked to diabetes complications.
Continuous Glucose Monitoring

It is important to understand some of the terminology often used for CGM. There are CGM devices, which provide real-time unblinded data (real-time continuous glucose monitoring—rtCGM) with alarms and alerts for hypoglycemia and hyperglycemia to the users. Such CGMS devices are used in most of the published randomized controlled trials. Interstitial glucose, which is measured by the rtCGM correlates well with plasma glucose and provides near real-time data on blood glucose. The glucose data received in real time allows the patient or the caregiver to take a treatment decision and allows for the timely intervention to avert severe hypoglycemic episodes. Some devices have options of sharing the glucose values with family members and friends enabling the timely alert for hypoglycemia.

The other types of devices are the ones which provide data to the patients and their health-care providers retrospectively for the analysis—intermittently viewed CGM (iCGM). The CGM device has to be physically scanned by a health-care provider (Fig. 1).

iCGM is also called flash CGM. There are studies to show that there is an improvement in overall time spent in hypoglycemia with rtCGM when compared to iCGM. Some rtCGMs require calibration, and frequency of calibration is variable based on the type of the device. CGM systems for which self monitoring of blood glucose (SMBG) is required to guide treatment decisions are called adjunctive while the one that does not require SMBG is called non-adjunctive. SMBG alone improves glycemic control and quality of life; however, it cannot predict impending hypoglycemia.

CGM Devices Working

CGM measures interstitial glucose levels with a delay of 5–15 minutes with rapidly changing plasma glucose levels; however, it correlates well with the plasma glucose. CGM devices can measure glucose levels every 5–15 minutes. An electrochemical enzyme sensor is placed subcutaneously by the applicator and glucose readings are transmitted automatically to a receiver, which can be a smartphone, smartwatch, or any other smart device. Some CGM devices use fluorescence based sensors implanted subcutaneously with a transmitter either placed on or worn over the skin for transmitting the receiver. The sensor can record interstitial glucose values for 90 days.

Interpretation of CGM Data

Data from the CGM devices can be downloaded for analysis. The glucose data is displayed in the form of current glucose values as well as in the form of trends and the direction of glucose change. The data is very helpful in titrating the doses and helps in fine tuning the treatment. The ambulatory glucose profile (AGP) represents a standardized glucose reporting format in the form of mean glucose, percent of time in range (70–180 mg/dL), percent of time spent in hypoglycemia (<70 mg/dL) and percent of time spent in hyperglycemia, that is, more than 180 mg/dL.

Variability in glucose levels is reported in the form of standard deviation and percent coefficient of variation. A minimum of 10 days of data is required to accurately predict or estimate the HbA1c levels as calculated from glucose management indicator (GMI). Estimated HbA1c calculated by GMI uses a conversion based formula. The estimate is based on data from clinical trials and modern CGM devices and estimated HbA1c may be the same, low or more than the laboratory HbA1c. CGM devices are also used with insulin pump therapy and are helpful in identifying glycemic patterns and deciding the insulin dose and rate for continuous subcutaneous insulin infusion.

When blood glucose levels rise rapidly the interstitial glucose concentration takes time for equilibration between the venous and interstitial fluid compartments and because of this reason CGM may yield lower glucose readings. The CGM values are less accurate at the extremes of hypoglycemia (<40 mg/dL) and hyperglycemia (>400 mg/dL) with a mean absolute relative difference of less than 11%. It is difficult to compare the variability between different devices due to different sample sizes, study designs, methodologies, etc.; however, the reliabilities of newer CGM devices are improving (Fig. 2).

It has been found that patients on high-dose vitamin C and on paracetamol may show falsely elevated CGM glucose values (in some CGM devices acetaminophen is oxidized by CGM electrodes).

Glycemic Variability

Glycemic variability is an independent risk factor for diabetes complications. It represents the amplitude, frequency, and duration of glycemic excursions. Glycemic variability also has an effect on quality of life and cognitive
Fig. 1: The glucose patterns shown by a real-time continuous glucose monitoring (rtCGM) (above) and Intermittently scanned CGM (iCGM) (below) 
(Source: Centre for Diabetes Care)
Fig. 2: A typical CGM report describes several metrics depicting glucose data
(Source: Centre for Diabetes Care)

<table>
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<tr>
<th>Excursion Summary (mg/dL/day)</th>
<th>Tue 26 Mar</th>
<th>Wed 27 Mar</th>
<th>Thu 28 Mar</th>
<th>Fri 29 Mar</th>
<th>Sat 30 Mar</th>
<th>Sun 31 Mar</th>
<th>Mon 1 Apr</th>
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<tr>
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<tr>
<td># Low Excursions</td>
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<td>2.2</td>
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<th>12 am</th>
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</thead>
<tbody>
<tr>
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<td>112 mg/dL</td>
<td>117 mg/dL</td>
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<td>120 mg/dL</td>
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</tbody>
</table>

(Source: Centre for Diabetes Care)
Fig. 3: Glycemic variability in four different patients (Source: Centre for Diabetes Care)
Fig. 4: Time in range values in a patient
(Source: Centre for Diabetes Care)
functions and is now a well-accepted clinical marker of glycemic control. Availability of CGM has made it easy to assess glycemic variability. CGM data reflects all the three components of variability. Standard Deviation (SD), mean amplitude and, coefficient of variation (CV – SD divided by mean) are used to quantify glycemic variability. Stable glucose levels are defined by a coefficient of variation less than 36% while CV more than 36% defined unstable glucose levels. Clinicians should look at glycemic variability also while interpreting CGM data as a key clinical marker of glycemic control (Fig. 3).

**Time in Range**

As discussed earlier, time spent by an individual in the target glucose range is called Time in Range (TIR). TIR provides valuable information on current glycemic control, which cannot be derived from HbA1c. TIR alone cannot be taken as a marker of good glycemic control; however, it effectively illustrates metrics for clinicians as well as researchers. The future studies must report TIR along with other parameters of glycemic control to better understand the glycemic variations and diabetes-related complications and outcome (Fig. 4).

**CGM in Clinical Practice**

Patients with type 1 diabetes or type 2 diabetes on multiple daily insulin injections are required to frequently check their blood sugar levels as it is necessary for adjusting insulin regimens to optimize glycemic controls. A six- or seven-point SMBG often provides useful information on glucose patterns; however, there are still many limitations to the conventional SMBG. An rtCGM can be of great value in detecting and avoiding potentially dangerous hypoglycemia, in identifying unrecognized hypoglycemia. A CGM glucose rising or falling trend can alert the patient, and the patient can adjust the dose of insulin accordingly. CGM data when coupled with information on food intake, physical activity and insulin dose can help in discovering some glucose patterns, which will otherwise go unnoticed. The information can be used to make necessary changes in diet and insulin. However, use of CGM requires adequate training and education of the patient. Contact dermatitis may be a common side effect of CGM devices.

**CGM Guidelines/Guidance**

The most recent and updated guidance on use of CGM are given by American Diabetes Association (ADA). ADA states that CGM devices are useful tools in adults with both type 1 and type 2 diabetes and should be considered in patients who are not meeting glycemic goals have hypoglycemic unawareness or had severe episodes of hypoglycemia. However, their proper use requires robust diabetes education, training, and support. ADA also recommends the use of CGM in all children and adolescents on insulin injection or insulin pumps to improve glycemic control. In pregnant women with diabetes ADA states that use of rtCGM can improve HbA1c, TIR, and neonatal outcomes. A position statement by EASD and ISPAD have stated that use of CGM devices may be helpful in determining carbohydrate intake before, during, and after exercise as per the trends of the rate of rise and fall in glucose levels.

**Conclusion**

CGM is the future of diabetes monitoring. CGM data provides a lot of information on glycemia, including variability and rate of rise and fall of glucose levels. The data can help in improving glycemic control, reduce complications, and improve quality of life of a person living with diabetes. However, there are challenges like cost, standardization, reliability of data, ever changing technology. Nevertheless CGM finds a place in all the guidelines and recommendations, latest being provided by ADA. The year 2021 marks the centenary year for insulin, but at the same time it gives us an opportunity to realize that “How Diabetes Technology is assuming a greater role in diabetes care.”

**References**


Abstract
Understanding the pathophysiology of type 2 diabetes seems to be never ending, despite a leap of knowledge in the last decade. In addition to the ominous octet, newer pathophysiologic defects and disturbances are described to contribute to the development as well as progression of diabetes. Although β-cell failure and insulin resistance are the critical components in diabetes, brain, fat, and muscle influence both these core defects. Brain, Brown and Brawn—the 3 ‘B’s have a considerable role to play in obesity and type 2 diabetes. Their major function is not limited to improving insulin sensitivity, but also in food intake regulation, glucose homeostasis, and also β-cell preservation. This novel concept would pave way for more research in therapeutic aspect by directly addressing the pathophysiological defects in type 2 diabetes rather than a guideline-based management.

Introduction
Obesity and type 2 diabetes are rampantly increasing in the developed as well as developing world. Weight gain occurs as a result of deregulated balance between calorie intake and calorie output. In order to achieve weight reduction, the focus has always been on the ways and means to increase the calorie expenditure. However, newer understanding on the physiology of calorie intake and its modulation in the management of metabolic dysfunction like obesity and type 2 diabetes has gained a lot of attention. Calorie intake and energy homeostasis revolves around Agouti-Related Peptide (AgRP), Brown Adipose Tissue (BAT) and skeletal muscle (SM) that form a circuit where hormonal and nutrient feedback from the periphery is signaled to the CNS. In this topic, the new and important role of these 3 ‘B’s—Brain, Brown, and Brawn in diabetes will be discussed.

3 ‘B’s and their Role in Glucose Homeostasis
The knowledge and understanding about glucose homeostasis is increasing steeply and steadily. The role of brain especially hypothalamus and the arcuate nucleus (ARC) has been recognized as a key regulator of energy homeostasis, thus supporting the center driven control in regulation of food intake. Nevertheless, the brain integrates metabolic signals from peripheral tissues like liver, pancreas, adipose tissue, gut and skeletal muscle. Adipocytes in the brown fat also utilize glucose by UCP1-mediated thermogenesis as well as independent mechanisms thus contributing to glucose homeostasis. This has been postulated to be one of the reasons behind the increasing prevalence of type 2 diabetes due to global warming. Thus, brain, brown fat, and brawn have a major role in glucose homeostasis and dysregulation of which contribute to obesity and type 2 diabetes.

Role of Brain in Diabetes
The role of brain in glucose homeostasis has been demonstrated by physiologist Claude Bernard in 1854 when he found glycosuria in a rabbit after puncture of the fourth ventricle. Ever since then in the last few decades, tremendous experiments prove the precise role
of brain and glucose sensing neurons in the hypothalamus. Glucose sensing neurons are of two types: Glucose-excited neurons in the Ventromedial Hypothalamus (VMH), Paraventricular Nucleus (PVN) and ARC that are stimulated by rise in extracellular glucose levels; Glucose-inhibited neurons in Lateral Hypothalamus (LH), PVN, and ARC that are activated by fall in glucose concentrations.

**Brain in Feeding Control and Glucose Homeostasis**

Neural circuits including AgRP neurons control appetite as well as glucose homeostasis. As a response to hunger, AgRP neurons induce eating and on the other hand, inhibit insulin-stimulated glucose uptake by SM. This effect of insulin resistance (IR) in the SM occurs due to the expression of muscle related genes in BAT. The effect of AgRP on the BAT and SM is shown in Figure 1. Acute regulation of AgRP plays the major role in feeding control and mice studies have shown that ablation of these neurons have resulted in cessation of hunger. In addition to AgRP, Neuropeptide Y (NPY) an orexigenic peptide co-released by ARC and the neurotransmitter gamma-aminobutyric acid (GABA) also contribute in the food intake regulation. AgRP also plays a crucial role in glucose homeostasis apart from the feeding control. It has been demonstrated that suppression of hepatic glucose output by insulin occurs partially by inhibiting AgRP neurons in mice. IR in obesity is also presumed to be due to obesity associated hypothalamic inflammation and consequently alteration of AgRP neuronal activity.

**Brain Integrates Peripheral Signals**

Brain also puts together peripheral signals to regulate glucose metabolism. Hormonal input signals include insulin through hypothalamic insulin signaling pathway, leptin by leptin mediated regulation of glucose metabolism, long chain fatty acids through hypothalamic lipid sensing and more importantly glucose through glucose sensing. Glucose sensing mechanism in hypothalamus is better understood and is very similar to that in pancreatic β-cell. The sequence of events that occur in glucose-excited neurons following elevated plasma glucose is shown in Figure 2. On the contrary, the mechanism of glucose-inhibited neurons is unclear.

**Brain and Effector Pathways**

Besides the neuronal role and integration of peripheral signals, brain also has effector pathways to ensure glucose...
metabolism. These pathways target organs as mentioned here.

- **Liver**: Insulin receptor in both liver and brain is required for the ability of insulin to effectively suppress hepatic glucose output. This has been proven in rodents where knockout of insulin receptor in brain sparing the liver did not completely produce hepatic glucose production (HGP) suppression.

- **Pancreas**: Autonomic nervous system controls the secretion of glucagon and insulin. Parasympathetic activity stimulates insulin and sympathetic nerves inhibit it while both stimulate glucagon secretion.

- **Skeletal muscle**: Leptin has shown to increase glucose uptake in skeletal muscle by translocation of GLUT4 glucose transporter. It also promotes glucose uptake via AMPK signaling pathway in SM through sympathetic nervous system.

### Role of Brown Fat in Diabetes

White adipose tissue (WAT) stores energy and is known for its association with metabolic disease. The role of BAT, which burns energy for thermogenesis, was unrecognized until few years ago due to underestimation of its existence in adults. Now, we know that the total amount of brown and/or beige fat is at least tenfold higher than previously calculated owing to studies with advanced PET scans. Brown adipocytes regulate energy expenditure by their abundant and large mitochondria. Uncoupling Protein 1 (UCP1) is BAT specific protein located in the inner mitochondrial membrane, which when activated, generates heat instead of ATP and thus mediates BAT thermogenesis.

### Glucose Uptake in BAT

Besides thermogenesis, BAT also plays a significant role in glucose homeostasis. At the cellular level, glucose uptake by BAT occurs through GLUT1 and GLUT4 contributing significantly to systemic glucose disposal. This glucose uptake and utilization is extremely responsive to β-adrenergic stimulation and insulin. Cold induced stimulation of BAT has demonstrated improvement in glucose metabolism in type 2 diabetes. Obesity attenuates GLUT1 translocation and thus glucose utilization in BAT. It has also been shown that 16.5% body weight reduction following chronic calorie restriction increased brown adipocytes in subcutaneous fat by 10%. Furthermore, the fasting plasma glucose and fasting insulin levels improved. The glucose uptake in BAT is also influenced by AgRP as discussed earlier.

### Batokines and Glucose Metabolism

Batokines are the factors secreted exclusively by BAT in contrast to the adipokines secreted by WAT, which includes leptin, adiponectin, etc. These batokines regulate hepatic glucose output, hepatic lipogenesis in addition to glucose uptake and disposal by skeletal muscle. The paracrine effect between BAT and WAT and the mechanisms by which they control systemic metabolic regulation are shown in Figure 3. Thus, brown and beige adipocytes have very good therapeutic potential in modulating glucose uptake, utilization, and glucose metabolism. Hence, several studies are on the way looking at increasing BAT size and function.

### Role of Brawn in Diabetes

Function of skeletal muscle in glucose metabolism has been known for ages. IR has been the hallmark abnormality that is observed in SM. Several mechanisms have been hypothesized for IR including dysregulated GLUT4 translocation, insulin receptor downregulation, defective post-receptor signaling etc. Myokines are protein factors secreted by SM, which exerts its action on multiple tissues. Recently, suppression of adaptive glucose stimulated insulin secretion has also been found.
to be an effect of these myokines on the pancreatic β-cell thus contributing even to the secretory defect of type 2 diabetes. Myostatin is another factor belonging to transforming growth factor-beta/bone morphogenetic protein (TGF-β/BMP) superfamily whose main role is inhibiting skeletal muscle growth. Myostatin inhibits skeletal muscle stem cell proliferation, differentiation and attenuates muscle fiber protein accretion and thereby result in decreased skeletal muscle mass. It also has a role in insulin stimulated glucose uptake as shown in animal studies. Myostatin knockout mice showed improved insulin sensitivity proving the impact of myostatin on liver and adipose tissue beyond SM. Myostatin mRNA levels were found to be increased in those with type 2 diabetes compared to controls. Resistance training has shown to reduce myostatin levels by 20%. This could possibly explain the benefit of inhibiting myostatin expression to achieve better lean body mass, enhanced insulin sensitivity, and improved glucose metabolism thus paving way for a potential beneficial target.

Recent studies prove the additional role of SM in improving β-cell mass and function that could also be regulated through myokines and protein factors. Exercise has shown to enhance β-cell viability to some extent through increased IL-6 release from SM that either act directly on β-cell or indirectly by increasing GLP-1 secretion from L-cells and α-cells. Other factors like Irisin are also released from SM that has been suggested to improve or protect β-cell mass and function. On the contrary, muscle secretome could exert a negative effect on the β-cell mass and function. The myotubes and their secretory factors differ significantly between those with and without type 2 diabetes. Studies have proven that the myotubes in controls retained their ability to protect or augment glucose stimulated insulin secretion compared to those with type 2 diabetes. This β-cell/SM communication and interaction remains to be understood further in type 2 diabetes.

**Future Research**

Despite several failures with BAT related therapies in the past, the future therapeutic targets seem promising. Pharmacological stimulation of BAT with BMP-7, FGF-21, protein regulator PGC-1α, etc. is being tried to produce favorable metabolic benefits. Even more interestingly, stimulation of precursor stem cells to differentiate into BAT is also being attempted. The ultimate challenge of BAT autotransplantation is currently under research. But whether increasing BAT mass be translated into augmented activity of BAT is questionable. Drugs to reduce myostatin activity like myostatin antagonist are in the pipeline.

**Conclusion**

The 3 'B’s—Brain, Brown fat and Brawn play a significant role in food intake regulation, integrating metabolic cues from peripheral tissues, controlling glucose homeostasis, modulating IR, and protecting β-cell mass and function. Recent understanding of these circuits, the effectors and their cross talks, paves way for more research with possible therapeutic targets in metabolic diseases. Exercise, once thought to be an additional simple intervention to improve glucose uptake in SM, has been found to be more beneficial by reducing myostatin expression in SM and even preservation of β-cell mass and function. Novel therapies for diabetes and obesity are quite reassuring in the near future, until then easy modalities like exercise should be diligently practised for the more clearly proven benefits.

**References**

Abstract
Sleep is an essential component of human life. Its disorders are gateway to metabolic syndromes. Sleep disorders and type 2 diabetes mellitus (T2DM) are closely associated and they enhance disease severity of each other and their complications as well. Sleep disturbances along with T2DM accelerate the cardiovascular, neurological, ocular, neuroendocrine, and sexual complications increasing morbidity and mortality significantly. Also sleep disorder is an important reason for inadequate glycemic control and vice versa despite of treatment. Its incidence in T2DM is well documented and its treatment improves quality of life significantly.

Introduction
Sleep is a complex, active, and physiologic event constituting more than 30% of human lifetime. It has its pivotal importance in maintaining metabolic homeostasis, memory consolidation, and in restoration of psychic structure and function. Sleep follows a particular rhythm comprising non-rapid eye movement (NREM) sleep (N1, N2, N3) and rapid eye movement (REM) sleep, derangement of which affects body functions. Association of quantity and quality of sleep with metabolic syndromes has been clearly established. So, deprivation of sleep, which is a part and parcel of modern lifestyle, may be responsible for booming of metabolic syndrome at present era.

Type 2 diabetes mellitus (T2DM), being the most prevalent noncommunicable disease, constitutes a significant health-care burden. United Nations General Assembly in 2006 declared T2DM to be the first noncommunicable disease that threatens the world health to the same magnitude as communicable diseases such as HIV and TB. Sleep disorders and T2DM are two events of a vicious cycle. Patients with T2DM report a higher rate of insomnia, sleep fragmentation, poor sleep quality, excessive day time sleepiness, and excessive use of sleep medications. The reason of the sleep disturbance in T2DM may be due to the disease itself or its complications.

India, being the diabetic capital of the world, there should be awareness among the physicians for the assessment of sleep disorders in T2DM.

Sleep Disorders in T2DM
Comparing with nondiabetics, sleep disorders constitute a higher health-care problem among diabetics. The higher incidence of sleep disorders in T2DM is likely due to painful diabetic neuropathy, sleep breaks due to nocturia, night hypoglycemic, and hyperglycemic episodes. Restless Leg Syndromes (RLS) & Periodic Leg Movement Syndrome (PLMS) were found to be more prevalent in T2DM. There can be associated autonomic neuropathy causing central sleep apnea in other breathing disorders. Depression occupies a significant proportion of health-related problems in diabetes that severely
Diabetes Mellitus affects sleep.\(^6\) Also T2DM itself affects sleep quality by directly affecting neurobehavioral, neurotransmitter, and autonomic functions.\(^7\)

The sleep complaints in T2DM are difficulty in initiating sleep (21.1%), difficulty in maintaining sleep (21.9%), and excessive daytime sleepiness (12.2%).\(^8\) Sleep disorders like obstructive sleep apnea (OSA), insomnia, sleep deprivation, excessive sleepiness, restless leg syndrome (RLS), periodic limb movements (PLMS) are associated with T2DM. Amongst them OSA has a strong association with T2DM.\(^9\)

**Sleep Disorders Leading to T2DM**

Among the sleep disorders, sleep disordered breathing (SDB), sleep deprivation, insomnia, excessive sleepiness, RLS dominantly affect glucose metabolism. A recent meta-analysis demonstrated that sleep disturbance is a significant risk factor for T2DM.\(^9\) Difficulty in initiating sleep increased the risk of T2DM by 55%, while difficulty in maintaining sleep increased the risk by 74%. Likewise, the risk of development of T2DM in insufficient sleep (<6 hours) or excessive sleep (>9 hours) is comparably similar with the risk of T2DM in physical inactivity. This shows the importance of routine assessment of sleep disorder in T2DM.

The probable mechanisms of glycemic variability due to sleep disorders are summarized in the **Flowchart 1**.

**Sleep Disorders and Neuroendocrine Control**

REM sleep deprivation is common in OSA patients. Fragmented sleep and sleep deprivation decrease the neuroendocrine regulation over appetite. So, it leads to overfeeding causing hyperglycemia. The reason of overfeeding is thought to be associated with OREXIN hyperactivity in sleep deprived patient. Increased level of GHRELIN (hunger promoting hormone) and decreased level of leptin (satiety maintaining hormone) in the circulation of patients with sleep disorders were also found, which again supports the neuroendocrine theory.

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*Flowchart 1: Probable mechanisms of sleep disorders leading to development of type 2 DM*
Sleep Deprivation Leading to Insulin Resistance

The presence of insulin resistance was demonstrated in sleep deprived patients. Studies depicted that there is a clear association between sleep apnea and insulin resistance. SDB and OSA are associated with cyclical hypoxia, which increases sympathetic and corticotropic effect. It increases level of catecholamines and cortisol in circulation causing “spill-over effect.” It is thought to be the cause of increased visceral adiposity and insulin resistance in these patients.

Sympathetic Hyperactivity in Sleep Disorder

Repeated episodes of apnea and hypopnea during sleep in patients with OSA cause hypoxia, which increases sympathetic activity. Increased level of catecholamines itself cause dysregulation of glycemic status. So, if not associated with T2DM, these patients present with fasting hyperglycemia with normal postprandial oral glucose tolerance test (OGTT). So, only fasting hyperglycemia should raise a suspicion of sleep disorder.

Diabetes and Sleep Disordered Breathing

Prevalence

SDB is a spectrum of disorders consisting snoring, upper airway resistance syndrome and sleep apnea. Sleep apnea can be obstructive, central, or mixed. Higher incidence of SDB is clearly evident in T2DM and OSA is most common amongst them. The prevalence of SDB among T2DM can be as high as 58% and of OSA is 23%. In Look AHEAD TRIAL (Action for Health In Diabetes), amongst the obese participants the prevalence of SDB reached up to 80%. Though OSA is most common SDB among T2DM, but central type apnea are also reported, when associated with autonomic neuropathy.

Clinical Features

OSA is characterized by collapse of the upper airway leading to deficient airflow despite of persistent respiratory effort. Though it usually occurs among obese, but nonobese, lean diabetics are also affected. Among the lean-diabetics anatomical factors of face and neck that promotes OSA include macroglossia, short neck, retracted chin or maxilla, neck circumference of more than 43 cm. So lean diabetics are to be screened for sleep disorders, as in India major proportion of diabetic patients are of low or normal body weight. Two prominent symptoms of OSA are habitual snoring and excessive day time sleepiness. Other symptoms are episodes of choking apnea, restlessness, diaphoresis, frequent change of posture during sleep, and difficulty in sleeping supine. Poor concentration, morning headache, mood swings, and irritability are commonly associated.

Complications

OSA independently increases the risk of developing insulin resistance, hypertension (HTN), and cardiovascular disease (CVD). Its causation can be defined by increased sympathetic activity, increased corticotropic action, altered lipid metabolism, hypoxia, oxidative stress, and systemic inflammation. Also T2DM has a clear association with CVD.

Hypothyroidism may be associated with OSA. Day time sleepiness and lethargy in obese patients with OSA can be confused with hypothyroid symptoms. So prescribing high doses of thyroxine without treating OSA can lead to higher mortality in CVD during sleep due to cardiac arrhythmia and cyclical hypoxemia.

Sexual dysfunction is a known consequence of OSA. In REM sleep, there occurs nocturnal penile and clitoral tumescence. So increased blood flow to these tissues possibly prevent excessive collagen formation maintaining their erectile function. So, REM sleep deprivation in OSA can be a possible explanation for it. Likewise, erectile dysfunction is a known complication of T2DM.

Cyclical hypoxemia during sleep in OSA has its deleterious effects on retina also. Sleep disorders in T2DM has been reported to play an etiological role in the development as well as progression of diabetic retinopathy. Also there are repeated association of OSA with several eye disorders that is optic neuropathy, anterior ischemic optic neuropathy (AION), floppy eyelid syndrome, glaucoma, etc. So, early treatment of OSA/SDB in T2DM may have a good retinal outcome.

Having above complications in common OSA/SDB can additively augment diabetic hazards. It can also be a cause of ineffective treatment of T2DM. Treatment of OSA with Continuous Positive Airway Pressure (CPAP) might correct the metabolic complications, but its effect over glycemic control is some-how mixed. Treatment of OSA/SDB is of prime importance as it significantly improves quality of life and blood pressure control.
Diagnosis and Management of Sleep Disorders

American Diabetes Association 2017 guideline recommends assessment of sleep pattern, sleep quality, duration, as part of comprehensive medical evaluation in persons with T2DM. As reasons of sleep disruption in T2DM are multifactorial, so a detailed history and clinical evaluation is the primary tool toward diagnosis. Frequency of hypoglycemic and hyperglycemic episodes, frequency of nocturia, and associated causes are to be looked after. Proper neurological evaluation for peripheral neuropathy or associated autonomic neuropathy should be done. Association of depression should be given importance as its treatment is beneficial and diagnosis is easily overlooked. Keeping a sleep diary of past few weeks should be encouraged. However, when it’s suspected for SDB/OSA, an overnight polysomnography should be done. Newer and more feasible technique like ACTIGRAPHY is also now widely available for detecting sleep disorders. Appropriate treatment of the sleep disorder requires finding out its cause and treating the same, some of which are enlisted in Table 1. A proper sleep discipline, sleep hygiene, sleep restrictions along with cognitive behavioural therapies, and relaxation therapies are required for primary insomnia and other refractory sleep disorders.

Recent Advances in Management of OSA

Looking into the progression of metabolic syndromes in untreated sleep disorders, there has been lots of studies for the treatment aspect, as well as the compliance of the patients toward it. As OSA is the most common SDB, there have been some new therapies specifically looking into the inconvenience of CPAP/BiPAP. In mild cases along with weight loss, positional therapy and oral appliances are advised. PROVENT therapy (Fig. 1) based

![Fig. 1: PROVENT therapy](image)

### Table 1: Associated comorbidities for poor sleep in persons with diabetes and possible measures rectify them

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Measures to rectify</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fluctuation in blood glucose</td>
<td>• Optimum glycemic control avoiding hypoglycemia</td>
</tr>
<tr>
<td>• Restless legs syndrome &amp; Periodic leg movement syndrome</td>
<td>• Identifying and correcting iron deficiency, thyroid disease</td>
</tr>
<tr>
<td></td>
<td>• Rule out RLS mimics</td>
</tr>
<tr>
<td></td>
<td>• Dopamine agonists, dopamine precursors</td>
</tr>
<tr>
<td></td>
<td>• Antiepileptics (gabapentin, pregabalin, carbamazepine)</td>
</tr>
<tr>
<td></td>
<td>• Opiates in severe cases (oxycodeine, methadone)</td>
</tr>
<tr>
<td></td>
<td>• Analgesics</td>
</tr>
<tr>
<td>• Peripheral neuropathies</td>
<td>• Antidepressants (such as TCAs, SSRIs)</td>
</tr>
<tr>
<td>• Obstructive sleep apnea</td>
<td>• GABAergic agents (gabapentin, pregabalin)</td>
</tr>
<tr>
<td>• Depression</td>
<td>• Weight loss, positional therapy</td>
</tr>
<tr>
<td></td>
<td>• Oral appliances</td>
</tr>
<tr>
<td></td>
<td>• Identification and treatment of upper airway obstruction</td>
</tr>
<tr>
<td></td>
<td>• Nasal continuous positive airway pressure</td>
</tr>
<tr>
<td></td>
<td>• Modafinil in res-OSA*21</td>
</tr>
<tr>
<td></td>
<td>• Antidepressants and behavioral therapy</td>
</tr>
</tbody>
</table>

*Residual sleepiness in OSA despite of using CPAP; GABA, gamma-aminobutyric acid; SSRIs, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants
Upper airway stimulation therapy on nasal expiratory positive airway pressure (EPAP) is a new FDA approved therapy for mild to moderate OSA. Mini-CPAP consisting of battery powered micro-blowers, not requiring any hoses and masks, seems promising but still awaits FDA approval. Upper airway stimulation (UAS) therapy (Fig. 2) is an emerging option for refractory cases of moderate-severe OSA. Modafinil is found useful in OSA patients with residual sleepiness despite of using CPAP.21

**Conclusion**

Sleep disorders and T2DM are two events of a vicious cycle. So, ignoring sleep disorders not only leads to improper treatment of T2DM, but also helps in progression of its complications. OSA is no more considered to be a sleep disorder rather it’s a gateway to metabolic syndrome. So, a routine assessment of sleep in T2DM should be done with a higher clinical suspicion in order to diagnose sleep disorders. Proper treatments of sleep disorder and its prevention by maintaining sleep hygiene should be enforced.

**References**

Abstract

Gestational diabetes mellitus (GDM) is a serious complication of pregnancy, in which women without prior overt diabetes develop chronic hyperglycemia during gestation. Risk factors for GDM include overweight and obesity, advanced maternal age, and a family history of any form of diabetes. GDM can have an impact, not only on normal fetal development, and lead to birth complications, but also raises the risk of development of type 2 diabetes later in life. The rising prevalence of GDM globally and in India, in recent years, has placed the spotlight on better management strategies. Glycemic control has traditionally been based on a combination of diet and insulin therapy. More recent data has focused on the role of oral hypoglycemic agents, specifically metformin and glyburide.

Introduction

Gestational diabetes mellitus (GDM), is defined as “the type of glucose intolerance that develops in the second and third trimester of pregnancy, resulting in hyperglycemia of variable severity.”1 It is a severe and neglected threat to maternal and child health, with women experiencing multiple adverse pregnancy outcomes.2 Approximately half of women with a history of GDM develop type 2 diabetes mellitus (T2DM) within 5–10 years after delivery2 and the offspring are at increased risk for the development of obesity and T2DM early in life.3

There has been a steady rise in the prevalence of GDM. According to the 2019 data of the International Diabetes Federation (IDF), an estimated 223 million women between 20 and 79 years of age are living with diabetes. Twenty million or 16% of live births had some form of hyperglycemia in pregnancy and an estimated 84% were due to gestational diabetes.2 A vast majority of cases of hyperglycemia in pregnancy occurs in low- and middle-income countries.2

It is important for women with diabetes in pregnancy or GDM to carefully control and monitor their blood glucose levels to reduce the risk of adverse pregnancy outcomes with the support of their health-care provider.

Etiological Factors for GDM

The rise in number of women with GDM has been attributed to increasing obesity prevalence and advancing maternal age.1 Several risk factors, attributed to the development of GDM, are listed in Table 1.1

Pathophysiology of GDM

Normal physiology in pregnancy raises the risk of insulin resistance due to physiological increases in homeostatic hormones including cortisol, growth hormone, human placental lactogen, progesterone, and prolactin.5 While there is a compensatory increase in the release of insulin of up to 250% in normal women,5 in beta cells in women with GDM, are unable to compensate with sufficient insulin secretion due to pre-existing beta cell failure.4
When insulin secretion does not increase sufficiently to counterbalance the insulin-resistant state of the later trimesters, maternal glucose intolerance leading to GDM occurs. β-cell secretory impairment is an important aspect of GDM, which is probably a pre-existing one, and thereby confers a high risk of overt diabetes post-pregnancy. Insulin mediated suppression of lipolysis is reduced contributing to increases in free fatty acids and severe insulin resistance in late gestation. There is a reduction in glucose transporter type 4 (GLUT4) translocation and decreased insulin uptake. Adiponectin levels decline and excess lipolysis and inflammation precipitates severe insulin resistance in liver, muscle, and adipose tissue.3

Management of GDM

The primary goal of therapy is aimed at lowering the risk of adverse perinatal outcomes, by achieving euglycemia. Plasma glucose threshold goals for fasting and postprandial plasma glucose have been provided in the guidelines of the American Congress of Obstetricians and Gynecologists and the American Diabetes Association. Consensus evidence-based guidelines for management of GDM in India are also available.6

Initial treatment of GDM includes medical nutrition therapy and moderate physical activity. However, half of the women may not achieve established glucose goals with diet modifications alone and will require pharmacologic therapy.5 Traditionally insulin has been the mainstay of therapy for GDM as it is not known to cross the placenta. However, use of insulin in GDM comes with many challenges, the need for patient education and poor compliance, being the most common.6 Insulin is also required to be administered as multiple-daily injections, with up to 70% risk of hypoglycemia in women, sometime during their pregnancy.5

Oral Antidiabetic Agents

Oral antidiabetic agents are a suitable alternative due to the lower risk of hypoglycemia, and the ease of taking the medications, without need for self-injections. In addition, the pathophysiology of GDM also indicates the use of oral antidiabetic agents. The use of oral agents in pregnancy, however, involves the balancing of risk of hyperglycemia with potential medication side effects, transplacental passage and teratogenicity, and the long-term effects of the medication on the child.5

Among the oral antidiabetic agents, the biguanide, metformin, and the sulfonylurea, glyburide are the two well-studied agents in pregnancy. There is significant data on pharmacokinetics in pregnancy, placental transfer, and maternal and neonatal outcomes when compared to insulin use in women with GDM.8

Metformin

Metformin is a biguanide, “insulin sensitizer” and its mechanism of action in controlling hyperglycemia is still a topic of research. Metformin is known to inhibit gluconeogenesis, suppress hepatic glucose output, and increase intestinal glucose absorption. It is also known to stimulate glucose uptake in the liver and peripheral tissues.5 The most widely accepted model of the anti-hyperglycemic action of metformin is the suppression of hepatic gluconeogenesis as a result of mitochondrial inhibition, via 5 AMP-activated protein kinase (AMPK). AMPK is also believed to play a key role in long-term effects of metformin by improving lipid metabolism and mitochondrial function in the liver.9

Metformin-Pharmacokinetics

Metformin is absorbed from the duodenum and jejunum within about 6 hours of ingestion. It has an absolute oral bioavailability of 40–60%. The drug is rapidly distributed following absorption and does not bind to plasma protein. No metabolites or conjugates of metformin have been identified. The parent drug is excreted unchanged through
the kidneys and in bile, with a half-life of about 6 hours. About 30% of the drug is excreted directly through the feces.³

**Placental Transfer of Metformin**
Metformin freely and readily crosses the placenta. Metformin is rapidly transferred across the placenta with a simultaneous decline in maternal metformin levels and increases in fetal levels in pregnant women.² Placental concentrations of metformin can reach at least 50% of circulating maternal levels.³ Metformin, however, does not cross through cell membranes by passive diffusion and metformin transfer was found to be dose dependent.⁸

**Effectiveness of Metformin in GDM**
Metformin has been used for decades in early pregnancy in women with polycystic ovarian syndrome (PCOS). Prepregnancy metformin helps in restoring normal ovulation and improving conception. Continuing to take it through the first trimester lowers the risk of spontaneous abortion.⁵

The Metformin in Gestational Diabetes Trial (MiG) by Rowan et al., published in the New England Journal of Medicine in 2008, was the first randomized trial comparing use of metformin and insulin for treatment of GDM.¹⁰ A total of 751 women with GDM at 20–33 weeks of gestation were initiated treatment with metformin (with supplemental insulin if required) or insulin. Of the 363 women assigned to metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin. Metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin. Metformin was preferred over insulin, with more women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76.6% vs. 27.2%, P<0.001).¹⁰

Subsequent studies have found metformin to be an acceptable alternative to insulin, to effectively achieve glycemic control in normal or slightly overweight women or those with mildly elevated fasting glucose values.

In the 2-year follow-up of offspring in the MiG-TOFU study group, no adverse outcomes above baseline risk were seen in infants born of women randomized to metformin or insulin during pregnancy. No differences were observed in central fat measures, total fat mass or percentage body fat for the infants in the metformin group. However, compared with the insulin group, the metformin group had larger upper arm circumferences, bigger biceps and subscapular skin folds, and a more favorable pattern of fat distribution suggesting a potential protective effect against later development of insulin resistance in the offspring.¹¹ In 2018, the MiG-TOFU study group published the longest offspring follow-up study for metformin exposure at 7 and 9 years at two individual study sites. Metformin or insulin for GDM was associated with similar offspring total and abdominal body fat percent and metabolic measures at 7–9 years.¹²

**Safety in Pregnancy and Lactation**
Since metformin does not stimulate secretion of insulin, it does not cause maternal hypoglycemic episodes as seen with insulin. No congenital anomalies, or teratogenic effects have been reported in the over two decades of its use in the preconception and early pregnancy period.¹³ Gastrointestinal side effects, including diarrhea, flatulence, nausea, and vomiting, affect 5–15% of women. The potential side effect of lactic acidosis, can be avoided by gradually increasing dose. This side effect has not been reported in neonates. Metformin is classified as FDA Pregnancy Category B.⁵

It is safe to breastfeed if metformin is to be continued after delivery, as levels of metformin in maternal milk are low. There are no reports of developmental or growth problems in infants of mothers using metformin while breastfeeding.⁵

**Metformin Dose**
Metformin is available in 500, 850, and 1,000 mg regular and extended-release tablets. The currently recommended starting dose is 500–800 mg/day, with a maximum daily dose of 2,500 mg/day, in divided dosing.⁵

**Glyburide**
Glyburide (also known as glibenclamide) is a second-generation sulfonyurea, which increases insulin secretion and sensitivity in peripheral tissues and reduces hepatic insulin clearance by binding to pancreatic beta-cell ATP-calcium channel receptors.⁷

**Glyburide-Pharmacokinetics**
Glyburide is well-absorbed with oral administration and is metabolized by the liver. It reaches peak concentration
in approximately 3 hours and has a half-life of 8 hours. Glyburide decreases circulating glucose by approximately 20% and is most effective in patients who are normal weight or slightly overweight.\textsuperscript{14}

**Placental Transfer**

Hebert et al. reported that there is significant placental transfer of glyburide with fetal cord blood levels that were 70% of maternal serum levels.\textsuperscript{15}

**Effectiveness of Glyburide in GDM**

Glyburide was the first oral antidiabetic agent to be tested in GDM. Effectiveness of Glyburide in GDM versus standard-of-care insulin was tested and published by Langer et al. in the New England Journal of Medicine, in 2000.\textsuperscript{16} A total of 404 women with singleton pregnancies and gestational diabetes that required treatment were randomly assigned between 11 and 33 weeks of gestation to receive glyburide or insulin according to an intensified treatment protocol. Glyburide was equivalent to insulin in achieving glycemic control. Important neonatal outcomes were similar between glyburide and insulin-treated women included large for gestational age, macrosomia more than 4,000 g, hypoglycemia, neonatal intensive care unit admission, and fetal anomalies.\textsuperscript{16} Subsequent meta-analysis of 9 studies, including 745 glyburide-treated and 637 insulin-treated showed similar results.\textsuperscript{15}

It has, however, been seen that 4–21% of women with GDM may not achieve adequate glycemic control with glyburide. The characteristics of women who failed glyburide therapy included older women, multiparous, and more likely to be diagnosed at less than 25 weeks of pregnancy, with higher fasting glucose values. It has been suggested that such women may represent a group with undiagnosed T2DM and should probably not to be treated with glyburide as primary therapy.\textsuperscript{16}

**Safety in Pregnancy and Lactation**

Glyburide is known to cross the placenta, and umbilical cord concentration may reach as much as 70% of maternal

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Comparison of glyburide and metformin in GDM</th>
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<tbody>
<tr>
<td><strong>Glyburide</strong></td>
<td><strong>Metformin</strong></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Increase insulin secretion, reduce hepatic insulin clearance</td>
</tr>
<tr>
<td>Peak concentration</td>
<td>3 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>8 h</td>
</tr>
<tr>
<td>Action and hypoglycemia</td>
<td>Action can directly cause maternal hypoglycemia</td>
</tr>
<tr>
<td>Proof of efficacy</td>
<td>Glyburide=insulin in achieving glycemic control Failure rate: 4–21%</td>
</tr>
<tr>
<td>Maternal safety-hypoglycemia</td>
<td>Symptomatic hypoglycemia in 1–5%</td>
</tr>
<tr>
<td>Maternal safety-other side effects</td>
<td>GI, dermatologic side effects, rare elevation in liver function tests</td>
</tr>
<tr>
<td>Fetal safety</td>
<td>Placental transfer demonstrated No known congenital anomalies</td>
</tr>
<tr>
<td>Lactation safety</td>
<td>Levels in breast milk likely negligible Do not recommend breastfeeding avoidance or discarding breastmilk if glyburide indicated postpartum</td>
</tr>
</tbody>
</table>
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Conclusion

Glyburide and metformin have emerged as potential oral antidiabetic agents for GDM by virtue of their efficacy and safety, over insulin and can benefit women who prefer oral medication over multiple daily insulin injections. With increasing prevalence of GDM, oral antidiabetic agents may be treatments to be considered. However, there is a paucity of long-term offspring safety data, which could be the reason why most professional societies still recommend insulin as the sole first-line option for treatment of GDM.

References


Dosing

The currently recommend starting dose of glyburide is 2.5 or 5 mg daily or twice daily, with a maximum daily dose of 20 mg, in twice daily dosing.

Glyburide or Metformin?

Glyburide and metformin have been compared in GDM. In one study by Moore and colleagues’ women randomized to metformin were more than twice as likely to fail oral hypoglycemic therapy, compared with glyburide, while another study reported similar failure rates for metformin and glyburide. Table 2 details the differences between metformin and glyburide in GDM.

<table>
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<tbody>
<tr>
<td><strong>Metformin</strong></td>
<td><strong>Glyburide</strong></td>
</tr>
<tr>
<td>Lower incidence of hypoglycemia</td>
<td>Higher incidence of hypoglycemia</td>
</tr>
<tr>
<td>Less frequent use of insulin</td>
<td>More frequent use of insulin</td>
</tr>
<tr>
<td>Smaller body weight loss</td>
<td>Greater body weight loss</td>
</tr>
<tr>
<td>Fewer adverse effects</td>
<td>More frequent adverse effects</td>
</tr>
<tr>
<td>Higher pregnancy success rates</td>
<td>Lower pregnancy success rates</td>
</tr>
</tbody>
</table>

No congenital anomalies have been found with the use of glyburide in pregnancy. It has been placed in FDA Pregnancy Category C. In a comparative study, women using insulin experienced 4.1 asymptomatic hypoglycemic episodes whereas those taking glyburide experienced 2.1. Further, insulin-related episodes were more frequently severe at less than 40 mg/dL and predominantly nocturnal, unlike the glyburide episodes which occurred equally between day and night.

Gastrointestinal symptoms including mild nausea, heartburn, or feeling full, dermatologic effects including mild itching or skin rash, and elevated liver function tests were common, but more manageable.

If glyburide is initiated to manage GDM, it should be discontinued after delivery. In case there is a need to continue, levels of glyburides in maternal breast milk are negligible and undetectable in infant blood with a 5-mg daily dose.

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Conclusions

Glyburide and metformin have emerged as potential oral antidiabetic agents for GDM by virtue of their efficacy and safety, over insulin and can benefit women who prefer oral medication over multiple daily insulin injections. With increasing prevalence of GDM, oral antidiabetic agents may be treatments to be considered. However, there is a paucity of long-term offspring safety data, which could be the reason why most professional societies still recommend insulin as the sole first-line option for treatment of GDM.
Abstract
Diabetes mellitus (DM) is one of the most prevalent non-communicable diseases that lead to a significant morbidity and mortality. Worldwide, the pandemic of DM was 9.3% of global population in 2019 and projected to increase to more than 10% by 2030. In India, the estimated number of people living with diabetes was 77 million in 2019 and will reach to 101 and 134 million by 2030 and 2045, respectively. The prevalence of diabetes in children and adolescents is increasing worldwide, with profound implications on the long-term health of individuals. Young-onset type 2 diabetes also affects more individuals of working age, accentuating the adverse societal effects of the disease. The diagnosis and management of diabetes in youth presents several unique challenges. Although type 1 diabetes is more common among children and adolescents, the incidence of type 2 diabetes in youth is also on the rise, particularly among certain ethnic groups. The management of diabetes in children and adolescents is challenging in some cases due to age-specific issues and the more aggressive nature of the disease.

Introduction
Type 2 diabetes mellitus (T2DM) is a global epidemic and its prevalence is continuously increasing. Initially it was considered as a disease of elderly population, but in current scenario it is equally seen in young population. Early appearance of this disease is associated with long-term major complications like microvascular and macrovascular complications. T2DM is most common type of diabetes and it is an estimation that by 2025, ~7.7% world’s population will be affected with T2DM.¹ Under 40 years of age its prevalence is now increasing and early exposure will be having more complications in later part of life.² The development of T2DM at early age leads to serious health problem due to prolonged exposure to adverse risk factors like hyperglycemia and other components of the metabolic syndrome. And that is why it has become a major public health concern. Major concerns of T2DM in young adults are firstly it will be very aggressive as it develops at very young age and leads to various complications; secondly there is not long-term outcome studies are available to evaluate T2DM impact on young adults and lastly it certainly affects socioeconomic health of society.³ This review article aims to explore the magnitude of the evolving problem and challenges physicians face in managing T2DM in younger adults.

Global Scenario of Diabetes Mellitus
Globally, 463 million population is living with diabetes mellitus, wherein china has the highest number of DM population, followed by India, which has 77 million diabetic population. From the current DM population, it is anticipated that by 2045, with the growth of 51%, globally total DM population will be 629 million; wherein currently 75% are from working-age between 30–55 years.¹⁰ It is estimation that currently 5.8–6.4 years of life are lost in diabetes at the age of 50 years,¹ which can
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lead to adverse social and economic complications. For instance reported incidence varies from 0–330/100,000 person years depending on the age, gender, geography, and ethnicity of the study population and geographical region (Table 1). Globally many prevalence studies on T2DM are available but focusing on young T2DM patients is still waiting.

**Challenges in Diagnosis of Diabetes in Young Patients**

Insulin resistance is a pathological hallmark of T2DM and it is commonly associated with other conditions like obesity, polycystic ovarian disease (PCOD), and non alcoholic fatty liver disease (NALFD). These all metabolic conditions are overlapping with each other. In young people with T2DM it is frequently associated with conditions like obesity and other cardiovascular risk factors such as hypertension, dyslipidemia, and nephropathy, which appear quite prevalent at the time of diagnosis and probably estimate abnormal glucose metabolism. Many times, patients will not have any symptoms of T2DM and it is detected incidentally, while in some case it may present with overt symptoms of T2DM like extreme weight loss, urinary tract infections, frequent urination, thirst or hunger, etc. Differential diagnosis between T1DM and T2DM is very challenging as previous one is commonly associated with young age group of patients. And incorrect diagnosis of both diseases will cause adverse complications in patients. Incorrectly diagnosing T2DM in a young patient with T1DM could be life threatening if the situation is managed with oral diabetes medication rather than insulin. Likewise, misdiagnosing T1DM as T2DM can result in unnecessary life-long treatment with insulin, when alternative glucose lowering therapies may be more appropriate. Through biochemical test it can be differentiated, where in persistently high serum insulin and C peptide concentration is characteristic of T2DM and would be unusual in T1DM. However, at initial phase of diagnosis, these biochemical features are overlapping and may lead to misdiagnosis as well (Table 2).

**Challenges in Management of Diabetes in Youngs**

In T2DM, long-term evaluation and treatment is very challenging among many patients. Especially in young adults, to achieve target HbA1c and reduce blood sugar is difficult compared to adults. Even in 5 years of follow-up with therapy, young population find difficulties to achieve target with lesser complications. It is concerning to note that the proportion of young T2DM patients with suboptimal glycemic control was as high as 57% in the primary care setting in the UK.

**Proper Education**

Appropriate education and life style modification certainly delay new onset of DM and also reduces severity of complications. But young T2DM patients have more depression and T2DM related stress, and they are failed to follow on regular guideline recommendations.

**Glucose Lowering Therapy**

In the management of T2DM along with glycemic control and HbA1c level <6.5% is an utmost important goal but along with that appropriate lifestyle modification, weight control is also required to get desired medication.

### Table 1

Prevalence estimates of Type 2 diabetes in adolescents and youth from the USA and UK studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of T2DM</th>
<th>Age group (years)</th>
<th>Year assessed</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>The SEARCH study (USA)</td>
<td>0.34/1000</td>
<td>&lt;19</td>
<td>2001</td>
<td>Cross-sectional active surveillance and case ascertainment</td>
</tr>
<tr>
<td>The SEARCH study (USA)</td>
<td>0.46/1000</td>
<td>&lt;19</td>
<td>2009</td>
<td>As above</td>
</tr>
<tr>
<td>Ehtisham (UK)</td>
<td>0.21/100,000</td>
<td>&lt;16</td>
<td>2000</td>
<td>Cross-sectional questionnaire survey of pediatric diabetes centers</td>
</tr>
<tr>
<td>Hsia (UK)</td>
<td>1.9/100,000</td>
<td>&lt;18</td>
<td>2005</td>
<td>Retrospective cohort study: analysis of antidiabetic prescription for children from GP data</td>
</tr>
<tr>
<td>Royal College of Pediatrics and Child Health (UK)</td>
<td>3/100,000</td>
<td>&lt;18</td>
<td>2009</td>
<td>Cross-sectional survey by secondary care clinicians in England</td>
</tr>
</tbody>
</table>

T2DM: Type 2 diabetes mellitus
effect. Physical exercise like aerobic activity, alone or in combination with diet, can reduce weight, body lipid level, elevated blood pressure and also helps to maintain healthy mental status as well. For pharmacological management approach, metformin is the most appropriate starting point for any age group with T2DM. Results of the TODAY study suggest that monotherapy with metformin was associated with durable glycemic control in children and adolescents. Apart from this in young age group patients, currently, many newer oral anti-diabetic agents are recommended which not only control sugar level but also reduce cardiovascular mortality as well like sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1), dipeptidyl peptidase-4 (DPP-4) inhibitors. Metformin is always considered as first-line therapy until any contraindications, but after metformin or along with metformin if the patient has any marked CV risk factor then SGLT2 inhibitors, GLP-1 analogues are preferred agents. Treatment with these agents may increase the cost of therapy but proper counselling of patient may improve adherence to this therapy. In alternative cases, along with metformin other agents like sulfonylureas, meglitinides, thiazolidinediones, α-Glucosidase inhibitors, DPP-4 inhibitors are preferred options. In case of uncontrolled sugar level after dual oral antidiabetic drugs, or HbA1c level is more than 9% or T1DM; insulin injections and its analogues are preferred option to manage DM. Bariatric surgery has emerged as a viable treatment option in young individuals with type 2 diabetes and evidence has shown that it is safe and effective in obese adolescents.

**Conclusion**

Type 2 DM is going to be epidemic in younger adults and they are on high risk for development of diabetes-related complications such as nephropathy and CVD at early in the disease process with high mortality at a relatively young age. However, there are many gaps and lack of evidence for intervention to either optimize glycemic control or to address CV risk factors also results in non-standardized treatment and inevitable variations in standards of care in a young population. There is a need for sufficient scientific data and focused guideline-based approach for management of DM in young population for having a balanced socioeconomic condition in future.
References

Abstract

Diabetes is increasing all over the world, so are its complications. There is much evidence that postprandial hyperglycemia is a major contributing factor for atherosclerosis development, causing cardiovascular morbidity and mortality in diabetic patients. There are rapid and high blood glucose levels after meals in diabetic patients known as hyperglycemic spikes responsible for cardiovascular complications. Hyperglycemia generates free radicals, which lead to atherosclerosis formation by multiple mechanisms. Early recognition and treatment of postprandial hyperglycemia by pharmacological and non-pharmacological means can prevent cardiovascular complications.

Introduction

Diabetes mellitus (DM) is a metabolic disorder due to defects in insulin secretion, insulin action, or both, thereby causing hyperglycemia. Chronic hyperglycemia is associated with long-term damage and dysfunction of different organs such as the eyes, kidney, nerves, heart, and blood vessels. Many studies have shown that increased plasma glucose in the body is an independent risk factor for morbidity and mortality in diabetic patients due to cardiovascular complications. Isolated postprandial hyperglycemia (PPHG) blood sugar >140 mg/dL (7.8 mmol/L), with normal fasting sugar <110 mg/dL and normal HbA1c (<6.1) is associated with a twofold increase in cardiovascular deaths. Management of PPHG becomes necessary as increased fasting glucose level alone is not a risk factor to cause cardiovascular complications. This is a well-established fact that controlling blood sugar levels (HbA1c <7.0%) can reduce the progression of diabetic complications. The risk of cardiovascular disease can be prevented by proper control of postprandial glucose. Management of PPHG is more difficult than FPG because there are no standard guidelines and treatment practices among diabetologists and physicians. However, treatment modalities are now available to treat PPHG, such as AGI, Glinides, Short-acting SU, Insulin analogs, DPP4 inhibitors, and GLP-1 derivatives.

Diagnosis

ADA in 2013 defined PPHG as a 2-h plasma glucose level of more than 200 mg/dL (11.1 mmol/L) for diabetes and 140–199 mg/dL for IGT by oral glucose tolerance test. The glucose load is 75 gm glucose dissolved in water as per the recommendation of WHO. IDF defines PPHG as a plasma glucose concentration of 140 mg (7.8 mmol/L) or more after 1–2 hours of food ingestion.

Current guidelines recommend self-monitoring of blood glucose (SMBG) for assessing plasma glucose levels in diabetic patients. The timing and frequency are individualized according to the treatment regime and glycemic control. Some emerging technologies for evaluating postprandial glucose levels are CGM and plasma 1.5-anhydroglucitol (1.5AG). CGM measures plasma glucose every 1–10 minutes by a sensor; this is
transmitted to a storage device. 1.5AG is a natural dietary polyol that is the marker for postmeal hyperglycemia, but it is not readily available at this time.\textsuperscript{8,9,10} HbA1c values can give many indications of PPG. Monnier et al. in 2003 demonstrated that contribution of PPG to glycemic load varies with the degree of glycemic control. In poorly controlled (HbA1c >10.2%), it was only 30% of the 24 hours. AUC, in better-controlled patients (HbA1c <7.3–8%), the contribution of PPG was 70–50%\textsuperscript{11} (Fig. 1).

Flash glucose monitoring is a new noninvasive glucose monitoring launched by Abbott, using a sensor applied on the back of the arm, which measure and stores glucose values for 14 days. Compared to SMBG, which is painful and inconvenient, this is a safe, effective, and better alternative method.\textsuperscript{12,13}

Pathophysiology

In nondiabetic individuals, the blood glucose levels begin to rise ~10 minutes after the start of a meal, with a peak at 60 minutes and returning to pre-prandial levels within 2–3 hours. Even after that, the absorption of ingested carbohydrates continues for 5–6 hours after a meal. PPHG depends on carbohydrate absorption, insulin, and glucagon secretion and their effect on glucose metabolism in peripheral tissue and the liver. In T2DM, peak insulin levels are delayed and insufficient to control PPG excursions, while in T1DM, peak insulin levels depend on the type of insulin injected as there is no endogenous insulin secretion. In diabetic patients, abnormalities in secretion of insulin and glucagon, hepatic glucose uptake, decreased hepatic glucose production, and peripheral glucose utilization lead to higher and prolonged PPG excursions than nondiabetics. Isolated PPHG doubles the risk of cardiovascular deaths,\textsuperscript{16} and it is the earliest abnormality of glucose homeostasis in T2DM and further progress to fasting hyperglycemia.\textsuperscript{25} During the meal, insulin is secreted in two phases. In the first phase, a small amount of insulin is secreted over approximately a 10-minute period, which controls postprandial glucose excursions. More sustained second phase insulin secretion occurs as plasma glucose levels increase and depend on the meal’s glycemic load. The earliest manifestation of diabetes is the loss of first-phase insulin release, leading to increased PPG and free fatty acids, which delays second-phase insulin response (Fig. 2). PPHG leads to increased lipid levels, triglycerides, and lipoprotein particles. This is known as postprandial dysmetabolism, which is a major risk factor for cardiovascular events.

Fig. 1: As patients get closer to A1c goal, the need to manage PPG increases.

Epidemiology

PPHG is a frequent and under-diagnosed condition. Dickson et al. reported that Asian Indians had a marked increase in postprandial sugar after 75 gm of bread meal.\textsuperscript{14} There is a direct relationship between CVDs and glycemic control in patients with type 2 DM (T2DM).\textsuperscript{15} One study of 90 patients with T2DM demonstrated that isolated PPHG was seen in 24.4% of patients.\textsuperscript{15} The mean HbA1c was a good indicator of IHD, as observed in the UKPDS study.\textsuperscript{16} There was a ~10% increase in cardiovascular disease risk with each 1% increment in HbA1c. In the interventional version of UKPDS, intensive treatment with ~1% reduction in HbA1c leads to a 16% less MI incidence.\textsuperscript{17} Many other studies such as Hoorn Study, Honolulu Heart study, Chicago Heart Study,\textsuperscript{18} and DECODE study\textsuperscript{19,20} have reported that postprandial glucose is a major CV risk indicator. This was confirmed by Coutinho et al.\textsuperscript{21} and with pooled data of Whitehall Study, Paris Prospective Study, and Helsinki Policeman Study.\textsuperscript{22} Diabetes Intervention Study favors PPHG as an independent risk factor for MI.\textsuperscript{23} STOP-NIDDM data indicates acarbose for treatment for IGT can reduce 36% risk in progression to diabetes and 34% in the development of new hypertensive cases, and 49% in cardiovascular complications. A significant decrease in the progression of intima-media thickness was seen in a subgroup that is a surrogate for atherosclerosis.\textsuperscript{24}
CHAPTER 69
Management of Postprandial Hyperglycemia

Fig. 2: Delay of first phase insulin in early type 2 DM

The main pathophysiological mechanism leading to cardiovascular damage is endothelial dysfunction, oxidative stress, and activation of inflammation, and coagulation mechanisms, thus facilitating lipoprotein particles’ penetration into the arterial wall. Hyperglycemia generates free radicals, promoting atherogenesis through peroxidation of LDL, fibrinogen oxidation leading to increased coagulation products, increased platelet activation by collagen, and decreased production of nitric oxide. Recent studies suggested that hyperglycemia causes an overproduction of superoxide by the mitochondrial electron-transport chain, leading to an increase in NO generation due to endothelial NO synthase (eNOS) and inductively NO synthase (iNOS) uncoupled state, which leads to the formation of strong oxidant peroxynitrite, which damages DNA. DNA damage stimulates activation of nuclear enzyme poly (ADP ribose) polymerase. This leads to depletion of the intracellular concentration of NAD+, decreases the rate of glycolysis, electron transport, ATP formation, and produces an ADP ribosylation of the GAPDH (glyceraldehyde-3-phosphate dehydrogenase). All this results in acute endothelial dysfunction in diabetic blood vessels, which leads to the development of CVD (Flowchart 1). Many direct and indirect evidence support this concept.

Management

Management of PPG includes non-pharmacological and pharmacological interventions. These are as follows.

Screening Tests

ADA recommendations for screening for PPG in all asymptotic patients who are overweight (BMI >25 kg/m²) and have additional risk factors. Also, in other conditions such as IGT, high-risk CVD, GDM, Hypertension, Dyslipidemia, PCOD, Acanthosis nigricans, and first-degree relatives of people with diabetes. SMBG is important for detecting and treating PPHG, which is to be monitored in gestational diabetes and patients having high HbA1c and normal FBG.

Non-pharmacological Therapy

In patients with IGT and T2DM with suboptimal glycemic control (HbA1c 7–8%), lifestyle modifications such as weight reduction, exercise, and dietary control can maintain normal glucose levels, thereby reducing the risk of development of diabetes. Exercise helps in glycemic control by increasing insulin sensitization. Dietary modification for PPHG control depends on the type and quantity of carbohydrates taken. Foods with a high glycemic index (GI), such as rice, pasta, potatoes, white and brown bread, and breakfast cereals, have more glycemic load (GL), which is the product of carbohydrate content of the diet and its average GI. Low GI foods such as legumes, most of the fruits, which are slowly digested and absorbed, will cause less GL. The higher GL in the Indian diet causes more prandial glycemic excursions, increased incretin and glucosidase activity in the gut leading to high lipemic peaks resulting in CVS diseases. It is recommended that the diet should contain 45–65% carbohydrates of total calorie intake, food with a low GI, unsaturated fat, high fiber, fruits and vegetables, and pulses.

Pharmacotherapy

Pharmacotherapy is indicated when lifestyle modifications do not control the PPHG. Drugs that target PPHG may be given as monotherapy or in combination, which includes alpha-glucosidase inhibitors (AGI), Glinides, short-acting Sulfonylureas (SU), DPP-4 inhibitors, glucagon-like peptides (GLP-1) derivatives, and rapid-acting insulin. SU and insulin sensitizers (metformin and thiazolidinediones) mainly affect fasting blood sugar; however, a combination of metformin and glyburide has shown a reduction in postprandial glucose excursion in some studies.
Meglitinides (Repaglinide and Nateglinide)

These are non-sulfonylurea insulin secretagogues that bind to islet beta cells at different sites than SU with different kinetics, which mainly affect early insulin release. They are recommended just before meals for early insulin release and a short half-life. Repaglinide is a new class of non-sulfonylurea secretagogues, which after oral administrations with meals, has rapid and short-lived insulinotropic action. This is less hypoglycemic and weight neutral than SU. It is used as mono or combination therapy with metformin, insulins, and thiazolidinediones. Nateglinide is rapid-acting with a shorter duration of action than repaglinide. It is less effective and causes less hypoglycemia than repaglinide.

Alpha-glucosidase Inhibitors (Acarbose, Miglitol, and Voglibose)

Inhibits glucosidase enzyme in the brush borders of the small intestine, which breaks down the disaccharides and more complex carbohydrates, thereby delaying the carbohydrate digestion, which reduces PPHG. Acarbose also increases the secretion of glucagon-like peptide (GLP-1). AGI causes abdominal pain, diarrhea, and flatulence.

GLP-1 Analogs

It is an incretin hormone secreted by gut L cells into the circulation after meals, which lowers glucose by stimulating glucose dependent insulin secretion through activation of cyclic AMP dependent protein kinase in pancreatic Beta cells, inhibits glucagon secretion, delays gastric emptying, and induce satiety. Liraglutide and Exenatide are commercially available GLP-1 analogues. Subcutaneous injection of GLP-1 effectively reduces PPHG in people with T2DM with a low risk of hypoglycemia.

DPP-4 Inhibitors

Inhibits the DPP-4 enzyme causing degradation of GLP-1, which increases the active form of the hormone. This
stimulates glucose-dependent insulin secretion and suppresses glucagon release. DPP-4 inhibitors improve HbA1c by decreasing postprandial glucose without causing hypoglycemia. These are used as monotherapy or in combination with other oral hypoglycemia agents.

**Insulin and Insulin Analogs**

Injection of regular or long-acting insulin before meals will decrease postprandial glucose. Genetically engineered insulins are insulin analogues that are more beneficial than human insulin and cause less risk of hypoglycemia, improved physiological profile, and negligible weight gain. Rapidly acting insulin analogues effect is the same as normal insulin secretion, having faster absorption, shorter duration of action, and peaks about 1 hour after injection. These are insulin aspart, insulin lispro, and insulin glulisine.

**Conclusion**

PPHG alone can cause both microvascular and macrovascular complications in diabetic patients, thereby leading to cardiovascular morbidity and mortality. It is a better indicator of glycemic control than fasting blood glucose (FBS). Patients having normal fasting blood sugar and HbA1c, control on diet, exercise, and medical therapy may have uncontrolled PPHG. The main pathophysiology for PPHG is impaired early insulin secretion in diabetic patients. Early detection, optimal glycemic control, and treatment by effective medications can reduce diabetic complications. The emerging new treatment modalities such as meglitinides, AGI, GLP-1 agonists, insulin analogues, and DPP-4 inhibitors that target PPHG are now available to control PPHG, thereby preventing cardiovascular complications.

**References**


**Abstract**

Diabetes mellitus is reaching near to pandemic state and causes many psychological and sexual problems other than retinopathy, neuropathy, nephropathy, and other macrovascular complications. Sexual dysfunction is one of the most common complications and most under diagnosed complications of diabetes mellitus. This is common in both male and female because of end organ damage and psychological stress caused by diabetes mellitus. Sexual dysfunction maybe an early sign of diabetes mellitus and can occur in any phase of sexual process. Male sexual dysfunctions include disorders of libido, ejaculatory problem, and erectile dysfunction. All these can cause significant problems and affect the quality of life. Erectile dysfunction is three times more common in diabetic patients than in non-diabetic. There is multifactorial pathology but the common is endothelial dysfunction and autonomic neuropathy. Sexual dysfunction in females is difficult to identify and there are limited studies on it but there can be many problems such as arousal, lubrication, and orgasmic dysfunction. Diabetic patients do not volunteer their problems, hence the health-care professionals should routinely question about the sexual problems because it can cause deleterious effect on relationship and quality of life of both the partners. Many treatment options are now available to manage the sexual problem in time.

**Introduction**

Diabetes mellitus (DM) is one of the most common chronic diseases in almost all countries; its increase is near to pandemic assumptions. As per the 2015 reports of the International Diabetic Association (IDA), more than 371 million people had diabetes in 2012; by 2040, the number of people with diabetes is expected to be 642 million.¹ It is a well-known fact that DM causes different medical, psychological, and sexual complications.² Both macrovascular (including CVD) and microvascular (including retinopathy, nephropathy, and neuropathy) complications are associated with complications of diabetes.³ Sexual dysfunction (SD) is a common occurrence in diabetic patients in both men and women due to diabetes-induced end-organ damage and psychological stress.⁴ In some instances, SD can be an early sign of DM.⁵ SD can occur in any of sexual function phases: desire, arousal, plateau, orgasm, and resolution.⁶

**Sexual Dysfunction in Men**

Diabetes is a known risk factor for SD in men. Most common SD in men with diabetes is erectile dysfunction (ED). ED is three times more common in people with diabetes compared to non-diabetic men.⁵,⁷ Factors responsible for ED in diabetes varies from psychological, physical, and social. Anxiety is an essential factor responsible for erectile disorder and premature ejaculation in diabetes. Low sexual satisfaction, sadness, low self-esteem, distress, and depression can express in persons suffering from SD. ED may be defined as the perpetual inability to attain or maintain penile erection for successful sexual intercourse causing the compromised quality of life in men.⁸,⁹
Incidence of ED is directly proportional to the age. By the year 2025, the worldwide prevalence of ED is expected to reach 322 million patients.\textsuperscript{13}

**Diagnosis of Male Sexual Dysfunction**

Diagnosis of ED in a person can be made using standardized questionnaires involving his sexual activity. One such suitable questionnaire commonly used is the International Index of Erectile Function (IIEF)-5, which comprises items 5, 15, 4, 2, and 7 from the full-scale IIEF-15. A score of 21 or less suggests the possibility of ED.\textsuperscript{14} Other scales used are the Sexual Functioning Questionnaire—male, Arizona Sexual Experience Questionnaire (ASEX), Male Sexual Health Questionnaire (MSHQ), and Premature Ejaculation Profile (PEP) (Table 1). To work out your level of erectile function/dysfunction, add the numbers corresponding to questions 1-5. The Sexual Health Inventory for Men further classifies erectile dysfunction as 1–7 severe, 8–11 moderate, 12–16 mild to moderate, and 17–21 mild ED.

**Sexual Dysfunction in Women**

The link between SD and diabetes is well established in men. However, among women, the data to support this association is lagging despite a significantly higher prevalence of female sexual dysfunction (FSD) in women who have diabetes as compared with women without diabetes.\textsuperscript{15,16} As per the American Foundation of Urological Diseases (AFUD), female sexual dysfunction (FSD) comprises four components:

- Hypoactive sexual desire disorder (HSDD; reduced frequency of sexual intercourse, aversion to intercourse)
- Female arousal disorder (FAD; inability to achieve arousal)
- Female orgasmic disorder (FOD; inability to achieve orgasm)
- Sexual pain disorder (SPD; dyspareunia).

Also decreased sexual desire, lack of sexual satisfaction, decreased vaginal lubrication, and orgasmic dysfunction have been documented in a few studies conducted in women suffering from DM.\textsuperscript{17} Anxiety and depression in women lead to difficulty in arousal, orgasm, and achieving pleasure.\textsuperscript{18} Furthermore, SD interferes in cordial relationship with the partner. It increases emotional stress, and in the absence of regular communication, it may end up with divorce due to less marital satisfaction, difficulty in resolving problems and decreased self-care behavior, which may result in poor glycemic control.\textsuperscript{19} FSD is caused

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>The sexual health inventory for men (SHIM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How do you rate your confidence that you could get and keep an erection?</td>
<td>Very high</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?</td>
<td>No. Sexual activity</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered your partner)?</td>
<td>Did not attempt intercourses</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>During sexual intercourses, how difficult was it to maintain your erection to completion of intercourse?</td>
<td>Did not attempt intercourses</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>When you attempted sexual intercourses, how often was it satisfactory for you?</td>
<td>Did not attempt intercourses</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
by disturbances in psychophysiological factors and alters the sexual response cycle in the female, which consist of disorders of sexual desire, arousal, pain, and orgasm.

**Diagnosis of Female Sexual Dysfunction**

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) combines sexual desire and arousal disorders into the “female sexual interest/arousal disorder” category, whereas vaginismus and dyspareunia together constitute “Genito-pelvic pain/penetration disorder” category. A woman suffering from these symptoms for a minimum of 6 months fits into the criteria for making a diagnosis. For distinguishing transient sexual difficulties from more persistent SD, severity criteria are used.

The Diagnostic tools used to diagnose SD in females are:

- **Female Sexual Functioning Index**: It consists of 19 questions with six domains, desire (2 questions), arousal (4 questions), lubrication (4 questions), orgasm, satisfaction and pain (3 questions each). Sexual activity of the last 4 weeks is evaluated, and a score of less than 26.55 confirms SD.

- **Arizona Sexual Experience Questionnaire (ASEX)**: It consists of 5 components scale with five domains—sex drive, arousal, lubrication, orgasm, and satisfaction following orgasm. It evaluates the sexual activity of last week, including the consulting day. A total ASEX score of ≥19, anyone component with a score of ≥5, or any three components with a score of ≥4 suggests SD.

- **Sexual Functioning Questionnaire (SFQ)**: 28 items with six domains—Desire, Arousal, Orgasm, Pain, Enjoyment, and Partner relationship.

- **Female Sexual Distress Scale-Revised (FSDS-R)**: 13 items, and one domain included is distress about sexual life. Sexual Interest and Desire Inventory (SIDI)—15 items for Hypoactive Sexual Desire Disorder Domain.

**Pathophysiology**

Pathophysiology of ED in diabetes is manifold which develops gradually. Usually, psychological and biological factors work together resulting in an erection. In an average person, psychological arousal results in parasympathetic stimulation leading to nitric oxide (NO) release from local endothelial cells. NO release causes smooth muscle and vascular relaxation resulting in increased arterial flow in penile corpora cavernosa. This increased blood flow hampers venous return by causing compression of penile venules, which maintains the penile erection. The mechanism of ED in diabetic patients is the result of vasculopathy, neuropathy, insulin resistance, visceral adiposity, and hypogonadism. Vasculopathy is the result of endothelial dysfunction, macroangiopathy and microangiopathy. Macrovascular complications of diabetes lead to atherosclerotic damage in blood vessels causing decreased blood flow to the penis. Microvascular complications impair distal circulation leading to ischemic damage, autonomic and peripheral neuropathy. This results in impairment of sensory impulse from the penis to reflex erectile center thereby inhibiting parasympathetic activity necessary for smooth muscle relaxation of corpus cavernosum. Norepinephrine and acetylcholine positive fibers in the corpus cavernosum are reduced in people with diabetes which impairs muscle relaxation. Endothelial dysfunction in diabetes is caused by decreased nitric oxide bioavailability, which impairs relaxation of the vascular smooth muscle of corpora cavernosa. Accumulation of advanced glycation end products, increased free radicals levels, decreased bioavailability of NO are few causative factors in endothelial dysfunction, which leads to increased vasoconstriction due to imbalance between vasoconstriction and relaxation.

Around 25% of diabetic males have low testosterone levels with low luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Testosterone is necessary for the erectile function. It regulates smooth muscle relaxation, the endothelial function of corpora cavernosa. It regulates the timing of erection, sexual desire, and maintains the penile erection during sex. Overweight and obese diabetic males having insulin resistance and visceral adiposity have proinflammatory state leading to decrease the bioavailability of NO causing ED.

SD in diabetic female includes loss of sexual desire, arousal, lubrication difficulties, dyspareunia, and loss of orgasm. Diabetes causes vascular and nerve dysfunctions, which impair sexual response by causing functional and structural changes in female genitalia. Vascular abnormalities causing atherosclerosis and endothelial dysfunctions are responsible for reduced clitoris engorgement and vaginal lubrication, which attenuates arousal and causes dyspareunia during coitus.
Diabetic neuropathy also alters normal transduction of sexual stimuli and initiating a sexual response. FSD maybe because of imbalance in hormonal levels in diabetic females. Some epidemiological studies suggest an association between sexual problems in diabetic females and levels of estrogens, androgens, and sex hormone-binding globulin. Many endocrinal dysfunctions of thyroid, hypothalamic-pituitary, polycystic ovarian syndrome also contribute to this problem in such females (Flowchart 1 and Fig. 1).

Management

There are many treatment modalities for SDs in both males and females, which include:

Lifestyle modification: Regular exercise, weight reduction, blood glucose monitoring, thereby maintaining a reasonable glycemic control, control of hypertension, cessation of alcohol intake, smoking cigarette, and avoiding drugs which cause ED will help and lowers the risk of developing SD. The effect of lifestyle modification on ED in diabetic patients is modest.

Phosphodiesterase type 5 inhibitors (PDE5I): PDE5I revolutionized the treatment of ED, this class of oral agents are the treatment of choice. FDA approved sildenafil, vardenafil, tadalafil, and avanafil for the treatment of ED. The action of PDE5I depends on the NO/cGMP pathway. Sexual stimulation causes the release of NO from cavernous nerves and endothelial cells. By multiple mechanisms, cGMP causes penile smooth muscle relaxation, which is deactivated by PDE5 found in the penis. PDE5I prevents the deactivation of cGMP, resulting in persistently elevated levels of cGMP, which in turns maintain continued smooth muscle relaxation of the penis. The release of NO is mediated by neuronal and endothelial NO Synthase (NOS). Diabetic patients develop neuropathy and endothelial dysfunction, which blunts the efficacy of PDE5I. That is why the effect of PDE5I is better in non-diabetics than diabetic patients. These drugs are to be taken 1–2 hours before intercourse, and their effectiveness require sexual stimulation. Side effects are headaches, light-headedness, flushing and dizziness. These are contraindicated in patients taking nitrates IHD, CHF, HOCM, and hypertension. Another oral drug

Flowchart 1: Flowchart of pathophysiology of erectile dysfunction
is alpha2 adrenergic receptor blocker Yohimbine, which increases cholinergic and decreases adrenergic tone. It stimulates the midbrain and increases libido; this is more effective in psychogenic ED and less effective in diabetics.

Other treatment modalities (in those patients who are non-responders to oral treatment):

Vasodilators: Directly administered to the penile erectile tissue. These are papaverine, phentolamine and Prostaglandin E-1 (PgE1). These are used in combinations; only PgE1 is approved by the FDA. PgE1 and papaverine may be injected Intracavernosal in the shaft of the penis with sterile techniques and under supervision of urologist 10–15 minutes before intercourse. Prostaglandins are also used as intraurethral suppository Medicated Urethral Suppository for Erections (MUSE). Side effects are pain, priapism, urethral burning, and irritation of partner’s mucous membranes.

Mechanical therapy such as Vacuum Erection Devices (VED): It is used in non-responders of injections and urethral suppository. Vacuum pressure increases arterial inflow, and occlusive tension rings decrease venous outflow from penile corpus cavernosa. The penis is placed in a cylinder, a vacuum is created by a pump, which increases blood flow in the penis than a tension ring is applied at the base of the penis, and the erection lasts till the ring is removed.

Penile prostheses are the best substitutes for ED in persons who have diabetes if other modalities fail and give dissatisfaction. Prosthetic surgery is irreversible because it causes permanent alteration of corporal tissue, and thus, the physiological erection is not possible. Many materials, flaps, grafts have been tried, and most recent is hollow silicon cylinders inflated with saline or semi-rigid roads. The prosthesis has the highest satisfaction rate among all modalities for the management of ED, around 95% as
demonstrated by two large studies. A future version of prosthesis will be remote control devices similar to the garage door opener. The complication of surgical implant is the risk of infection.

**Testosterone therapy:** Persons having low testosterone and suffering from hypogonadism such as decreased libido, decreased energy, depression, fatigue, weight gain, anxiety may get benefitted with this therapy.

Future therapies can be gene therapy, penile low-intensity shock wave lithotripsy, which consists of 1,500 shocks twice weekly for 3–6 weeks to stimulate neovascularization to corporal bodies to improve penile blood flow and endothelial function. Some are NO-releasing polymers injected in cavernosa, which may improve ED.

**Conclusion**

SD in diabetes is an under-discussed, unrecognized, and usually untreated complication. It equally affects both the partners and is one of the treatable diabetic complications. This is due to vascular, neurological, and hormonal disturbances caused by diabetes. Sexual problems in diabetes include ED, sexual desire and ejaculatory dysfunction in men and many sexual problems in the female. Awareness about sexual problems is now increasing among diabetic patients. Many treatment options are now available such as oral medications, injectable drugs, vacuum devices, and inflatable prostheses. Controlling diabetes, discussing sexual problems, and management in time may improve sexual life in diabetic patients.

**References**

Abstract

Nowadays good move is without CVOT trail and FDA approval no antihyperglycemic drugs can enter the market. EMPA REG outcome trail and LEADER trail had shown superiority and beneficial effects on CV safety in type 2 diabetics. SGLT2 inhibitors have shown to decrease the progression on renal dysfunction in long standing diabetics. All SGLT2i had shown significant reduction in hospitalization for heart failure.

Introduction

Patients with type 2 diabetes mellitus in general are more prone for atherosclerosis induced vascular disease like myocardial infarction and cerebrovascular accident with a tenfold increased risk. The is also increased risk of heart failure in diabetic patients. As diabetic patients are started on long-term oral hypoglycemic agents, the drugs should have a detrimental effect on cardiovascular safety. FDA imposed that "every newer antihyperglycemic agent have to undergo a CV safety trial" when there was a controversial results of rosiglitazone trial, which increased the risk of myocardial infarction and deaths due to CV disease. In cardiovascular outcome trial (CVOT) design, the newer glucose-lowering drug is added to standard of care (SoC) treatments in patients at high risk of CV events, and compared with SoC alone or added to an active comparator. The primary outcome is known as the 3-point MACE (major adverse cardiovascular events) which includes any CV death, nonfatal MI and nonfatal stroke and 4-point MACE which includes composite- or add hospitalization for unstable angina (HUA). Few of the studies has also included heart failure and renal protection effects. As per the guidance, CVOTs comparing an antihyperglycemic agent with a comparator must demonstrate that the upper bound of a two-sided 95% CI is <1.8. Few of the newer antihyperglycemic agents have also showed beneficial effects on CVD beyond glycemic control. The current chapter will elaborate on the various trials done in CV safety in type 2 diabetes mellitus. The first trial (SAVOUR-TIMI) was started in 2003 and many trials have been completed since then. It is done in DPP4 inhibitors, GLP-1 analogues, sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin analogues. (Flowchart 1).

DPP4 Inhibitors

SAVOUR-TIMI involving Saxagliptin and EXAMINE trial that involved Alogliptin, Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS), CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA), and CARdiovascular Safety & Clinical outcoME with LINAgliptin (CARMELINA). SAVOUR-TIMI showed a non-inferiority in CV safety compared to the placebo but there was an observation of increased hospitalization due to heart failure. EXAMINE trial also showed the rates of major composite events were not increased with alogliptin as compared with placebo in a follow-up to 40 months.
Flowchart 1: Approved CVOT trails between 2013 and 2020

- **2013**
  - Savor-TIMI 53
    - n = 16,492
    - 3-P MACE
  - Examine
    - n = 5,380
    - 3-P MACE
  - Tecos
    - n = 14,671
    - 3-P MACE
  - **EMPA-REG outcome**
    - n = 7,002
    - 3-P MACE

- **2015**
  - Elixa
    - n = 6,068
    - 4-P MACE
  - **Leader**
    - n = 9,340
    - 3-P MACE
  - **Canvas program**
    - n = 10,142
    - 3-P MACE

- **2016**
  - Freedom-CVO
    - n = 4,156
    - 3-P MACE
  - Sustain-6
    - n = 3,297
    - 3-P MACE
  - Devote
    - n = 7,637
    - 3-P MACE
  - IRIS
    - n = 3,876
    - Fatal or nonfatal stroke or MI
  - - DPP-4 inhibitors
  - - SGLT2 inhibitors
  - - GLP-1 receptor agonists
  - - Insulin
  - - TZD
  - - α-Glucosidase inhibitors

- **2017**
  - Pioneer 6
    - n = 3,176
    - 3-P MACE
  - ACE
    - n = 6,522
    - 3-P MACE (3-P MACE + hospitalization for HF or unstable angina)
  - Harmony outcomes
    - n = 9,901
    - 3-P MACE

- **2018**
  - Vertis CV
    - n = 8,000
    - 3-P MACE
  - Dapa-HF
    - n = 4,500
    - CV death, HF hospitalization, urgent HF visit
  - Credence
    - n = 4,464
    - ESRD, doubling of creatinine, renal/CV death
  - Declare-TIMI 58
    - n = 17,276
    - 3-P MACE: CV death + HF hospitalization

- **2019**
  - Rewind
    - n = 9,901
    - 3-P MACE
  - Harmony outcomes
    - n = 9,901
    - 3-P MACE
  - Dapa-CKD
    - n = 4,000
    - >50% sustained decline in eGFR or reaching ESRD, CV death, or renal death

- **2020**
  - **Emperor-reduced**
    - n = 2,850
    - CV death or HF hospitalization
  - **Emperor-preserved**
    - n = 4,126
    - CV death or HF hospitalization
Alogliptin neither increased CV morbidity or mortality, nor worsened preexisting heart failure, including in those patients with a very recent acute coronary syndrome, after a median duration treatment of 18 months. CAROLINA is first in kind head-to-head comparison between a SU and a gliptin (linagliptin) in high CV risk patients which showed a non-inferior risk of a composite CV outcome. CARMELINA trial showed that across all GFR, there is no increase in CV and renal events.

**SGLT2 Inhibitors**

There are four SGLT2 inhibitor trials with a composite 3-point MACE is the primary end point; in two, a composite renal outcome is the primary end point; and in three, a composite of HF outcomes and CV death is the primary end point in people with established HF. These include CANVAS, CREDENCE (ongoing), EMPA-REG outcome, EMPA-CKD, DAPA-HF, EMPEROR trials.

**CANVAS**

Canagliflozin compared with placebo was associated with a lower frequency of adverse cardiovascular events. Canagliflozin was also associated with a lower rate of progression of albuminuria; however, amputation occurred more frequently.

**EMPA-REG Outcome**

This trial was an event driven trial in CVOT trials that has shown a superiority in CV events by. Further it appears to have a salutary effects on renal outcome including the need for renal replacement therapy. It also reduced heart failures an hospitalizations for heart failure. The patients were receiving 10 and 25 mg of empagliflozin and the results include in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).

**DAPA-HF**

In patients with type 2 diabetes, inhibitors of SGLT2 reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. This was shown by the DAPA-HF (dapagliflozin heart failure) trial among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo.

With all these trials showing major CV benefits, ADA 2020 recommends in type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor can be added after metformin therapy.

**GLP-1 Analogues**

The CV safety is been studied in eight trial involving GLP-1 analogues out of which four trials have been completed.

**ELIXIR**

The first trial ELIXIR where lixisenatide was studied in patients with recent acute coronary syndrome (ACS) where it had a noninferiority in 4-point MACE, but showing no superiority in CV outcome.

**LEADER Trial**

Liraglutide was employed in this double blind trial where the rate of death from any cause was lower in the liraglutide group [381 patients (8.2%)] than in the placebo group [447 (9.6%)] (hazard ratio, 0.85; 95% CI, 0.74–0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events.

**SUSTAIN-6**

This trial involved long acting semaglutide with weekly injection of 0.5–1 mg which has a favorable effect on 3-point MACE with a significant decrease in nonfatal stroke, nonsignificant decrease in nonfatal MI with no trend on CV deaths or all cause mortality.

**EXSCEL Trial**

This was performed in a usual-care setting among patients with type 2 diabetes with or without previous CVD. It was
shown to have noninferiority in 3-point MACE, but not superiority, of once-weekly treatment with 2 mg of the long-acting extended-release exenatide (HR 0.91 [95% CI 0.83–1.00], P=0.06).

**REWIND Trial**

Once-weekly dulaglutide administered via subcutaneous injection is superior to placebo in improving glycemic control and reducing CV events in patients with type 2 diabetes and higher CV risk. There was also a significant reduction in nonfatal strokes. In addition, the drug had a moderate effect on the composite renal outcome, and reduced new macroalbuminuria in this patient population.

**Insulin**

Two major trials were done with both the Basal insulin namely glargine and degludec. Increased fasting blood glucose is an independent risk factor for adverse cardiovascular outcome in patients with long-term diabetes. Control of fasting blood glucose less than 100 mg% by basal insulin has shown a clear cardiovascular benefit.

**ORIGIN**

This a 6.2-year study where glargine was used to control the fasting blood glucose, the therapy with basal insulin glargine had a neutral effect on cardiovascular outcomes and cancers. Limitations of the study are that metformin was ultimately used by 47% of the insulin-glargine group. Evidence that metformin is cardioprotective raises the possibility that any cardiovascular harm of insulin may have been mitigated by metformin.

**DEVOTE**

The risk of hypoglycemia was more with glargine compared with degludec insulin once daily. This trial was done comparing the CV outcome of glargine and degludec insulin which showed the noninferiority, if degludec on CV events compared to glargine with lesser hypoglycemic events.

The ADA guidelines have been revised regarding the second drug after metformin after CVOT trial outcomes individualizing the patients’ associated CV risk factors. SGLT2 inhibitors and GLP-1 analogues have become the choice after metformin therapy with CV risk.

**BOX 1 Changes to consensus recommendations**

We previously recommended that, in the setting of type 2 diabetes, established CVD was a compelling indication for treatment with a GLP-1 receptor agonist or SGLT2 inhibitor. We now further suggest the following:

**General consideration**

- In appropriate high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hHF, CV death or CKD progression should be considered independently of baseline HbA1c or individualised HbA1c target.
- Providers should engage in shared decision making around initial combination therapy in new-onset cases of type 2 diabetes

**GLP-1 receptor agonist recommendations**

- For patients with type 2 diabetes and established atherosclerotic CV disease (such as those with prior myocardial infarction, ischemic stroke, unstable angina and ECG changes, myocardial ischemia on imaging or stress test, or revascularisation of coronary, carotid or peripheral arteries) where MACE is the graver threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists
- To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR < 60 mL/min (173 m)² or albuminuria

**SGLT2 inhibitor recommendations**

- For patients with or without established atherosclerotic CVD, but with HFrEF (EF <45%) or CKD (eGFR) 30 to ≤60 mL/min (1.73)² or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors
- SGLT2 inhibitors are recommended in patients with type 2 diabetes and HF, particularly those with HFrEF, to reduce hHF, MACE and CV death
- SGLT2 inhibitors are recommended to prevent the progression of CKD, hHF, MACE and CV death in patients with type 2 diabetes with CKD
- Patients with foot ulcers or at high risk for amputation should only be treated with SGLT2 inhibitors after careful shared decision making around risk and benefits with comprehensive education or foot care and amputation prevention
Fig. 1: Treatment of T2D for primary prevention of CVD

Flowchart 2: Managing patients with established ASCVD and T2D

*The available evidence for cardiovascular event reduction in patients with T2D and clinical ASCVD is derived from trials where most participants were on metformin at baseline.

*Until further data from ongoing clinical trials become available, patients at high risk or HF (and possibly those with established HF) may derive more benefit from an SGLT2i with demonstrated CV benefit. Das SR et al. J Am Coll Cardiol 2018. https://doi.org/10.1016/j.jacc.2018.09.020
Flowchart 3: Choosing glucose lowering medication in those with indicators of high risk or established ASCVD, CKD, or HF

CHOOSEING GLUCOSE-LOWERING MEDICATION IN THOSE WITH INDICATORS OF HIGH-RISK OR ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD), CHRONIC KIDNEY DISEASE (CKD), OR HEART FAILURE (HF)

Use metformin unless contraindicated or not tolerated

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- If individualized HbA1c goal achieved and already on dual therapy or multiple glucose-lowering therapies when adding SGLT2i or GLP-1 RA, consider stopping or reducing dose of other glucose-lowering therapy to reduce the risk of hypoglycemia.

ASCVD predominates

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years + LVH or coronary, carotid, lower extremity artery stenosis >50%)
- Preferably: GLP-1 RA with proven CV benefit¹
- OR: SGLT2i with proven CV benefit² if eGFR adequate³
- If HbA1c above target

- Preferably: SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate⁴
- OR: If SGLT2i not tolerated or contraindicated or if eGFR less than adequate⁵ add GLP-1 RA with proven CV benefit⁶
- If HbA1c above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a GLP-1 RA, consider adding SGLT2i with proven CV benefit¹
  - DPP-4i if not on GLP-1 RA • TZD⁶
  - Basal insulin⁶

1. Proven CV benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labeling varies by region, individual agent with regard to indicated level of eGFR for initiation and continued use.
3. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary failure outcome data from DAPA-HF.
4. Updates to the 2018 consensus report are indicated in magenta font.
5. Caution with GLP-1 RA in ESRD.
6. DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
7. Choose later generation SUs to lower risk of hypoglycemia.
A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) has been shown in Box 1.

The treatment of diabetes for primary prevention of CVD is given in the Figure 1.

Managing patients with established ASCVD and T2D have been shown in the Flowchart 2.

Choosing glucose lowering medication in those with indicators of high risk or established ASCVD, CKD, or HF have been shown in the Flowchart 3.

**Conclusion**

- The CVOT trials, after the usage of rosiglitazone which had a detrimental effects on CV outcome.
- FDA has given a CV safety trial for all newer antihyperglycemic drug.
- Few of the studies showed a superiority in decreasing the deaths due to CV events and has a beneficial effects on CV outcome. These include EMPA-REG OUTCOME trial and LEADER trial which had shown clear beneficial effects on CV safety in type 2 diabetic adult patients and with this favorable outcome combined ADA and EASD has given clear guideline about the place after metformin therapy in diabetic population.
- SGLT2 inhibitors have shown to decrease the progression on renal dysfunction in long standing diabetes.
- DAPA-HF had shown that there is a significant decrease in hospitalization and deaths due to heart failure in long standing diabetes with heart failure with decreased ejection fraction when dapagliflozin is employed.

**Suggested Readings**

CHAPTER 72
Diabetic Fatigue Syndrome
Puneet Saxena, Deepak Chadha, Rishika Goyal

Abstract
Fatigue occurring in diabetes is a multispectrum disorder with etiology touching many horizons ranging from glycemia related and endocrinal/iatrogenic to nutritional and lifestyle factors. In this article we tried to illustrate fatigue in general and from neurological standpoint alongside enumerating the etiology of fatigue in diabetes with further mentioning the pathogenesis behind causation of fatigue in diabetes and ways to diagnose and manage the problem. The recognition and timely management of fatigue in diabetes is of paramount importance as it hinders with the self management tasks of diabetes on part of the patient. The diabetes self management is the cornerstone in management guidelines of diabetes in current scenario. The major aim of this literature is to highlight the topic of diabetic fatigue syndrome and engrave the path for more focused studies on this subject in the near future.

Introduction
Diabetes mellitus is a major public health threat with a global prevalence that has expanded enormously over past decades and is affecting approximately 6% of total world’s adult population. Among those affected, there are frequent symptoms of fatigue including decrease ambulation, frailty, generalized muscle weakness, and loss of independence thereby regarding fatigue as one of the omnipresent but distressing complaint and is a strong predictor of functional limitations, disability, and increasing mortality. The fatigue in diabetes has a multifactorial causation and is not just only limited to poor glycemic control. Currently there is paucity of focused studies on diabetes fatigue syndrome describing the severity of problem thereby highlighting the need for further clarification over this neglected, but extremely important aspect of diabetes care.

What is Fatigue (In General)?
Fatigue is a subjective sensation with no measurable signs and is defined as physical or mental exhaustion leading to decrease the quality of life. There is no proper standardized quantification of measurement of fatigue thereby explaining the position of no proper defining criteria till now. Hence, fatigue is mainly identified on subjective grounds or decrement in physical performance. The causation of fatigue touches multiple horizons that range from physiological to psychological and pathological disease states. At the onset fatigue can occur in normal daily activities where it is regarded as the protective mechanism that signals the body’s requirement of rest. This kind of fatigue is mainly acute in onset and relieves off by taking adequate rest whereas on the other side of spectrum is chronic fatigue that is majorly associated with multiple disease states like diabetes, malignancies, fibromyalgias, and even chronic pulmonary obstructive disorders. It typically does not relieve on rest and is initiated by mild to moderate level of activity.

The physiological mechanism behind fatigue broadly classifies fatigue into main types: peripheral and central fatigue. In peripheral fatigue, the underlying pathogenesis is attributed largely to the neuromuscular transmission...
defect, muscular metabolic defects, or rarely to circulatory failure states. In this type, patient complains of physical fatigue where he is unable to sustain adequate force during exertional activities. On the other side, in central fatigue there is failure of initiation of attentional tasks (mental fatigue) and physical activities requiring self motivation (physical fatigue) in the absence of any obvious motor weakness or neurological deficit. The central fatigue can be of short duration as evident by normal individuals after loss of sleep, following stress, in females during menstruation and also after episodes of viral illness or persistence of central fatigue mainly seen in central disorders like Parkinsonism.

Fatigue can even be psychological in origin as is evident in clinical depression, stress, and burnout states.

**Fatigue in Diabetes: Etiopathogenesis**

The fatigue in diabetes is multifactorial in origin and is largely attributed to physiological, psychological, and lifestyle factors pertaining to diabetes as explained in Flowchart 1.

**Physiological Factors**

The physiological factors responsible for causation of diabetic fatigue syndrome (DFS) are mainly discussed under three subheadings like:
- Poor glycemic control
- Presence of diabetes-related complications
- Concomitant other endocrinopathies.

**Poor Glycemic Control in Diabetes**

- As evidenced by number of studies in the literature acute episodes of hyperglycemia are frequently associated with fatigue along with alteration in the mood states and decreased cognition. This association is notably seen with fasting plasma glucose levels rather than HbA1c thereby corroborating the strong relation between fatigue and acute rather than chronic hyperglycemia.
- Similarly acute episodes of hypoglycemia are also linked up with bouts of fatigue as evident by one of the controlled study conducted among type 1 diabetics.
- There are fewer data available to establish linkage between chronic hyperglycemia and its contribution to fatigue, but still no association has been found between HbA1c and fatigue symptoms. The excursions of HbA1c are linked up with sleepiness, but not with fatigue.
- There is also a strong association between symptoms of fatigue and glucose variability that is defined as fluctuations in glucose levels occurring over minutes to hours that are not revealed by single measurement of blood glucose or even by HbA1c. The frequency and magnitude of glucose variability is more marked in type 1 diabetics who are under the effects of exogenous insulin than in type 2 diabetics. The exogenous insulin is more responsible for alteration in the levels of counter regulatory hormones like glucagon or nor-epinephrine thereby responsible for more frequent episodes of hypoglycemia. Among type 2 diabetics, the glucose fluctuations occurring during post prandial phase are frequently associated with bouts of fatigue.

**Diabetes-related Complications**

- There are many notable chronic complications of diabetes that are frequently associated with fatigue.
- Peripheral vascular diseases often present in diabetic patients and causes deep aching pain in the calves owing to perfusion defects in the lower extremities among diabetics and such patients frequently report fatigue.
- Similarly, neuropathic pain in hands and feet of diabetic patients with concomitant dysesthetic sensations also are linked up with onset of fatigue.
- The leading cause of end stage renal disease is diabetes. This form of chronic kidney disease is largely linked with anemia that directly attributes to causation of increased fatigue.
Other Accompanying Endocrinopathies

Patients with type 1 diabetes are prone to develop other concomitant endocrinopathies like hypothyroidism, hypogonadism, Cushing syndrome, and Addison’s disease. These conditions if left untreated may further worsen DFS.

Psychological Factors

It encompasses two main states namely:
- Diabetes emotional distress
- Diabetes-related depressive symptom complex.

Diabetes Emotional Distress

- It also known as diabetes burnout phase is a state of psychological disturbances that arises while managing and living with diabetes. There are many factors that directly or indirectly responsible for DFS in diabetes emotional distress.
- Stress of living with diabetes causes depletion of energy and fatigue with disruption of sense of well-being.
- The increase burden of self management of disease especially in type 1 diabetics with self adjustment of insulin dosages associated with sense of psychological or emotional fatigue apart from improve physiological blood levels.
- Also in diabetes burnout phase, the patient feels cynicism, emotional fatigue, and sense of detachment from recommendations of health-care providers when patient experience negative results during the course of self management of diabetes. The sense of ineffectiveness prevails during this phase.

Diabetes-related Depression

- Diabetics are more likely to suffer from depression than general population.
- The elevated depressive symptoms further likely contribute to sense of physical and mental fatigue.

Lifestyle Factors

There are several factors linked up with DFS like the following:

Increased BMI

It has been found that type 2 diabetic patients are majorly overweight and obese that are two independent factors causing fatigue. There is increased level of proinflammatory cytokine production that plays a major role in the pathogenesis of fatigue. This increased production of proinflammatory cytokines storm further causes oxidative stress and initiate apoptotic pathways in the central neural circuits that contribute to symptom complex of fatigue.

Reduced Level of Physical Activity

- Regular physical activity especially vigorous exertion helps in building up of muscle mass, increases substrates usage for energy production, improves aerobic exercise capacity, decreases lactic acid production at the cellular level, and finally improves mood. Therefore, physical activity and exhibition of fatigue symptoms exhibit inverse relationship with increase activity; there occurs little or no fatigue at all.
- Moreover physical activity helps in rejuvenation of mood and alleviation of multiple somatic symptoms like depression.

Erratic Nutritional Factors

Increase calorie consumption can precipitate excursions of glycemia that further play a role in fatigue. Even excessive dietary restriction causing very low calorie consumption leads to protein energy malnutrition and starvation ketosis that can precipitate DFS.

Miscellaneous Causes

Common medical conditions associated with DFS are:
- Multiple vitamin deficiencies, especially low vitamin D levels and vitamin D deficiencies are markedly notable in diabetic patients that are further associated with fatigue, depressive symptoms, and low quality of life. The prolonged muscle weakness associated with musculoskeletal pains is associated with vitamin D deficiency.
- Anemia in diabetes is also one of the medical conditions in causation of DFS as being described previously. Apart from being the stigmata of chronic kidney disease, anemia is also evident in patients with excessive blood loss or with worm infestations.

Approach to Patient with DFS

As the pathogenesis of DFS touches multiple horizons so the clinical approach in patients with DFS is not
only centered on poor glycemic variability but should thoroughly follow hierarchy of responsible factors that need to be evaluated before labeling patient with DFS. All of the major causes are tabulated in Table 1.

- The initial assessment begins with lifestyle-related factors followed by endocrinal assessment. The evaluation of daily routine of patient with special emphasis on exercise habits, pattern, and quality of sleep, dietary habits. If the patient is having more sedentary lifestyle then motivation to be given for increase physical activities in the form of aerobic exercise or joining a game or simply doing cycling.

- For the assessment of glycemic control and presence of chronic diabetic complications, the search begins with thorough history and physical examination of the patient.

- When the symptoms of fatigue occur characteristically in the early morning and are associated with headache, sweating and relives on taking breakfast simply suggests hypoglycemia as the cause of fatigue.

- The appearance of pallor in patient with long standing diabetes accompanied by symptoms of breathlessness on exertion signifies prompt investigations for nephropathy and hypothyroidism. When symptoms of fatigue accompany breathlessness along with inability to do exercise suggest decrease cardiac reserve in the form of heart failure.

- The prominence of symptoms of pain in the calves while walking along with neuropathic symptoms suggests development of diabetic neuropathy responsible for DFS. When fatigue is accompanied by symptoms of weakness of proximal muscles then ruling out vitamin D deficiency is important, similarly if patient complains of bony pain and tenderness then osteomalacia or hypoparathyroidism are more notable to exist.

- When fatigue occurs with symptoms of sexual dysfunction or loss of libido may suggest menopause, andropause, or even hypogonadism.

- Before labeling patient to be psychiatric, thorough evaluation for diabetes emotional distress and diabetes-related depression should be sought for.

- Drugs like centrally acting anti-hypertensives, diuretics, statins, and beta blockers also causes fatigue and are considered iatrogenic causes of fatigue.

Subjective Evaluation of Fatigue

There are multiple questionnaires for evaluation of fatigue as well like:

- Avlund Fatigue Scale
- The 36 Item Short Form Health Survey
- Sleep Quality Scales Like Pittsburg Sleeping Quality Index
- Multidimensional Sleep Inventory

What Fatigue does to Diabetic Patients?

The major drawback of fatigue is that it completely affects the self-rated health and quality of life in a very negative sense, and therefore is taking a huge toll over the diabetic patients. The patient characteristically present with decreased physical functioning and inability to manage the daily routines of life. The most dreaded effect of fatigue in patients with diabetes is that fatigue acts as a strong barrier in patient’s health promoting behaviors like
participation in self-care regimens of diabetes, following a regular exercise plan, and participation in healthy eating habits.\textsuperscript{28} Thereby fatigue remains a challenging problem to manage on the part of health-care providers. The lack of standardized definition and paucity of diagnostic criteria makes the management part more difficult.\textsuperscript{27}

**Important Differentials of DFS**

**Differentiating DFS from Chronic Fatigue Syndrome**

Chronic fatigue syndrome (CFS) is UNEXPLAINED and PERSISTENT fatigue that is not due to any exertional activity and not relieved by taking rest but leads to significant limitation of activity. There are few cardinal hallmarks of CFS that must be present for at least a period of 6 or more months like:

- Myalgias
- Multiple joint pains with no underlying inflammatory signs
- Impair attention span
- Headaches
- Unfresh even after sleep

The most important point differentiating CFS from DFS is that CFS is a diagnosis of exclusion and indeed requires a thorough evaluation of underlying mental status of the patient in terms of mood, personality, intellectual functions, and memory. Apart from psychological factors, there are also many biological factors responsible for causation of CFS like:

- Genetic factors.
- Immune etiologies like increase in number of natural killer cells CD16/CD3 causing abnormal cytotoxicity of natural killer cells and increase in immune activation markers.
- Infectious causes linked up with CFS are infectious mononucleosis, glandular fever, parvovirus B19, nipah virus human herpesvirus 4-6-7, and borna virus disease.

Hence, diagnosis of CFS requires a holistic biopsychological approach.

**Fibromyalgia**

Fibromyalgia syndrome denotes symptom complex of chronic pain, muscle fatigue, de arranged sleep, and many functional symptoms. The underlying mechanism for causation is based on oxidative stress and modified inflammatory response with baseline predisposition attributed to genetics as well. The diagnostic criteria defined by American College of Rheumatology states at least 3-month duration of pain both above and below the waist along with presence of 11 out of 18 possible tender points that are not explained by other disorders.

**Management of DFS**

There are many aspects of management scheme.

**Improving Lifestyle Factors**

Counseling and constant motivating the patient for:

- Initiating physical activity regimen in the form of playing outdoor games, aerobic activity like jogging, cycling and swimming. The patient should be motivated to do at least 150 minutes of moderate activity per week.
- Indulging in eating healthy diet.
- Participating in meditation for stress control.
- Good sleep pattern.

**Maintenance of Euglycemia**

The health-care providers should assess the condition of the patient in totality and initiate the drug regimens for complete and effective control of glycemia. There should also be optimization of other endocrinal and medical aspect of patient like correction of thyroid status if concomitant hypothyroidism ensues, correction of hormonal deficits in a patient with hypogonadism.

**Mitigation of Diabetes Distress**

As diabetes is a self-managing disease, so distress occurs when patient is unable to cope with the demands of life with diabetes that further makes the patient incapacitating in managing and monitoring the disease as well. This psychological aspect can be overcome by:

- Utilization of external support
- Enhancing coping skills on the part of patient
- Enhancing self perception of the patient
- Making the patient to understand to minimize the discomfort of change.

**Pharmacological Intervention**

There are no practical prospective studies available for addressing fatigue in diabetes, but there is a list of drugs...
available based on experience of clinician in regards to treatment of depression and presence of fatigue in other conditions like CFS, fibromyalgia, or HIV as mentioned in Table 2.

**Conclusion**

Fatigue is very common and neglected problem for the people living with diabetes and its causation is indeed multifactorial interplay of physiological, psychological, and lifestyle-related factors. The poor self management of diabetes is both the causative factor and net result of DFS. Therefore, regular screening of fatigue along with other complications of diabetes is of paramount importance to prevent or retard the course of DFS. Lastly, to improve the quality of life and obtaining a good control of diabetes, early detection and management of DFS are very essential.

**References**


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**TABLE 2**

Drugs important in treatment of DFS

**SSRI:**
- Fluoxetine
- Paroxetine
- Sertraline

**SNRI:**
- Duloxetine
- Venlafaxine
- Desvenlafaxine

**Atypical antidepressants:**
- Milnacipran

**Stimulants:**
- Modafinil
- Methylphenidate

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**CHAPTER 72**

Diabetic Fatigue Syndrome

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**431**
Poor glycemic control is a major risk factor for long-term micro- and macrovascular complications of diabetes. In the day-to-day practice clinicians frequently encounter patients with high dysglycemic patterns. Measuring Glycated hemoglobin A1c (HbA1c) does not take into account the fluctuations in blood glucose levels. The intraday and interday swing in blood glucose levels including episodes of hyper- and hypoglycemia is known as glycemic variability (GV). GV can be due lifestyle related causes, pharmacological causes, biomedical related causes. It is now strongly suggested that diabetes management strategies should include minimizing GV and must focus on decreasing the postprandial glycemic excursions along with HbA1c levels to lower the risk for long-term complications.

Clinical Implications and Management of Glycemic Variability in Diabetes

Ashutosh Chaturvedi, Girish Mathur, Divyansh Mathur, Mihika Sinha

Introduction

Diabetes mellitus (DM) is now a rapidly growing global epidemic with type 2 diabetes mellitus (T2DM) accounting for over 90% of cases. As per estimated by International Diabetes Federation (IDF), worldwide every 1 in 10 people or 592 million individuals will suffer from diabetes by the year 2035. Poor glycemic control is a major risk factor for long-term micro- and macrovascular complications of diabetes. This poor blood glucose control in diabetes results due to both acute glucose fluctuations and chronic hyperglycemia over time. Thus, the main aim of diabetes management is to decrease the risk of diabetes complications by optimizing blood glucose levels and minimizing blood glucose variability and episodes of hypoglycemia. Glycated hemoglobin A1c (HbA1c) is considered the gold standard for assessment of glycemic control in diabetic patients, but it does not take into account the fluctuations in blood glucose levels. This intraday and interday swing in blood glucose levels including episodes of hyper- and hypoglycemia is known as glycemic variability (GV). Studies suggest that GV contributes to diabetes-related complications and also impacts patient’s psychological well-being and quality of life (QoL). Newer therapeutic strategies like glucagon like peptide-1 (GLP-1) analogs and dihydropeptidyl peptidase-IV (DPP-IV) inhibitors targeting multiple pathophysiological mechanisms are most promising in control of HbA1c and decreasing GV. It is important today to understand the clinical implications of GV and its management in diabetic patients.

Glycemic Variability: A Rising Concept

In the day-to-day practice clinicians frequently encounter patients with high dysglycemic patterns. Few individuals have extreme fluctuations in glucose levels during a particular day, while others present with variable blood sugar readings from day to day. GV may be associated with symptomatic hypoglycemia, impaired QoL, failure to titrate doses of anti-diabetic drugs, unwanted chronic complications and subsequently increased cost of treatment. Thus, it has become a challenge for good diabetes care. Two important pathophysiologic
mechanisms proposed for the development of various micro- and macrovascular complications in diabetes are excessive advanced glycation end products (AGE’s) and activation of oxidative stress. Lowering of hyperglycemic excursions that leads to reduction in GV also decreases the oxidative stress markers. Studies also suggest that fluctuating glucose levels that produce harmful effects on endothelial function and oxidative stress may be more damaging for the cardiovascular system than is chronic sustained hyperglycemia. Traditionally, diabetes management plans mainly targeted to decrease the triad of fasting and postprandial blood glucose and HbA1c. Nowadays GV and QoL have been added to the known components and these five elements are collectively termed as “glycemic pentad.” The need was felt because even studies like DCCT, UKPDS, and ADVANCE trials failed to show any benefits of intensive treatment to retard the development of various chronic complications of diabetes. In recent studies it was observed that HbA1c is not sufficient to justify all the uncertainties of diabetes complications and that GV might be a better indicator of glycemic control than HbA1c.

**Causes of Glycemic Variability**

GV can be broadly classified under three main categories:
- lifestyle related causes
- pharmacological causes, and
- biomedical related causes (Table 1).

Before evaluating the etiology of GV in a particular patient Spurious or Fictitious GV must be excluded, which can be due to wrong technique of self monitoring of blood glucose (SMBG) being used. It is important to assess the instrument and strips used, method of pricking the finger, how the instrument is being used and results are being read and recorded. Everything must be in order. Venous blood glucose estimation can be simultaneously ordered to check and confirm GV. It is now well known that continuous glucose monitoring systems (CGMS) and ambulatory glucose monitoring (flash) much more accurately confirm GV.

**Lifestyle-related GV**

After confirmation of GV, first of all variability in lifestyle needs to be excluded. This can be due to either variation in diet, physical activity, or management of stress in life. Proper history taken from the patient reveals the variation in the composition, pattern, or quality of food taken, sleep pattern and timing, duration or intensity of physical activity/exercise, psychological or social stress. All these day-to-day variations in lifestyle can lead to fluctuations in glycemic levels.

**TABLE 1** Causes of glycemic variability

<table>
<thead>
<tr>
<th>Cause</th>
<th>Type of variation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle related</strong></td>
<td>Diet</td>
<td>- Composition of diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Diet pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Quality of diet</td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td>- Exercise timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Exercise duration</td>
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<tr>
<td></td>
<td></td>
<td>- Intensity of exercise</td>
</tr>
<tr>
<td></td>
<td>Management of stress</td>
<td>- Psychological stress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Sleep cycle issues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Social environment</td>
</tr>
<tr>
<td><strong>Pharmacological</strong></td>
<td>Type of preparation</td>
<td>- Long acting/ultra long acting insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Immediate release/controlled or sustained release tablets</td>
</tr>
<tr>
<td></td>
<td>Type of regimen</td>
<td>- Human insulin/analogue insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Premixed/bolus insulin</td>
</tr>
<tr>
<td></td>
<td>Drug delivery related</td>
<td>- Site of injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Injection at hypo-perfused or euperfused site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Gap between drug/injection and meal</td>
</tr>
<tr>
<td></td>
<td>Drug interactions</td>
<td>- Rifampicin increases metabolism of sulfonylureas (SUs)</td>
</tr>
<tr>
<td></td>
<td>related</td>
<td>- Azoles inhibit the metabolism of pioglitazone and SUs</td>
</tr>
<tr>
<td><strong>Biomedical</strong></td>
<td>Neuroendocrine causes</td>
<td>- Pancreatic exocrine deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Glucagon deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hypoglycemia unawareness</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>- Malabsorption syndrome</td>
</tr>
<tr>
<td></td>
<td>causes</td>
<td>- Diabetic gastroparesis</td>
</tr>
</tbody>
</table>

Pharmacological GV
The GV can also arise due to variation in the selection of drug regimens, drug formulations, and manner and method of drug delivery. For a particular patient’s glucophenotype the selected drug regimens, drug formulations, and manner and method of drug delivery may not be appropriate. For example, for a person having severe hyperglycemia prescribing a basal insulin and using human insulins which have higher coefficients of variability as compared to analogue insulins which have lower. The physician, therefore, should be well-versed with the pharmacokinetics and pharmacodynamics of the each anti-diabetic drugs and various insulin regimes while prescribing them.

Biomedical Causes of GV
When the lifestyle related and pharmacological etiologies are ruled out, it is important to look for the biomedical causes of GV. Biomedical causes can be gastrointestinal, neuroendocrine or drug-drug interactions related. Disorders of absorption and motility result in a nutrient-insulin mismatch that leads to variable changes in the absorption of nutrients. Neuroendocrine reasons include endocrine and exocrine disorders of various glands of body and of the autonomic nervous system (resulting in hypoglycemia unawareness) that leads to GV through different mechanisms. Another type of biomedical cause is the drug-drug interaction occurring when new drugs are prescribed to treat the secondary illness like antifungal drugs (fluconazole and ketoconazole) to treat mycoses, anti-tubercular drugs (rifampin) for treating tuberculosis, and anti-seizure drugs (phenobarbital) for any neuropsychiatric illnesses.13

Measurement of GV
With the development of increasing interest in the clinical implications of GV in diabetes, a lot of methods and metrics has been described for assessment of GV which is at times really confusing for both physicians and patients. For those clinicians who want to apply GV in their routine clinical practice, unavailability of a uniformly accepted standard method of measurement of GV is a real challenging issue. Among all these methods the four most clinically relevant and commonly used methods are coefficient of variation (CV or % CV), standard deviation (SD), interquartile range (IQR), and mean amplitude of glycemic excursions (MAGE).

Most of the physicians commonly use SD to measure GV, but still it has been pointed out that SD is not regularly distributed around the mean glucose; therefore, the IQR, which is also strongly correlated with SD, can be used as a preferred method to measure GV. IQR is a part of the proposed international standard or uniform one-page glucose profile report [Ambulatory Glucose Profile (AGP)] and can be easily recognized on a standard day or 24-hour glucose profile plot and can be actually clinically relevant in decision-making for the clinician and patient. For the purpose of research work, the coefficient of variation (CV or % CV) is still the preferred GV metric which is least influenced by fluctuations in mean glucose level or HbA1c. MAGE is another long-used measure of GV which is defined as the average of all blood glucose excursions (up or down) that are of a magnitude greater than 1 SD of all glucose measures.15 Different aspects of GV parameters which are commonly used in research and clinical practice are summarized in Table 2.

Timing of Glucose Excursions
It is the clinically most important metrics that give us the time which the patient spends within, above, and below the target blood glucose range. With the increasing availability of CGMS in recent years, such time-related GV metrics have become more well-known. Time in targeted blood glucose range (TIR) provides useful information on the level of glycemic control although it gives an incomplete picture of overall glycemic control. Clinically, assessment of TIR can help patients to know better than over the time how hypoglycemia or hyperglycemia improves with treatment.

Clinical Implications of GV
GV and Microvascular Complications of Diabetes
Due to the lack of consensus on the most reliable method of assessment of GV, ambivalent conclusions have been made from the studies examining the relationship between GV and development of complications of diabetes till now. In epidemiological studies while GV was an independent predictor of the prevalence of peripheral neuropathy, while mean blood glucose (MBG) was significantly associated with the development of diabetic retinopathy but not with that of nephropathy.
TABLE 2  Summary of GV metrics\textsuperscript{15}

<table>
<thead>
<tr>
<th>GV metric</th>
<th>Definition</th>
<th>Advantages</th>
<th>Clinical implications of GV metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>The amount of variation or mean dispersion of all glucose readings in a set of data</td>
<td>Widely used, straight forward and easy to calculate</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Provides a measure of inter- or intraday GV depending on frequency of blood glucose measurements</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Does not take into account the number of glycemic swings</td>
<td></td>
</tr>
<tr>
<td>% CV</td>
<td>It is the corrected measure of dispersion in relation to the mean blood glucose</td>
<td>It is useful in two or more groups with different glucose tolerance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Probably the best research metric to compare GV over time or between data sets</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Does not consider the number of glycemic swings</td>
<td></td>
</tr>
<tr>
<td>IQR</td>
<td>It consists of values 25% above and 25% below the median</td>
<td>Likely the best method to visualize GV around the median glucose curve</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>It is easier to spot and give attention what time of day has the most GV by plotting the IQR around the median glucose curve</td>
<td></td>
</tr>
<tr>
<td>MAGE</td>
<td>It is the average amplitude of glucose excursions that are more than 1 SD</td>
<td>Most commonly used in literature and reflects both upward and downward glucose fluctuations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can be applied to SMBG or CGMS data as well</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reflects intraday GV but it excludes minor fluctuations and is dependent on sampling frequency</td>
<td></td>
</tr>
<tr>
<td>CONGA</td>
<td>(Continuous overall net glycemic action)</td>
<td>It is the standard deviation of the differences of glucose readings for a defined period of hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>It can capture smaller glycemic swings over shorter time intervals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It measures intraday GC and is specifically developed for CGMS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Provides measures of short- or long-time intervals but requires software for calculation</td>
<td></td>
</tr>
<tr>
<td>MODD</td>
<td>(Mean of daily differences)</td>
<td>It is the mean absolute difference between blood glucose values derived from SMBG data at the same time on consecutive days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>It shows the consistency and stability of day-to-day blood glucose patterns</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>It is measure of interday GV but it is affected by different daily lifestyle patterns</td>
<td></td>
</tr>
</tbody>
</table>

GV and Hypoglycemia

Cox et al. proposed GV as a better measure of predictor of future severe hypoglycemia than HbA1c.\textsuperscript{18} The association of risk of hypoglycemia was found to be as much related to glucose variability as to the mean glucose value in the diabetes outcomes in veterans study (DOVES).\textsuperscript{19} Limiting glycemic excursions along with maintaining the MBG and HbA1c in target range can be a key factor in achieving glycemic control.

GV and Cardiovascular Disease Risk

In patients with DMT2 and acute myocardial infarction, increased risk of mortality was observed in patients with increased visit-to-visit GV.\textsuperscript{20} Kilpatrick et al. showed that pre- and postprandial blood glucose, MBG were significantly related to cardiovascular disease risk but there was no association between HbA1c and glucose variability.\textsuperscript{21}

GV and QoL

Increased frequency of fluctuations in blood glucose with hypoglycemia and hyperglycemic excursions can lead to mood changes, depression and poor QoL. High GV was shown to be associated with low QoL than HbA1c and 24-hour average blood glucose.\textsuperscript{22}

Management of Glycemic Variability in Diabetes

Glycemic management of diabetes should focus on achieving near euglycemia without episodes of hypoglycemia; hence, reducing the risk for complications. It is now strongly suggested that diabetes management strategies should include minimizing GV and must focus on decreasing the postprandial glycemic excursions along with HbA1c levels to lower the risk for long-term complications.\textsuperscript{21}
For improving the glycemic control management can be strategized into four possible categories of treatment which can be called as 4Ts:

- **Targets:** Setting the individualized glycemic goals carefully.
- **Team approach:** Use of team care along with self-management training to patient and sharing the process of decision-making.
- **Therapeutics development:** Developing new oral and injectable anti-diabetic drugs.
- **Technology:** Application of new technologies in management like continuous glucose monitors, smartphone apps for tracking glucose, insulin pumps, tools for remote communication between the patient and team.

### Lifestyle Measures

It is well known that weight loss through dietary restrictions and exercise are capable of decreasing blood glucose levels and improving the insulin sensitivity thus delaying the progression from impaired glucose tolerance (IGT) to diabetes. In a study it was shown that a diet based on whole cereals, legumes, vegetables, and fruits and rich in dietary fiber led to reduction in postprandial glycemic (PPG) excursions subsequently reducing GV.23

### Oral Hypoglycemic Agents

Minimizing the PPG excursions is an important aspect of overall glycemic management, and a major barrier to optimal control of diabetes. Selection of diabetes medications and blood glucose goals must be beneficial for the individual, simultaneously reducing the risks of hypoglycemia. Sulfonylureas have been shown to be associated with significant GV, and can lead to an increase hypoglycemic episodes and mortality. Rationally glimepiride must cause less GV than glibenclamide because of the insulin-releasing activity which is high with glibenclamide and lowest with glimeperide.24 In a study controlled-release glipizide combined with acarbose was found to be more effective in decreasing MAGE than controlled-release glipizide monotherapy.25

The DPP-4 inhibitors secrete insulin and suppress glucagon in a glucose-dependent manner, controlling postprandial glucose excursions as well as reducing the overall hyperglycemia without increasing the risk of hypoglycemic episodes. As compared to glimepiride and pioglitazone, sitagliptin, and vildagliptin significantly reduced GV in patients with type 2 diabetes not sufficiently controlled on metformin monotherapy.26

### Prandial and Basal Insulins

Newer rapid prandial insulin analogs closely mimic the normal physiological insulin response to meals. Rapid acting insulin analogs such as insulin lispro, aspart, and glulisine better reduce the GV by reducing the periods of acute hyperglycemia, with lower rates of hypoglycemia than regular human insulin. In metformin-treated patients, as compared to insulin glargine alone, a premixed basal insulin glargine and rapid-acting insulin lispro was shown to result in reduced GV.27 In type 1 diabetics, continuous subcutaneous insulin infusion (CSII) was considered as alternative when glycemic targets were not achieved with use of multiple dose insulin regimen in type 1 diabetic patients.

### GLP-1 Analogs

When added to background therapy of oral antidiabetic drugs or high-dose basal-bolus insulin therapy, glucagon-like peptide-1 (GLP-1) receptor agonists like exenatide, liraglutide and lixisenatide have shown remarkable decrease in GV in the comparative studies. Heine et al.28 compared the efficacy of insulin glargine (once-daily) or the GLP-1 agonist exenatide (twice daily) in suboptimally controlled type 2 diabetes. It was found that glargine lowered fasting glucose levels to a greater degree than exenatide, while exenatide decreased postprandial variability to a greater extent than glargine. HbA1c lowering was same in both groups but exenatide decreased glycemic excursions by almost 50% in the end when compared with baseline.

### Conclusion

GV is a physiological phenomenon that contributes to increased mean blood glucose levels and also plays a key role in the development of chronic diabetes complications. Newer technologies in the field of diabetes education, monitoring, and therapy, especially in type 1 DM, have made it easier to identify GV as a promising target for betterment of overall diabetes management. By using CGMS, it is now possible to detect glucose fluctuations and relate their dynamics to relevant clinical implications. By carefully using SMBG and available

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Contd...
newer pharmacologic agents to avoid hyperglycemia and decrease hypoglycemic episodes, the burden of complications, disability, and mortality events associated with diabetes can be significantly reduced. However, due to lack of consensus for a standard metric and also difficulty in measuring GV, it remains a challenge for the clinicians to find out the most optimal approach for managing diabetes.

References

CHAPTER 74

Stem Cell Therapy in Diabetes

Sandeep K Mathur, Anshul Kumar

Abstract

Achievement of normoglycemia and a life free of insulin or oral anti-diabetic drugs has always been the goal of diabetes research and management. Stem cell therapy is the closest that we have ever got to the achievement of the above-mentioned goals. Here, in this chapter we aim to summarize the latest advancements in the use of stem cell therapy as a treatment modality in diabetes.

Introduction

Diabetes mellitus is a major pandemic that has been plaguing humanity since long and is growing tremendously with each passing year and is responsible for causing roughly four million deaths each year. The trends for diabetes prevalence and incidence are particularly worrisome in developing countries. Diabetes, which touched 230 million marks in 2008, is expected to affect over 300 million worldwide by the year 2025.

Curative approach to diabetes that would make the administration of drugs such as insulin secretagogues, insulin sensitizers, or insulin itself redundant has long been sought. Pancreatic (whole organ) transplantation or islet transplantation following the Edmonton protocol has shown to be quite successful in achieving this “endeavor” of curing diabetes, primarily Type 1 Diabetes (T1D). However, the main pitfall has been the lack of donors and the requirement of lifelong immunosuppression and thus, limits the application and benefit of this approach to only a few candidates.

Stem cell therapy heralds a promising new era in the management and possibly curative modality of advanced diabetes. Particular concerns regarding the type of stem cell, the transplantation procedure, and the long-term effects remain to be seen. Several animal trials have shown the potential advantages of using stem cells for treating diabetes mellitus. However, given the numerous hurdles in the procedure and the ethical questions attached, human trials are still few and far between.

In this chapter, we briefly aim to review the treatment approach, the advances, the complexities, and the future directions in the treatment of both T1D and T2D using stem cell therapy as this might prove to be the one therapeutic approach that humanity has been searching.

What is a Stem Cell?

Stem cells are cells that can differentiate into a large number of cells; they are undifferentiated or partially differentiated cells. They are the first cells to form in the body and a particular cell lineage and tissue. They have the unique ability to proliferate without the loss of differentiation potential. They can broadly be classified into five different types:

- Totipotent stem cells: Also called omnipotent stem cells, they can differentiate into any embryonic or extraembryonic tissue, e.g., Totipotent cell from a zygote.
Pluripotent stem cells: They can divide and differentiate into any of the three germ layers, i.e., ectoderm, mesoderm, or endoderm, e.g., Embryonic stem cells.

Multipotent stem cells: These cells can multiply and give rise to a specific type of cells, e.g., Mesenchymal stem cells can differentiate into the osteoblastic lineage, myocyte lineage, adipocyte cell lineage, or chondrocyte lineage.

Oligopotent stem cells: They are like the multipotent stem cells but are further limited in their capacity to differentiate, e.g., Hematopoietic stem cells are of mesodermal origin and can differentiate into all types of blood cells.

Unipotent stem cells: These have the potential to differentiate into a single lineage of cells, e.g., Muscle stem cells.

Pancreatic Islet Cell and Its Development

The human pancreas has dual functions: exocrine as well as endocrine. The exocrine part secretes various digestive enzymes. In contrast, the endocrine part is involved in the secretion of hormones that regulate body metabolism. The endocrine portion is organized into islets. These islets are composed of a variety of cells with each cell serving a different function; α cells, which secrete glucagon, β cells that secrete insulin, δ cells secrete somatostatin, ε cells secrete ghrelin while PP cells secrete pancreatic polypeptide. The chief action of all these various hormones is to maintain glucose homeostasis. It is primarily the dysfunction of the β cells that leads to diabetes mellitus in T1D; there is autoimmune destruction of the β cell, and in T2D, there is β cell dysfunction combined with end-organ insulin resistance, but in both cases, the result is the same dysglycemia.

The development of stem cell-based therapy for diabetes requires the knowledge of underlying transcription factors that control the underlying islet cell differentiation process. However, this has been difficult owing to the relative unavailability of fetal endocrine tissue, and most of our knowledge of the development of endocrine pancreas comes from rodent experiments. Nevertheless, the development of islets in both rodents and humans is similar, and several generalizations can be made.

The human endodermal tissue becomes dedicated to pancreatic development before the evagination of dorsal and ventral pancreatic buds. These buds contain multipotent pancreatic progenitor cells (MPCs), which under the influence of several transcription factors, get committed to endocrine or exocrine fates. After committing, these endocrine progenitors further differentiate and mature under the influence of lineage-specific transcription factors.

Here, we briefly discuss the transcription factors with involvement in β-cell development. The various stages in β-cell development and the different transcription factors expressed during that stage are shown in Figure 1.

![Figure 1: Schematic representation of progression from hESC to mature beta-cell. The various stages and the different transcription factors expressed are shown](image)
**Transcription Factors Involved in Early Stages of Development**

- **FOXA2:** This is an early transcription factor and is consistently expressed from week four onward,\(^{11-14}\) as shown in several fetal pancreas studies.
- **SOX 17:** This high mobility group box gene is seen before 4 weeks but disappears within 1-week. Studies in mice have shown that its early expression is required for endoderm formation. The continued expression represses pancreatic fate.\(^{15}\)
- **Hepatocyte nuclear factor (HNF6):** This transcription factor is consistently found to be expressed from weeks 7–21 of the human pancreatic development.\(^{12,13}\) In rodents, it has been shown to have broad development until just before birth when it becomes restricted to alpha and acinar cells.
- **Hepatocyte nuclear factor 1 homeobox b (HNF1b):** In humans, it is expressed as early as 7 weeks and persists throughout pancreatic development.\(^{16,17}\) Its heterozygous loss of function mutation leads to MODY 5.
- **PDX1:** It is also known as insulin promoter factor 1 (IPF1). It is present throughout the development, with high levels of expression limited to β cells only later in development and in adults.\(^{11,12}\) Homozygous inactivating mutations of PDX1/IPF1 result in pancreatic agenesis (MODY4).
- **Pancreas transcription factor 1A (PTF1A):** It is barely detectable in the human pancreas until mid-gestation, perhaps owing to its enriched expression in the acinar cells at that time point. One study has identified a mutation in the PTF1a enhancer region leading to pancreatic agenesis.\(^{18}\)
- **GATA binding protein 4 (GATA4):** These transcription factors are also expressed in the early development stages, and the late expression is limited to the mature acinar cells.\(^{11}\)
- **SOX9:** It is found in PDX1+ cells in the early human pancreas by about 4 weeks and is then excluded from the pancreas development.\(^{11,19}\)
- **Homeobox protein NK-6 homolog (NKK6.1):** This is expressed in the developing human pancreas after 4 weeks once SOX17 is excluded from the development.\(^{11}\) Then by 14–16 weeks, its expression becomes restricted to β cells.\(^{11,19}\) In adult pancreas, NKK6.1 is a key β cell identity factor and has severely reduced expression in human T2D islets.\(^{20,21}\)
- **Motor neuron and pancreas homeobox 1 (MNIX):** In humans, its expression is found as early as 7 weeks and, then its expression decreases by 14–16 weeks of gestation.\(^{12,13}\) Patient with a homozygous mutation in the DNA binding homeodomain of MNX1 presented with permanent neonatal diabetes.\(^{22,23}\)
- **Multipotent pancreatic progenitor cells:** These cells of developing pancreas are characterized by the continued expression of FOXA2, PDX1, SOX9, NKK6.1, and GATA4.\(^{10}\) These cells are further destined to form the ductal endocrine and the exocrine components of the pancreas. The various transcription factors expressed at this stage include:
  - **GATA6:** It is considered to be very important in the development of human pancreas with mutations in GATA6 leading to pancreatic agenesis.\(^{24,25}\)

**Transcription Factors Involved in the Production of Islet Endocrine Cell Lineages**

- **Neurogenin 3 (NGN3):** With the loss of SOX 9, as mentioned earlier, the expression of NGN3 initiates pancreatic endocrine commitment.\(^{26}\) Its first expression is seen around 8 weeks, peaks around 11 weeks, and then declines to low levels by 19 weeks.\(^{26}\) A case of permanent neonatal diabetes carrying a null mutation in NGN3 with low C-peptide levels has been reported.\(^{27}\)
- **Regulatory factor X 6 (RFX6):** As demonstrated by quantitative real-time PCR, the expression of RFX6 is limited to the adult human pancreatic islets and autosomal recessive mutations have been found to result in rare cases of neonatal diabetes with the absence of insulin, somatostatin and glucagon secreting cells in the islets.
- **Paired box gene 4 (PAX4):** Its expression is evident by 9 weeks of gestational age,\(^{13}\) and its mutation has been associated with MODY 9.
- **GLIS family zinc finger 3 (GLIS3):** Patients with an autosomal recessive mutation at this locus have been associated with inherited forms of diabetes and congenital hypothyroidism.\(^{28-30}\)
- **MAFB:** In humans, MAFB expression increases 7–21 weeks and after that continued expression is seen in adult α and β cells.\(^{13,31}\)
Endocrine Cell Differentiation and Maturation

In humans, pancreatic hormone expression is first evident at about 8 weeks of gestation, with insulin being the first islet hormone to be formed; this is followed by the appearance of glucagon at around 9 weeks of gestation.\(^{13,32,33}\)

Transcription Factors Involved in β-cell Differentiation

- **NKX2.2**: It is first seen around 8 weeks in the developing α and β cells with increased expression around 14–16 weeks.\(^{11}\)
- **Insulin gene enhancer protein ISL-1 (ISL1)**: It is also known as ISLET 1 and is thought to be essential for the development of the pancreas in humans.\(^{33}\) A nonsense mutation in ISL1 seen in a Japanese diabetic patient points toward the potential role of ISL1 in pancreatic β cell development.\(^{33}\)
- **NEUROD1**: It is first expressed at 15 weeks and is found in all islet cell types.\(^{11-13}\) Heterozygous NEUROD1 mutation has been found associated with MODY 6 and neonatal diabetes as well (autosomal recessive).\(^{34,35}\)
- **PAX6**: Its expression is seen around 14–16 weeks and persists in all cells throughout adulthood.\(^{12}\) Single nucleotide polymorphism at PAX6 has been reported to result in decreased insulin sensitivity and response.\(^{36}\)
- **MAFA**: In humans, MAFA is nearly undetectable in the human pancreas from 7–21 weeks, after which it is almost exclusively seen to express in human pancreatic β cells.\(^{13,31}\) Decreased expression of MAFA in human pancreatic β cells has been proposed as a sign of dysfunctional cells.\(^{21}\)

The sequence of development and expression of the various transcription factors is of immense importance in the proper development of the pancreas, and as noted above, any deviation resulting from mutation can result in pancreatic agenesis or diabetes mellitus.

Stem Cell-derived Treatment for Diabetes

The advances made in recent years in the field of stem cell research have opened up avenues toward newer approaches in treating both T1D and T2D. These advances have led us one step closer to finding the cure for diabetes and is now a real and achievable goal.

Significant progress in the generation of β cells from human stem cells has been made in the last decade, and the defining strategy is to emulate the development pathway closely from pluripotency to β cell.\(^{21,37}\) Efforts have also been made to generate β cells that are capable of producing glucose stimulated Insulin secretion (GSIS).\(^{38-42}\)

We shall review in brief the current state of generating human embryonic stem cell (hESC) derived pancreatic islet cells.

Stem Cell Niche Optimization for Islet Structure Generation

In vivo, the β cells do not occur in isolation. However, they are parts of intricate 3-dimensional islets composed of numerous cells, as noted earlier, whose products exert a variety of autocrine and paracrine effects on each other. As opposed to rodent islets where there is homologous cell-cell contact with a core of β cells surrounded the other types of islet cells,\(^{43,44}\) the human islet has heterologous cell-cell contact with all the islet cell types found intermingled with one another.\(^{45}\) This arrangement has several implications, for example, the homologous contact in rodents facilitates synchronous and simultaneous insulin secretion from islet β cells, while in humans, and there is an asynchronous release of insulin.\(^{45}\) Recent data from cell sorting and sequencing also suggests the existence of distinct β cell types in human islet cells.\(^{46}\)

Another critical interaction occurring in the islet cells is the interaction with non-endocrine cells, including mesenchymal, neuronal, perivascular, and endothelial cells.\(^{47-49}\) The developing islet recruits several endothelial cells by the secretion of VEGF-A.\(^{50}\) These endothelial cells help form the basement membrane, which a critical modulator of β-cell function, growth, and survival.\(^{48,51-53}\) This intricate relationship between the β cells and the surrounding non-endocrine cells only strengthens the fact emulating the native β-cell niche will help improve the survival and function of hESC derived β cells in vitro.

Various efforts have been made to engineer the islet structure into “pseudo-islets” in vitro.\(^{54}\) Several studies have shown enhanced functionality of these reaggregated “pseudo-islets” in vitro or in vivo after transplantation. Penko et al.\(^{55}\) also showed improved GSIS with reaggregated “pseudo islets” with endothelial cells compared to pseudo-islets composed of β cells alone.

To summarize, more work is needed to determine the optimal islet microarchitecture that will attain the
maximum functionality and survival. One available option is the generation of niche cells themselves from the hESC or from induced pluripotent stem cells (iPSC). Another challenge is that pseudo-islets generation relies on the property of endocrine and non-endocrine to align themselves; this can perhaps be solved using 3-D printing techniques of islet tissue, allowing us to enforce the desired islet structure. The use of microfluidic devices, the so-called “organ on a chip” approach, may provide further sophistication and optimization of function.

Transplant Site

The site chose for the transplant also has a significant bearing on the survival as well as the functionality of the transplant, for example, in case of the engrafted islets stem-cell-derived or otherwise via infusion through the portal vein often require multiple infusions. Another factor which is of significant importance is that the islets infused into the portal vein are not retrievable, and this is of concern for the clinical translation of trials using hESC-derived β cells until it has been indisputably proven that the cells have developed into mature human islet cells and all the possibility of neoplastic transformation has been ruled out completely. While, at the present stage of development, the risk of development of the transplant into a teratoma cannot be ignored, but the optimization and the generation of fully differentiated islet and β cells can negate this concern.

Learning from the information gained from solid organ and islet cell transplant, it is evident that a more optimal site for the transplant is required. Several investigators are evaluating subcutaneous and intramuscular sites for islet transplantation to increase engraftment and also allow for removal of the graft in case of tissue dysfunction or transformation. Successful pancreatic transplant in T2D patients suggests that given an unlimited source of β cells and may provide a benefit in a vast majority of T2D patients.

Immune Modulation in β-cell Replacement Therapy

Alloimmune and autoimmune systems remain significant barriers to the more widespread application of cell replacement therapies for curative treatment in T1D as well as T2D. Lifelong treatment with immunosuppressive drugs offers a solution to this problem but is riddled with its new problems like side effects and toxicities.

Engineered Stem Cell-derived β-cell to Protect against Immune Rejection

One of the major unresolved issues with the stem cell-derived islet cells is the task of evading the immune system and preventing rejection. Immune rejection is an even bigger issue in T1D where the immune cells are already primed to attack self β cells and, therefore, more likely to attack the stem cell-derived β cells. Furthermore, an allogeneic immune response to the stem cell-derived islets poses another obstacle in both T1D and T2D recipients.

Stem cell technology offers unique solutions to engineer the β cells to evade the immune system. The development of revolutionary gene-editing tools like CRISPR/Cas9 system provides the possibility to dismantle MHCs in the hESCs and thereby to prevent the presentation of alloantigens. This strategy would also work against autoimmune-mediated β-cell destruction in T1D patients. T cell-mediated recognition of the MHC molecules is the root cause behind alloseimmunity. At the same time, in T1D patients, autoimmunity against transplanted β cells is dependent upon MHC class 1 expression on islet cells. Thus, the strategy of using the CRISPR/Cas9 technique to dismantle MHC 1 and 2 can lead to a reduction of the immune rejection process of the transplanted β cells.

The abolition of HLA expression can abate the alloimmune as well as an autoimmune reaction. However, still, the islet autoantigens from the graft can be presented by the host antigen-presenting cells (APCs), thereby activating the autoreactive T cells leading to islet injury and rejection. Control of NFκB activation by overexpressing A20 and suppressing STAT1 activation by overexpressing SOCS 1 may prove effective in controlling inflammatory cascade against the β cells. Additionally, using other immunomodulatory approaches like enhancing immune checkpoints via forced expression of PDL1, it may also be used for the protection of β cells against autoreactive T cells.

Also, to be considered are NK cells, which can be activated against the HLA ablated stem cell-derived β cells Class1 HLA are major ligands for NK inhibitory receptors. So, complete ablation of Clas1 HLA expression
on stem cell-derived islet cells may make them vulnerable to NK mediated killing. HLA-e and G are less Hla A, B, and C and can be expressed in islet endocrine cells; these molecules have a strong inhibitory effect on NK cells. By retaining HLA-E and G alleles intact while deleting HLA-A, B, and C, it might be possible to inhibit NK cells while keeping a reduction in T cell responses.

Cell Encapsulation Strategies
Despite earnest efforts to develop immune tolerant β cells through genetic manipulations as discussed earlier or other methods, there is still a high likelihood of autoimmune and alloimmune reactions against the transplanted stem cell-derived islet cells.

We could also use another approach by utilizing a semi-permeable membrane/capsule to deliver the transplanted β cells, which would protect the cells against immune derived reactions while at the same time allowing the transfer of sufficient mass of insulin secretions. This encapsulation strategy would also serve to protect the patient against any stem cell-derived β-cell oncogenic transformation. This idea of encapsulation has been a pipe dream for many years. However, the development of an optimal device remains an elusive dream as the semi-permeable membranes that protect the cells against the immune reactions are not sufficiently permeable to the nutrients needed for the viability of the cells.

The use of a suitable device membrane as a physical barrier between the recipient and hESC-derived β cells could potentially enable the use of these therapies while eliminating the use of immunosuppressants. An idle encapsulation device would be one which provides blood supply for sustenance, biocompatible, immunoprotective, allow secreted insulin to pass, contain any tumorigenic transformation.

Encapsulation Strategies in Clinics
Microencapsulation based strategy is perhaps the only device that has made any headway in clinics; it uses microcapsules made from alginate, 300–400 microns in diameter, which are used to encapsulate allogeneic islets. These were delivered intraperitoneally and reduced insulin requirements. One of the significant limitations to these devices has been the lack of oxygen one company Beta-O2 developed the bAir device, this device exogenous oxygen to the transplanted tissue. The device consists of a compartment, which contains islets that are encapsulated within an alginate hydrogel slab, which is adjacent to a gas chamber where cells obtain oxygen by diffusion through a gas-permeable membrane. This device contains ports to allow for daily refilling of oxygen. A single case report on the device usage reported islet survival with a modest reduction in insulin requirement for 10 months.

Two devices, the “theracyte” device and the “sensol” cell pouch, aim to revascularize a subcutaneous site before implantation of the device, and this increased vascularization is aimed at improving the survival of the cells.

Microfabricated Devices
The use of microfabricated silicon membranes can lead to the achievement of high precision control over pore sizes, as shown by nanoporous biocapsules and nanogland. The resultant pore size control could potentially allow separating soluble inflammatory mediators and also provide immunoprotection while allowing insulin secretion. The surface of the silicon membranes can further be selectively grafted with biocompatible polymer thin films to ensure functional performance over extended periods.

Conclusion
We stand at the cusp of technology where history can be made; the use of hESC derived islet cells to cure diabetes is no longer a distant dream but a tangible reality. The use of cutting edge technology like CRISPR/Cas9 to modulate the immune response, the use of 3-D printers to design and fabricate islet cells, use of microencapsulation devices hopefully in the near future will bring forth the dream of humanity of finding a cure for diabetes.

References


Abstract

Complications of type 2 diabetes are broadly classified as macrovascular and microvascular. This spectrum usually encompasses conditions like chronic renal disease, heart failure, and atherosclerotic heart disease. While the older classes of anti-diabetic agents have demonstrated benefit in terms of microvascular outcomes, newer anti-diabetic agents like SGLT2 inhibitors and GLP1RAs have gone one step ahead to demonstrate macrovascular benefits. Both these classes have demonstrated CV safety in CV outcome trials. GLP1RAs demonstrate CV benefits mainly due to reduced atherosclerosis. On the other hand, benefits of SGLT2i are derived due to reduction of heart failure. These benefits of both classes are attributed to mechanisms independent of glucose control. Based on the benefits demonstrated in the CV outcome trials, recent global guidelines like the ADA guidelines have favored the use of these drugs in diabetes patients with renal and cardiovascular risk.

Introduction

Type 2 diabetes is a metabolic disorder that affects nearly 10% of the global population. Its prevalence is predicted to increase in the coming years. It is now established that a long-standing diabetes patient would be at increased risk of macro- and microvascular complications. Cardiovascular (CV) disease is a leading cause of mortality in patients with diabetes. It is up to 2–4 times more common in patients with diabetes as compared to the ones without. The older agents that control hyperglycemia like the sulfonylurea, metformin, meglitinides, thiazolidinediones, and dipeptidyl peptidase inhibitors have shown improvements in microvascular outcomes. However, they fall short in reducing the morbidity and mortality associated with macrovascular disease. This vacuum is addressed by the newer antidiabetic classes, Sodium Glucose Cotransport-2 inhibitors (SGLT2i), and Glucagon like peptide 1 analogs (GLP analogs). These molecules have demonstrated cardioprotection and were associated with reduced CV outcomes in the cardiovascular outcome trials (CVOTs). The recent American Diabetes Association (ADA) guidelines recommend these newer classes in type 2 diabetes patients with chronic kidney disease (CKD) and CV disease after monotherapy with metformin, which remains the mainstay.

This review dissects the data available with SGLT2i and GLP analogs in terms of CV protection and throws light on the proposed mechanism for these benefits.

CVOTs with SGLT2i

In the EMPA REG CVOT, 7020 subjects were treated for a duration of 3.1 years. The composite primary CV outcome was lower in subjects receiving empagliflozin. Death from CV causes, deaths from any cause and heart failure hospitalization was significantly lower in empagliflozin arm compared to placebo. There was no difference between groups in the rate of stroke and myocardial infarction (MI).
In the CANVAS trial program (CANVAS plus CANVAS Renal) with canagliflozin, 10142 type 2 diabetes subjects at high risk for CV disease were followed up for a duration of 188.2 weeks. Subjects on canagliflozin had significantly low risk of non-fatal stroke, non-fatal MI and death from CV causes compared to those on placebo. However, there was an increased risk of amputations. CANVAS Renal was designed to detect the effects of canagliflozin on albuminuria. Subjects on canagliflozin had less frequent albuminuria progression. These effects of canagliflozin were more prominent in CANVAS Renal as compared to CANVAS.3

In the CREDENCE trial, type 2 diabetes patients with albuminuria and CKD with a GFR of 30–90 mL/min/1.73 sqm body surface area received either placebo or 100 mg of canagliflozin. At a follow-up of 2.6 years, CV events and risk of renal failure were lower in patients on Canagliflozin as compared to placebo.4

In the DECLARE TIMI CVOT with dapagliflozin, 17160 subjects were followed for a duration of 4.2 years. With respect to major adverse CV events, dapagliflozin met the criteria for non inferiority to placebo arm. Heart failure hospitalization rate or CV death rate was lower in dapagliflozin arm. This was due to the lower rate of heart failure hospitalizations.5

**CV Benefits of SGLT2i**

There are numerous mechanisms proposed to explain the beneficial effects of SGLT2i on heart. They may improve bioenergetics and cardiac metabolism due increased ketone production. Ketones are more efficient source of myocardial energy as compared to fatty acids. Ketones improve myocardial oxygen efficiency as it requires lesser oxygen for metabolism. Thus, it increases the efficiency of cardiac function.

Furthermore, SGLT2i causes hemoconcentration, thereby improving the oxygen delivery to tissues. Hemoconcentration and shift in the metabolic myocardial substrate have a synergistic effect. Natriuresis and osmotic diuresis reduce blood pressure (BP) and arterial stiffness resulting in favorable conditions for ventricular loading.

Investigations are underway to determine the effects of SGLT2i on cytokine production and modification of cardiac fibrosis.

SGLT2i in addition to CV diseases, reduce progression of albuminuria and nephropathy. The possible explanation of these benefits is due to reinstatement of the tubuloglomerular feedback. Reduction of intrarenal hypoxia has also been proposed as a mechanism for the beneficial effect on renal system.6

**CV Outcome Trials with GLP Analogs**

ELIXA CV outcome trial with lixisenatide was the first of the CVOT among GLP analogs. It was conducted in subjects with acute coronary syndrome (ACS) within 6 months of screening. 6068 subjects were followed up for 25 months. The study concluded that lixisenatide did not significantly change the rate of major CV outcomes in subjects with type 2 diabetes and recent ACS.7

Liraglutide in the LEADER CVOT was compared with placebo. The study had 9340 subjects with CV condition or CV risk factor who were followed up for 3.5 years. The primary composite outcome was significantly lower in the patients receiving liraglutide. In addition, secondary endpoints like death from CV causes and death from any cause were significantly lower in the liraglutide group.8

SUSTAIN 6 CVOT compared semaglutide versus placebo in type 2 diabetes subjects with CKD, CHF, pre-existing CV disease, or at least 1 risk factor for CV disease. 3297 subjects were enrolled and followed up for 2.1 years. Non-fatal stroke, non-fatal MI, and CV death rate were significantly lower in subjects receiving semaglutide versus placebo.9

The EXSCEL CVOT with once weekly exenatide showed no difference in major CV events incidence as compared to placebo.10

Albiglutide in HARMONY CVOT demonstrated its superiority over placebo in terms of major CV events.11

Composite CV outcome and non-fatal stroke were lower with dulaglutide in the REWIND CVOT when compared to placebo.12

CV risk profile of semaglutide (oral) was non inferior to placebo as shown in PIONEER 6 CVOT.13

To summarize, on one hand dulaglutide, albiglutide, subcutaneous semaglutide, and liraglutide demonstrated significant benefit in lowering the composite CV outcomes; oral semaglutide, weekly exenatide, and lixisenatide demonstrated non inferiority.14

**GLP Analogs: Beneficial Effects on Cardiovascular System**

**Glycemic Control**

GLP analogs are effective in reducing A1c. In addition to lowering A1c, they reduce glycemic variability (GV)
thereby reducing oxidative stress. This reduction of GV may explain its beneficial effects in CV disease.15,16

Hypertension

Dysglycemia and hypertension significantly raise the risk of stroke, heart failure, and MI. Data from trials have shown GLP analogs to reduce BP values. However, the mechanism behind the BP lowering is not clearly understood. Studies have shown that the fall in BP happens early (within 2 weeks of GLP analog initiation). Several potential mechanisms have been suggested. GLP1 receptor activation in renal system and arteries resulting in vasodilation and improved endothelial function might explain this effect. It is also hypothesized that the lowering of BP may be GLP receptor independent due to nitric oxide-mediated vasodilation.16

Dyslipidemia

Risks of CV episodes are much higher in patients with elevated low density lipoprotein (LDL) levels and diabetes. Even though the mechanisms are unclear, clinical trials have shown GLP analogs improve dyslipidemia. While, improvement of dysglycemia itself improves lipid profile due to reduction in hepatic synthesis of triglycerides and improved insulin sensitivity, reduction in triglycerides may also be due to reduced apolipoprotein B48 secretion mediated by intestinal mucosal GLP 1 receptors.16

Weight

It is a well-known fact that obesity is associated with both CV disease and type 2 diabetes. GLP analogs cause modest weight loss in addition to glycemic control thereby improving patient’s quality of life and functional activity.16

Other Benefits

In a preclinical study, liraglutide, a GLP analog improved endothelial function by inhibiting expression of vascular adhesion molecule and plasminogen activator inhibitor 1.17

Studies have demonstrated cardioprotective effect of liraglutide. In patients who underwent coronary angioplasty, smaller infarct size along with lower levels of high sensitivity C reactive protein, and superior myocardial salvage index were seen in liraglutide arm compared to placebo.18

Effects of GLP Analogs/SGLT2i in Patients at Increased CV Risk

A network analysis published recently showed that as compared to patients on placebo, GLP analogs reduced incidence of stroke. Among the GLP analogs, odds were lower with dulaglutide and semaglutide administered subcutaneously.19

SGLT2i reduced heart failure related hospitalization. This was seen with all the 3 SGLT2i (dapagliflozin, canagliflozin and empagliflozin).19

The all cause mortality was reduced by extended release exenatide, liraglutide, dapagliflozin, and oral semaglutide. Liraglutide, empagliflozin, and oral semaglutide have lesser odds of death from CV cause compared to extended release exenatide, sulphonylureas, dulaglutide, pioglitazone, dapagliflozin, DPP4 inhibitors, and canagliflozin.19

Impact of CVOTs on Guidelines

In the 2017 guidelines, ADA recommended to begin with metformin monotherapy and add any one of the non-insulin agents for dual therapy.20 However, these recommendations dramatically changed in the next 2 years to include GLP analogs/SGLT2i as add on to metformin in type 2 diabetes patients with atherosclerotic cardiovascular disease (ASCVD) or CKD.21

In addition, the European Society of Cardiology now recommends GLP analogs/SGLT2i should be considered as the first choice ahead of metformin in type 2 diabetes patients with high risk for CV disease or known CV disease.22

Exploring Uses/Potential Uses of SGLT2i

Obesity is an established risk factor for type 2 diabetes development. SGLT2i in addition to improving hyperglycemia, induces weight loss thereby targeting the pathogenesis of type 2 diabetes. Patients on SGLT2i excrete about 60–80 g of carbohydrates per day. As mentioned, the recent ADA/EASD guideline recommends these classes of drugs are for patients with type 2 diabetes with heart failure or CKD and those with established or high risk of ASCVD.

In addition, in patients without type 2 diabetes who have heart failure with reduced ejection fraction,
dapagliflozin has showed improved CV outcomes. This suggests that dapagliflozin may be used as a heart failure drug irrespective of whether the patient has diabetes or not. Furthermore, trials exploring its role in heart failure patients with preserved ejection fraction or CKD patients without type 2 diabetes are underway. SGLT2i are even being tried in type 1 diabetes concomitant to insulin therapy due to its insulin independent mode of action.23

**Conclusion**

Due to the results of CVOTs and the recommendations of international bodies,24 SGLT2i and GLP analogs are preferred agents in diabetes patients with established CV disease and risk factor for CV disease. A physician can choose either of the therapies in case of atherosclerotic CV disease. However, in the presence of comorbid conditions like renal disease or heart failure, SGLT2i should be preferred over GLP analogs. The approach toward these patients should be personalized. In diabetes patients with very high CV risk, instead of choosing between these 2 groups, combining these 2 therapies has been speculated.25

**References**

Abstract

The management of type 1 diabetes during adolescent period poses unique challenges. The period of adolescence has a great impact on type 1 diabetes and the disease per se puts huge demands on the adolescent boy or girl. Thus the disease and this critical phase of development influence each other. The glycemic control during this developmental phase is often suboptimal, mainly due to poor adherence to treatment and the hormonal changes of puberty, among other reasons. There is also higher risk for emergence of complications of type 1 diabetes during this phase, and hence it is recommended to begin screening for vascular complications at this period. Another challenge which emerge during this phase is the risk of indulging in the use of alcohol, smoking, and various illicit drugs, which can directly or indirectly impact the glycemic control and complications. Other issues to be addressed is with regard to sexual health with special emphasis on contraception and planned pregnancy. Finally, the transition from pediatric to adult care should be a planned process for optimal outcomes.

Introduction

According to WHO, adolescents are individuals in the age group 10–19 years. Individuals in 15–24 years age group are designated "youth." The term "young people" covers both adolescence and youth and includes 10–24 years. Emerging adulthood usually refers to the developmental stage between 18 and 30 years. WHO emphasizes that adolescence should be considered as a phase of development rather than a fixed time frame in an individual's life. It should be viewed as an important developmental phase, which witness the appearance of secondary sexual characteristics (puberty) to sexual and reproductive maturity, the development of mental processes and adult identity and the transition from total socioeconomic and emotional dependence to relative independence.

In this chapter, we shall be discussing the unique challenges in diabetes management during this phase of development.

What is the Effect of Adolescent Period on Type 1 Diabetes?

This will be discussed under following two headings:
- Effect of adolescence on Glycemic control
- Effect of adolescence on diabetes complications

Effect of Adolescence on Glycemic Control

Only about one-fifth of adolescents with type 1 diabetes meet the HbA1c goals set by American Diabetes Association (ADA) or International Society for Pediatric and Adolescent Diabetes (ISPAD).

The suboptimal glycemic control during adolescence is due to varied reasons such as:
- Erratic meal and exercise patterns
- Risk taking behaviors
- Poor adherence
- Hormonal changes during puberty

Studies have shown that females are more likely to have worsening of metabolic control during adolescence.
Of the reasons listed above, poor adherence to treatment regimens and hormonal changes during puberty are discussed in more detail below.

Why Adolescents with Diabetes show Poor Adherence to Treatment Regimens?

Adolescence is a critical phase in the development when the individual’s priorities change and they try to cope up with the competing demands of social life.

Some of the intrinsic features of diabetes, like chronicity, need for frequent blood glucose measurements and dietary restrictions put more emotional stress on the adolescent. The negative emotions (like feeling frustrated, hopeless, guilty, angry, fearful), which arise from living with and managing diabetes is referred to as diabetes distress. Diabetes distress is reported in about one-third of adolescents with diabetes and it negatively affects the self-management behaviors and glycemic control. Parents of type 1 diabetes are also at risk of developing diabetes distress.

Psychological comorbidities like depression, anxiety, and disordered eating behaviors are also prevalent in adolescents with diabetes. Elevated depressive disorders and depressive symptoms are reported in about 25% and anxiety disorders in about 20% of patients with type 1 diabetes. The most common disordered eating behavior seen in people with type 1 diabetes is omission of insulin in order to lose weight.

Several other factors like family dysfunction, difficult peer relationships, and poor school performance also act as hindrances to treatment adherence during adolescent period.

The consequences to poor adherence could be immediate in the form of hypoglycemia or ketoacidosis or medium to long term in the form of early appearance of microvascular complications, especially retinopathy and nephropathy. So ensuring adherence to medical and lifestyle measures should be part of the routine diabetes care in adolescents.

To improve the adherence, clinicians caring adolescents with diabetes should emphasize on:
- Maintaining a comfortable and mutually respectable relationship with the youth
- Negotiating treatment regimens with the adolescent, which are attainable and sustainable
- Building emotional strength

Allowing adolescents to express their feelings
- Encouraging the successful activities or gains undertaken by the adolescent

Hormonal Changes during Puberty and Insulin Resistance

During puberty, insulin resistance occurs irrespective of the presence of diabetes. Insulin resistance is worse during all stages of puberty, but worst during mid puberty. Euglycemic insulin-clamp studies have shown that insulin sensitivity falls by around 30% during mid puberty (Tanner stages 2–4) in non-obese non-diabetic children when compared with prepubertal children or older adolescents (Tanner stage 5) and adults. This fall in insulin sensitivity is more marked during Tanner stage 3, in girls and in those with higher BMI. Insulin resistance during this phase is due to higher growth hormone (GH) levels during puberty.

Presence of diabetes cause a further dip in insulin sensitivity, mainly through alterations in GH-IGF-1 axis.

GH-IGF-1 axis in type 1 diabetes (Fig. 1):
- **Decreased upregulation of hepatic GH receptor**: In normal physiology, insulin has a permissive role in mediating GH action. Hepatic GH receptor (GHR) expression is upregulated by insulin in the portal circulation. Thus, insulin promotes the hepatic generation of insulin like growth factor-1 (IGF-1) by GH. In type 1 diabetes, where there is low insulin in portal circulation, there is decreased upregulation of hepatic GH receptor. This causes a decrease in hepatic IGF-1 generation.
- **Increase IGFBP-1**: Insulin causes a decrease in Insulin like growth factor binding protein-1 (IGFBP-1). IGFBP-1 binds to IGF-1 and causes a reduction in free bioactive form of IGF-1. Hypoinsulinemia causes upregulation of IGFBP-1 and therefore more IGFBP-1 binds to IGF-1 causing reduction in free IGF-1.
- **Chronic inflammation**: Presence of chronic inflammation in type 1 diabetes further decreases IGF-1.

In summary, decreased upregulation of hepatic GHR, elevated IGFBP-1, and chronic inflammation in type 1 diabetes causes low IGF-1, which leads to GH hyperssecretion due to loss of negative feedback by IGF-1, which in turn leads to insulin resistance.
Increased risk of Dawn phenomenon during puberty: Insulin requirements increase during early morning hours, generally between 5 a.m. and 8 a.m. causing prebreakfast hyperglycemia. This is known as “Dawn phenomenon.” The reason for this is postulated to be due to increased nocturnal secretion of GH \(^1\) and insulin clearance during early morning hours. \(^12\) Since GH secretion is at its peak during mid to late puberty, risk for Dawn phenomenon is at its peak during this phase of development. This highlights the importance of increasing the availability of insulin during the dawn period.

Other factors contributing to insulin resistance: During adolescence, increase in BMI frequently occurs, especially in females. \(^13\) Increase in BMI further increases insulin resistance.

Sexual dimorphism in insulin sensitivity during adolescence: Some studies have shown sexual dimorphism in insulin sensitivity during adolescence, where increase in insulin resistance is more marked in females compared to males. \(^9,11\) This sexual dimorphism is seen during early adolescence and by the completion of puberty, both sexes have similar insulin requirement. This is thought to be due to earlier increase in adrenal androgens, estrogens, and GH in females.

Effect of Adolescence on Diabetes Complications

The period of adolescence is considered as high risk for the emergence of complications of type 1 diabetes due to various reasons like difficult to achieve optimum glycemic control and pubertal risk factors like alterations in GH-IGF-1 axis and insulin resistance.

The first signs of vascular complications of diabetes often appear during adolescence. Subclinical manifestations like early increases in urinary albumin excretion, retinal microvasculature changes, and subclinical changes in large blood vessels, like increased aortic and carotid intima media thickness and increased arterial stiffness, are common during this period.

Puberty Accelerates Diabetes Complications

The most important determinant of diabetic retinopathy and albuminuria is the duration of diabetes. But this
becomes apparent only after puberty. Evidence suggests that risk for vascular complications is greater in those with diabetes during puberty than in those who develop diabetes after puberty.

**Diabetic Retinopathy**

The importance of age at diagnosis of diabetes and risk of complications is exemplified by the higher risk of developing retinopathy in those diagnosed with diabetes before 14 years compared to those diagnosed during adulthood.\(^{15}\) Compared to adults with diabetes, adolescents are at greater risk of progression to more advanced stages like severe non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and/or diabetic macular edema, which are vision threatening.\(^{16}\) The progression may be more rapid in the background of poor glycemic control.\(^{16}\) Retinopathy can regress with improvement in glycemic control.\(^{17}\)

**Diabetic Nephropathy**

Increased albumin excretion ratio is seen in children after 11 years of age or after puberty compared to children less than 11 years or before puberty.\(^{18}\) The adolescent type 1 diabetes cardiorenal intervention trial (AddIT) showed increased cardiovascular risk (as suggested by higher lipid levels, arterial stiffness, increased aortic intima media thickness, and signs of impaired cardiac autonomic function) in adolescents aged 10–16 years with increased urinary albumin excretion levels.\(^{19}\)

One interesting observation is that the risk of developing microalbuminuria or retinopathy during adolescence is higher for girls than boys.\(^{20,21}\) But in adulthood, men carry a higher risk.

Based on the understanding of adolescence as a high-risk period for diabetes complications and puberty accelerating vascular complications in diabetes, International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening for vascular complications starting at 11 years of age or at the onset of puberty, whichever is earlier, if duration of diabetes is 2–5 years (Table 1).\(^{22}\)

**Alcohol, Smoking, and Illicit Drugs**

**Alcohol**

Rates of alcohol and other illicit substance use among adolescents (15–18 years) and young adults (18–25 years) with type 1 diabetes seem similar or slightly lower than their non-diabetic counterparts.\(^{23}\)

Alcohol intake typically causes delayed hypoglycemia, which occurs about 6–8 hours after intake. Alcohol also causes exacerbation of hypoglycemia unawareness. Initially hepatic glucose production is maintained by glycogenolysis, but once hepatic glycogen stores are depleted, delayed hypoglycemia occurs due to inhibition of gluconeogenesis. Alcohol is metabolized to acetaldehyde and then to acetone. This process increases NADH and decreases the availability of NAD+, which is a cofactor for...
gluconeogenesis. Gluconeogenesis is further reduced by the inhibitory action of alcohol on GH release.

Adolescents with type 1 diabetes should be encouraged to refrain from binge drinking. For prevention of alcohol induced hypoglycemia, it is advisable only to drink alcohol with carbohydrates, maintain good hydration, check blood glucose levels before bedtime, and have snacks before sleep. Another issue with alcohol intake is that hypoglycemia might be confused with intoxication.

Smoking
Among adolescents and emerging adults with diabetes, smoking increases the risk of microalbuminuria and cardiovascular risk. It is also associated with very early onset of peripheral neuropathy. A smoking history should be elicited at initial and follow-up visits. Discourage cigarette smoking including e-cigarettes in those who do not smoke and smoking cessation should be encouraged in active smokers. Adolescents should be provided with specific interventions, which can help them to quit smoking like nicotine patches and cognitive behavioral therapy.

Illicit Drugs
Illicit drugs like cocaine, amphetamine, MDMA (ecstasy) can increase the risk of diabetic ketoacidosis. These drugs may also alter brain functions making diabetes management difficult.

Driving
The main factor that increases the rates of driving accidents in type 1 diabetes is hypoglycemia. To reduce this risk, ensure the following:
- To prevent hypoglycemia during driving, monitor blood glucose before driving and ensure appropriate food intake
- Encourage stable metabolic control
- Regular visual check ups

Contraception
Education about the risks associated with unplanned pregnancy should be part of the routine care of adolescents with type 1 diabetes.

Barrier Methods
- Male condoms are highly effective against unintended pregnancy and STIs when used consistently and correctly.
- Female condoms and diaphragms are not recommended for adolescents.
- Coitus interruptus is associated with a high pregnancy rate and is not recommended.

Long Acting Reversible Contraceptions (LARC)
- LARCs include intrauterine devices (IUDs) and implantable rods. They can be considered as first-line contraceptive choice for adolescents even if they are nulliparous.
- The contraceptive effectiveness of implantable rods and hormonal IUDs are better than that of oral contraceptives.
- Non-hormonal IUDs may be considered if hormonal contraception is contraindicated.
- LARC methods neither protect nor increase the risk of STIs.

Combined Hormonal Oral Contraceptives
- Patients with duration of diabetes less than 20 years and without micro- or macrovascular complications may use any hormonal method.
- Combined oral contraceptives (COCs) should be avoided in patients with diabetes more than 20 years or having micro- or macrovascular complications. They may use IUDs, progestin only methods or barrier methods.
- No unfavorable effects on weight, metabolic control, or lipid profile have been seen with newer oral contraceptives containing lower dose of estrogen (<35 mcg ethinyl estradiol) and newer progestins.
- Monitor blood pressure and side effects like headache, breast change, mood changes, and genital infections in young people taking oral contraceptives.

Sexual Health
Adolescent girls with diabetes should be counselled regarding following aspects of sexual health:
- Contraceptive practices
- Precautions to avoid STIs
- The importance of planned pregnancy
Hormonal Injectables

- Depot medroxyprogesterone acetate injections are not recommended in adolescents with type 1 diabetes as it has been associated with reduction in bone mineral density.27
- For type 1 diabetes patients with erratic lifestyle and at high risk of pregnancy, monthly injections of combined hormonal contraceptives may be considered if they do not have access to LARC methods. But the safety data on type 1 diabetes patients is not available.

The WHO eligibility criteria of contraceptives in women with type 1 diabetes (Table 2) may be used as a guide to choose the right contraceptive for the right patient.

Transition from Pediatric to Adult Care

Society for Adolescent Health and Medicine defines transition as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems."28

The transition period from pediatric to adult care is associated with deterioration of metabolic control, increased occurrence of acute complications, emergence of chronic complications, and psychosocial, behavioral, and emotional challenges.2,29

Pediatric health-care providers should ideally begin to prepare the teen for transition to adult health care during early adolescent years and no later than 1 year prior to the transfer.2

Conclusion

Management of type 1 diabetes in adolescence poses unique challenges. Glycemic control during this developmental phase is difficult due to the complex interaction of various physiological, psychosocial, and psychological factors. Adolescence is also a high-risk phase for development of diabetes complications, so screening for the same should begin during this period. Adolescents should be counseled regarding the effects of alcohol, smoking, and other illicit drugs on the disease course. Advice on safe contraceptive practices should be part of routine diabetes care. Transition from pediatric to adult care should be gradual planned process with proper coordination between pediatric and adult health-care providers.
References

Abstract
Hypoglycemia is an important entity causing the morbidity and mortality in patients with or without diabetes. This chapter deals with the risk factor, pathogenesis, and causes of hypoglycemia. The urgent treatment and long-term management are also discussed in detail. This chapter also deals with psychiatric aspect of hypoglycemia mimic. Physicians should have an open mind in finding the cause as well as aim should be decreasing the recurrence of hypoglycemia episodes.

Introduction
Hypoglycemia is a state of glucose deficiency which presents with episodic symptoms. Dysregulation of glucose regulatory mechanisms leads to development of hypoglycemia. The most common cause is drugs that are used to treat diabetes. Whipple’s triad is used to document hypoglycemia (Flowchart 1). The lower limit of the fasting plasma glucose level is approximately 70 mg/dL. Normally, during pregnancy and during prolonged fasting (>24 hours), lower venous glucose levels occur. Hypoglycemia can be fatal if severe and should be suspected in a patient with confusion, altered sensorium or seizure.1

Etiology of Hypoglycemia
Hypoglycemia is caused by drugs (including anti-diabetic drugs), alcohol, sepsis, critical organ failure, inanition, non-β-cell tumors, hormone deficiencies, prior gastric surgery, and insulinoma. More elaborate causes are discussed in Table 1. Hypoglycemia can also be broadly classified into hypoglycemia in diabetes and in non-diabetes conditions. Table 2 enlists causes of errors of metabolism which cause hypoglycemia.

Medications other than anti-diabetic drugs which commonly cause hypoglycemia are—Pentamidine (systemic), Trimethoprim-sulfamethoxazole, and renal failure, Propoxyphene and renal failure, Quinine, Quinidine, Salicylates, and renal failure.

Clinical Features
The symptoms are adrenergic symptoms and neurological symptoms. Adrenergic symptoms are shakiness, trembling, anxiety, nervousness, palpitations, tachycardia, calmness, sweating, dry mouth, hunger, pallor, and pupil dilation.
Diabetes Mellitus

**TABLE 1** Causes of hypoglycemia in adults

<table>
<thead>
<tr>
<th>Medicated or ill individual</th>
<th>Seemingly well individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs: Insulin/insulin secretagogue, alcohol, others</td>
<td>Endogenous hyperinsulinism: Functional β-cell disorders (nesidioblastosis) — Non-insulinoma pancreatogenous hypoglycemia, Insulinoma, Insulin autoimmune hypoglycemia — Ab (antibody) to insulin, Post-gastric bypass, Ab to insulin receptor, Insulin secretagogue, other</td>
</tr>
<tr>
<td>Critical illness: Hepatic, renal/cardiac failure, inanition, sepsis</td>
<td>Disorders of gluconeogenesis and fatty acid oxidation</td>
</tr>
<tr>
<td>Hormone deficiency: Cortisol, growth hormone, glucagon, epinephrine</td>
<td>Exercise</td>
</tr>
<tr>
<td>Non-islet cell tumor (e.g., mesenchymal tumors)</td>
<td>Accidental, malicious, or surreptitious hypoglycemia</td>
</tr>
</tbody>
</table>

**TABLE 2** Hypoglycemia caused by inborn errors of metabolism

<table>
<thead>
<tr>
<th>Fasting hypoglycemia</th>
<th>Postprandial hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen storage disease (GSD) type 0</td>
<td>Glucokinase, SUR1, and Kir6.2 mutations</td>
</tr>
<tr>
<td>GSD type I</td>
<td>Congenital disorders of glycosylation</td>
</tr>
<tr>
<td>GSD type III</td>
<td>Inherited fructose intolerance</td>
</tr>
<tr>
<td>GSD type IV</td>
<td>Exercise-induced hypoglycemia</td>
</tr>
<tr>
<td>Fanconi-Bickel syndrome</td>
<td>Increased β-cells monocarboxylate transporter 1 activity</td>
</tr>
<tr>
<td>Fatty acid oxidation defects</td>
<td>Glucoseoneogenesis defects (fructose-1, 6-bisphosphatase)</td>
</tr>
</tbody>
</table>

Neurological presentations are irritability, paresthesia, headaches, difficulty in thinking/speaking, confusion, abnormal mentation, slurred speech, diplopia, ataxia, seizures, stupor/coma. Neuroglycopenic manifestations are direct result of CNS glucose deprivation. Cholinergic symptoms which are mediated by Ach such as hunger, sweating, and paresthesia are seen. These are from sympathetic postganglionic neurons. Heart rate and SBP are typically increased. These changes are blunted in a person who has suffered recent and repeated hypoglycemia episodes. Occasionally transient focal neurologic deficits occur. Permanent deficits are rare.

**TABLE 3** Anti-diabetic drugs and hypoglycemia

<table>
<thead>
<tr>
<th>Hypoglycemia causing</th>
<th>Does not cause hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Metformin</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Glinides</td>
<td>α-glucosidase inhibitors</td>
</tr>
<tr>
<td>Glucagon-like peptide 1 (GLP-1) receptor agonists</td>
<td>Dipeptidyl peptidase IV (DPP-IV) inhibitors</td>
</tr>
</tbody>
</table>

**Differential Diagnosis of Symptoms of Hypoglycemia**

Many conditions are associated with episodes of symptoms similar to symptoms of hypoglycemia. These are Anxiety neurosis, Dumping syndrome, Thyrotoxicosis, Drugs (varenicline, decongestants, stimulants, and street drugs), Angina pectoris, autonomic neuropathy, renovascular hypertension, pheochromocytoma, withdrawal symptoms, hypogonadism, carcinoid syndrome, syncope and postural hypotension (including POTS), angina, cardiac arrhythmia, seizure disorders, atypical migraine, vertebral and ICA diseases, and psychiatric disorders.

**Hypoglycemia in Diabetes**

Recurrent morbidity is caused by hypoglycemia in most patients with type 1 diabetes and in many with advanced type 2 diabetes. It precludes the maintenance of euglycemia over a lifetime of diabetes and thus full realization of microvascular benefits of glycemic control. By producing hypoglycemia–associated autonomic failure, it also causes a vicious cycle of recurrent hypoglycemia—i.e., the clinical syndromes of defective glucose counter regulation and of hypoglycemia unawareness. Mortality rate of hypoglycemia is approximately 6–10% in T1DM. The hypoglycemia incidence is lower in T2DM than in T1DM (Table 3).

The risk factors for hypoglycemia in diabetes are identified whether relative or absolute insulin excess is the sole determinant of risk (Box 1).

**Hypoglycemia-associated Autonomic Failure (HAAF)**

In diabetes mellitus iatrogenic hypoglycemia is often a consequence of interaction between relative/absolute
therapeutic insulin excess in addition to compromised physiologic and behavioral defenses against decreasing glucose levels. Dysfunctional counter-regulatory mechanisms compromise physiologic defense (especially decrements in insulin and increments in glucagon and epinephrine), and behavioral defense is compromised by hypoglycemia unawareness (ingestion of carbohydrate).

**Hypoglycemia Unawareness**

Hypoglycemia unawareness is caused by the diminished sympathetic response, that is, majorly the decreased sympathetic neural response to hypoglycemia—i.e., loss of the warning autonomic symptoms that earlier allowed the patient to acknowledge developing hypoglycemia and thus to end the episode by eating carbohydrates. These patients are at sixfold higher risk of severe hypoglycemia by the intensive diabetes therapy.3

**Evaluation of Hypoglycemia**

**Hypoglycemia Evaluation in DM Patients**

Hypoglycemia is worrisome in a diabetic patient when the plasma glucose concentration on self monitoring is falling rapidly or ≤70 mg/dL (3.9 mmol/L). Glycemic control is advised to have long-term microvascular benefit in a diabetic patient but strict monitoring to be adhered to prevent hypoglycemia. Adjustment in treatment regimens are recommended for prevention of hypoglycemia in diabetes (Box 2).2

The typical risk factors and compromised defenses should be evaluated in recurrent treatment-induced hypoglycemia (Table 4).

**Hypoglycemia Evaluation in Patients without DM**

The history, physical examination, and all relevant laboratory data inferring to specific disorders like drugs, hormone deficiencies, critical illnesses, non-islet cell tumors must be reviewed. To ascertain the cause of hypoglycemia in an apparently well individual—plasma glucose, insulin levels, C-peptide levels, proinsulin levels, insulin antibodies, and β-hydroxybutyrate levels should be measured. Screen for intake of oral hypoglycemic agent (OHA) during spontaneous hypoglycemia episode and observe the response to glucagon 1.0 mg intravenously. These will differentiate endogenous versus exogenous causes.4,5

Two/three weeks of meticulous avoidance of hypoglycemia is advised in patients with known hypoglycemia unawareness with the probability that awareness of hypoglycemia will be back in most of them.

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**BOX 1**

**Causes of relative/absolute insulin excess**

- Insulin (insulin secretagogue) doses are ill-timed/excessive/of wrong type
- The influx of exogenous glucose is decreased (e.g., during an overnight fast, periods of temporary fasting, or after missed meals/snacks)
- Increased insulin-independent glucose utilization (e.g., during exercise)
- Increased sensitivity to insulin (e.g., with improved glycemic control, late after exercise, in the middle of the night, or with increased fitness/weight loss)
- Reduced endogenous glucose production (e.g., after alcohol ingestion)
- Reduced insulin clearance (e.g., in renal failure)

**BOX 2**

**Hypoglycemia prevention in diabetes**

- Diabetes self-management (supported by education and empowerment)
- Frequent self-monitoring of blood glucose
- Flexible and appropriate insulin/insulin secretagogue regimens
- Individualized glycemic goals
- Ongoing professional guidance and support
- Consideration of each of the known risk factors for hypoglycemia

**TABLE 4**

<table>
<thead>
<tr>
<th>Conventional risk factors</th>
<th>Compromised defenses against hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive/ill-timed dosing of insulin/secretagogue</td>
<td>Endogenous insulin deficiency degree</td>
</tr>
<tr>
<td>Wrong type of insulin/insulin secretagogue</td>
<td>Severe hypoglycemia history</td>
</tr>
<tr>
<td>Conditions which reduce exogenous glucose delivery or endogenous glucose production</td>
<td>Hypoglycemia unawareness</td>
</tr>
<tr>
<td>Increased glucose utilization</td>
<td>Recent antecedent hypoglycemia</td>
</tr>
<tr>
<td>Increased sensitivity to insulin</td>
<td>Prior exercise or sleep</td>
</tr>
<tr>
<td>Decreased insulin clearance</td>
<td>Lower glycemic goals per se</td>
</tr>
</tbody>
</table>
In cases where a spontaneous hypoglycemic episode is not observed, the circumstances which will lead to symptomatic hypoglycemia are recreated. One such method is a fast of up to 72 hours after a mixed meal. The findings of this test is—
- symptoms, signs, or both; with
- glucose plasma concentrations <55 mg/dL (3.0 mmol/L)
- insulin of 3.0 μU/mL (18 pmol/L) at least
- C-peptide of 0.6 ng/mL (0.2 nmol/L) at least
- proinsulin of 5.0 pmol/L document endogenous hyperinsulinism at least
- β-hydroxybutyrate levels of ≤2.7 mmol/L and rise in plasma glucose of 25 mg/dL (1.4 mmol/L) at least after IV glucagon indicate mediation of the hypoglycemia by insulin (or by an IGF)

In cases of documented fasting/PP endogenous hyperinsulinemic hypoglycemia, no circulating insulin antibodies, and negative screening for OHA suspect insulinoma. Imaging techniques used are CT or MRI, transabdominal and endoscopic ultrasonography, and selective pancreatic arterial calcium injections with insulin levels in hepatic vein measurement (Table 5).

Anxiety and Hypoglycemia
Anxiety associated with depression is quite commonly studied in those with diabetes mellitus. Specific phobias, in particular needle injection and fear of hypoglycemic episode, are commonly seen in those patients who are on insulin therapy. Hypoglycemic phobia is a very important aspect of treatment in diabetes as these group of patients are more likely to miss glucose monitoring or insulin administration. They might also maintain chronic hyperglycemic state because of the fear of hypoglycemic episode. Clinical features shared by both hypoglycemia and anxiety are sweating, tremor, anxiety, confusion, and tachycardia. This could lead to a diagnostic challenge. Those with long standing anxiety disorder the likelihood of missing warning signs of hypoglycemia are more. Medications for management of anxiety disorders—SSRIs, benzodiazepines, and beta-adrenergic blockers could interfere with glycemic control and physiological warnings of an hypoglycemic episode.

Alcohol Use and Hypoglycemia
Prevalence of alcohol use is around 50% in diabetics. Most common and a serious concern associated with alcohol use in diabetes is hypoglycemia. It includes a spectrum of alcohol-induced fasting hypoglycemia, potentiation of drug-induced hypoglycemia/reactive hypoglycemia in susceptible patients (Box 3).
it stimulates insulin secretion. Octreotide (somatostatin analogue) can be used in SU-induced hypoglycemia to suppress insulin secretion. These treatments raise plasma glucose and patients should eat soon to replete glycogen stores.

**Prevention of Recurrent Hypoglycemia**

This approach requires identification of cause of hypoglycemia. Discontinuation of offending drugs or reduction of their doses. Hypoglycemia caused by SU can persist for hours or days. Treatment of underlying critical illnesses should be prompt. Replacement of deficient cortisol and growth hormone. If the tumor cannot be cured surgical, chemotherapeutic, or radiotherapeutic reduction of a non-islet cell tumor can provide relief from hypoglycemia. In such patients glucocorticoid or growth hormone administration also may decrease hypoglycemic episodes. Surgical resection of an insulinoma is curative. Diazoxide/octreotide medical therapy can be used if resection is not advised. Also useful in people with a non-tumor β-cell disorder along with partial pancreatectomy. Autoimmune hypoglycemia treatment is difficult but these disorders are self limited sometimes. Treatment with glucocorticoid or immunosuppressive drugs is tried. Frequent feedings and avoidance of fasting should be followed if these treatments fail. In some patients administration of uncooked cornstarch at bedtime or an overnight intragastric infusion of glucose may be required.

**Conclusion**

Diagnosis of hypoglycemia by Whipple’s triad is well established. Broadly approach to evaluate hypoglycemia is based on the patient’s diabetes status and exogenous/endogenous factors. Prompt diagnosis and prompt treatment are the key to save permanent neurological damage in a patient with severe hypoglycemia. Avoidance of precipitating factors and patient counseling are very important aspects of reduced morbidity and mortality.

**References**

3. Reduced Awareness of Hypoglycemia in Adults with IDDM: A prospective study of hypoglycemic frequency and associated symptoms | Diabetes Care [Internet]. [cited 2020 Jul 7]. Available from https://care.diabetesjournals.org/content/18/4/517.short