

CHAPTER

85

## *“Prediabetes” - Early detection and interventions*

**M. V. Jali**

### **Introduction**

Diabetes is a global epidemic and it has been posing a biggest threat ever witnessed with devastating human, social and economic consequences. The disease claims as many lives per year as HIV/AIDS and places a severe burden on healthcare systems and economies everywhere with heaviest burden falling on low- and middle-income countries.<sup>1</sup> Diabetes Mellitus (DM) is a metabolic disorder of multiple etiologies that is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from the defects of insulin secretion, insulin action, or a combination of both.<sup>2</sup>

Type 1 diabetes is due to a virtually complete lack of endogenous pancreatic insulin production, whereas in type 2 diabetes, the rising blood glucose results due to a combination of genetic predisposition, unhealthy diet, physical inactivity, and increasing weight with a central distribution of abdominal adiposity resulting in complex patho-physiological processes under the shadow of environmental factors too. DM is associated with the development of specific long-term organ damage due to micro-vascular related diabetes complications. Patients with diabetes are also at a particularly high risk for cardiovascular, cerebrovascular, and peripheral artery disease.<sup>3</sup>

It is estimated that 246 million people worldwide have diabetes,<sup>1, 2, 4</sup> representing roughly 6% of the adult population (20-79 age group) and the number is expected to reach some 380 million by 2025, representing 7.1% of adult population (International Diabetes Federation-IDF). Perhaps, even greater concern is the simultaneous dramatic increase in the number with Prediabetes. This is occurring not only in adults but, in so far poorly quantified number, of children and adolescents is a great concern.

### **Prediabetes<sup>3</sup>**

it is also called impaired glucose tolerance (IGT), or impaired fasting glucose (IFG), depending on the test used to diagnose it. Prediabetes is a precursor condition to type 2 diabetes, and it is characterized by higher normal blood glucose levels. The transition from the early metabolic abnormalities that precede diabetes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes may take many years. However, current estimates indicate that most individuals (perhaps up to 70%) with these pre-diabetic states eventually develop diabetes.<sup>4, 5</sup> At some stage in the pre-diabetic state, the risk of a Cardio-Vascular Disease (CVD) event is modestly increased.<sup>6</sup>

Between 1997 and 2006, eight major clinical trials examine whether lifestyle or pharmacologic interventions<sup>7</sup> would prevent or delay the development of diabetes in populations at high risk by virtue of having IFG and/or IGT. The study populations often had other recognized risk factors for diabetes including obesity, a prior history of gestational diabetes, or a positive family history of diabetes.<sup>8</sup> All of these trials demonstrated reductions in the development of diabetes of 25 to 60% over the period of follow-up. The largest reductions (60%) were accomplished with lifestyle interventions aimed at weight loss and increasing physical activity and with thiazolidinediones.<sup>9, 10</sup> Lesser degrees of reduction (25 to 30%) have been achieved with other drugs.<sup>11</sup> The availability of intervention<sup>3</sup> that have been shown to decrease the development of diabetes has enthused consideration, whether such interventions should be recommended and implemented, in whom, and under what circumstances.

### History about Prediabetes

Although the exact origin of the term 'Prediabetes' is imprecise, the earliest known mention was made by Maranon<sup>12</sup> in the early 1940's, later in humans by Camerini-Davalos<sup>13</sup> in 1951 in relation to pregnancy. In the 1960's, 'Prediabetes' was more familiarly used to describe patients with no glycosuria and a usually normal fasting blood sugar level, but having a diabetic abnormality in standard glucose tolerance tests. In contrast and around the same time, the British Diabetic Association recommended that 'Prediabetes' should only be used retrospectively to describe the life of a diabetic before their diagnosis was confirmed.

The World Health Organization replaced the term 'Prediabetes' in the 1980's with statistical risk classes. The term impaired glucose tolerance (IGT) was developed in 1979-1980 (WHO)<sup>4</sup>, and it was only later in 1997 and 1999 (American Diabetes Association (ADA) and WHO<sup>4, 14</sup> that the term impaired fasting glucose (IFG) was brought into use.

'Prediabetes',<sup>14</sup> as it is currently known, owe its re-birth to Tommy G Thompson, the US Secretary of State for Health, in 2002. It was basically used to describe people with either IGT or IFG, in an attempt to warn Americans of their high future risk of developing diabetes. This modern use of 'Prediabetes' solely relates to people with IGT and IFG. Some people have both IFG and IGT. IFG is a condition in which the blood sugar level is high (100 to 125 milligrams per deciliter or mg/dL) after an overnight fast but not high enough to be classified as diabetes. The former definition of IFG was 110 mg/dl to 125 mg/dl. IGT is a condition in which the blood sugar level is high (140 to 199 mg/dL) after a 2-hour oral glucose tolerance test, but is not high enough to be classified as diabetes<sup>15</sup>.

### “Prediabetes” -- What's in a Name?

The term Prediabetes (which embraces impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]) has had a make sure history, as Professor George Alberti described in the opening lecture of the 1<sup>st</sup> International Congress on Prediabetes and the Metabolic Syndrome,<sup>16</sup> held in Berlin during 2005. On the one hand, it may be inappropriate to use the term Prediabetes when there is only a 50% chance of developing diabetes in the next 10 years following diagnosis. Moreover, the definition of Prediabetes does not include some people at risk of developing diabetes, such as those with a family history of diabetes or other normoglycemic risk groups of certain ethnic origins. On the other hand, the American Diabetes Association (ADA)<sup>17</sup>, and other national organizations recognize the difficulty of communicating to the general public the concept of a high-risk situation, and the term Prediabetes is certainly easier to promote than IGT and/or IFG.

Prediabetes is a relatively new clinical diagnosis and the new term<sup>15</sup> when introduced in 2002 by the Department of Health and Human Services (DHHS) and ADA, the sole reasons for renaming Prediabetes from its former clinical name of impaired glucose tolerance was to highlight the seriousness of the

**Table 1**

All diabetes and IGT	2003	2025
Total world population (billions)	6.3	8.0
Adult population (billions) (20-79 years)	3.8	5.3
Number of people with diabetes (millions) (20-79 years)	194	333
World diabetes prevalence (%)	5.1	6.3
Number of people with IGT (millions) (20-79 years)	314	472
IGT prevalence (%) (20-79 years)	8.2	9.0

Table 1 : 3<sup>rd</sup> edition, (IDF-Diabetes Atlas, International Diabetes Federation, 2006)

condition and to motivate people to get appropriate treatment. Revised definition means millions more have “Pre-Diabetes”. “Pre-diabetes” -- a condition that raises a person’s risk of developing type 2 diabetes, heart disease, and stroke.<sup>7,17</sup> The U.S. Department of Health and Human Services (DHHS) and the American Diabetes Association (ADA) estimated that 41 million Americans between the ages of 40 years to 74 years are living with Prediabetes, and most remain unaware of their condition. Without intervention and appropriate treatment, people with Prediabetes are at risk for developing type 2 diabetes within 10 years.<sup>16</sup>

“Prediabetes” and the Metabolic Syndrome are extremely prevalent and persons with “Prediabetes and the Metabolic Syndrome”<sup>16</sup> are at high risk for diabetes and CVD and they are the ideal target population for prevention or intervention programmes. In 2005, ‘Prediabetes’ was given a global overview,<sup>14</sup> in terms of isolated impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), or a combination of the two, and highlighted the necessity to conduct an oral glucose test before diagnosing IGT. Prevalence data from a number of countries has generally found that IGT is more prevalent than IFG.

**The epidemiology of Prediabetes**

On a global level,<sup>2</sup> the type 2 diabetes epidemic in 2025 will comprise 97 million known cases, and an

**Table 2 : South East Asia – diabetes prevalence and future projections<sup>1</sup>**

	2003	2005
Total Adult Population (millions)	705	1081
No. with Diabetes (millions)	39.3	81.6
Diabetes Prevalence (%)	5.6	7.5
No. with IGT (millions)	93.4	146.3
IGT Prevalence (%)	13.2	13.5

Table 2 : 3<sup>rd</sup> edition, (IDF-Diabetes Atlas, International Diabetes Federation, 2006)

equivalent number of unknown cases, with around 314 million people having IGT. By 2025, IGT is estimated that this will rise to approximately 500 million people raising concerns about a potential cardiovascular epidemic. (Table 1)

From global projections<sup>14</sup> the major changes will occur in Eastern European states, the Middle East and India. Between 10% and 25% of western populations may already have IGT. For example, in the 2000, Australian Diabetes, Obesity and Lifestyle Study,<sup>18</sup> the overall prevalence of diabetes was 7.4%, but the combined prevalence of IFG and IGT was more than twice as high, at 16.4%. These glucose-intolerant, but non-diabetic, individuals represent a reservoir of potential new diabetes cases. Approximately 4 to 9% of individuals with impaired glucose tolerance go on to develop type 2 diabetes each year. Declining levels of physical activity, increasing caloric intake and consequent rises in the rate of obesity are leading to increase in the number of people with IGT from most ethnic and cultural backgrounds.<sup>16</sup> Countries in the Middle East and Gulf States<sup>16</sup> too have a high prevalence of IGT, as does India and China<sup>19</sup> (Table 2). More than 50% of people with diabetes will come from Asia over the next decade.<sup>14</sup> In developed countries, the major increase in the number of people with diabetes will be among the young and middle-aged. However, additional data from Drs Söderberg and Ramachandran from Sweden and India, respectively, suggest that the ‘Prediabetes’ epidemic of IGT / IFG may be reaching a plateau in certain countries.<sup>16</sup> In addition, gender differences are evident between IGT and IFG with women

generally having a higher prevalence rate of IGT whilst men have a higher prevalence of IFG. On the contrary, the prevalence of IGT is higher in women than men in all age groups except over the age of 60 in Asian populations and over the age of 80 in the European groups.<sup>18, 19</sup> The unabated rise in the prevalence of childhood obesity has been accompanied by the appearance of a new pediatric disease, type 2 diabetes. Little is known about IGT in pediatrics.<sup>41</sup> In adding up to differences in the overall prevalence between IGT and IFG, there are now clear evidence of differences in phenotype between the two categories. Genetic marker Studies in South Indians showed the complex nature of genetic pathology in type 2 diabetes. Certain mutations of candidate genes related to insulin secretion and insulin action such as Calpain 10, Vitamin D, Insulin receptor substrate-1, UCP2, UCP3, Apo-lipoprotein D gene are associated with the disorder. However; the nature of the major gene(s) responsible for the disease remains elusive.<sup>20</sup>

IGT and IFG are not equivalent metabolically, and it is therefore not surprising that there are differences in their prevalence and in the people categorized as having one or the other. In most populations, IGT is considerably more prevalent than IFG.<sup>16, 19</sup> Furthermore, there is limited overlap between the categories - the majority of people with IGT do not have IFG, and the majority with IFG do not have IGT. Hence, the terminology of **'isolated IGT'** and **'isolated IFG'** has been given.<sup>3</sup> Thus, IFG and IGT identify substantially different segments of the population with impaired glucose regulation (Table 3). The mechanisms of IGT and IFG are likely to be different; IFG is thought to be associated with a defect in insulin secretion whilst IGT is thought to be associated with hyperinsulinemia or insulin resistance. Thus 'Prediabetes' may encompass two different mechanisms of disease, necessitating the need for further research into both the mechanism and outcome of these two states.

## Significance of IFG and IGT in Indians

One of the earliest studies in India<sup>21</sup> during 1986-87, in an urban population in a township in south India, the prevalence of 5% had diabetes and 14 had impaired glucose tolerance. A family history of diabetes was present in 16 of the 34 subjects with diabetes and nine of the 15 with impaired glucose tolerance. India has the highest number of IGT, prevalence of IGT and IFG are also high in India and south-east Asia in general.<sup>16, 19</sup> which is expected to increase from 85.6 million (2003) to 132 million by 2025.

## Prediabetes: Early recognition, its clinical significance and risks

As mentioned in the introduction, these early stages of glucose intolerance (Prediabetes) are not only forerunners of diabetes but also carry high risk for cardiovascular diseases. Indians have high insulin resistant background in adding together to the presence of all other cardiovascular risk factors. IGT occurs at a much younger age in Indians<sup>19</sup> and they are predisposed to get diabetes more or less a decade prior as compared to the rest of the high risk population worldwide.

Early recognition is of extreme importance in initiating early interventions to stop the onset of diabetes related complications. Prediabetes is diagnosed with one of two blood tests—a fasting plasma glucose test or a two-hour oral glucose tolerance test (OGTT). The fasting plasma glucose test requires an eight-hour fast (no food or drink except water), after which a blood draw is performed. It is usually done in the morning. For an oral glucose tolerance test, a patient is given a drink of 75 grams of glucose, and a blood draw is taken two hours later. The following laboratory values are the American Diabetes Association (ADA) practice guidelines for the diagnosis of Prediabetes and Diabetes.<sup>17</sup> (Tables : 3 & 4)

1. An oral glucose tolerance test plasma glucose value between 140 and 199 mg/dl (7.78 - 11.06 mmol/l) at 2 hours post-glucose load (indicating impaired glucose tolerance).

**Table 3 : Diagnostic Blood Sugar Values**

<b>Normal</b>
FBG : 70 to 99 mg/dL
OGT : Under 140 mg/dL
<b>Prediabetes</b>
FBG : 100 to 125 mg/dL
OGT : 140 to 199 mg/dL
<b>Diabetes</b>
FBG : 126 mg/DL and higher
OGT : Higher than 200 mg/dL

- The ADA recommends that men and women age 45 and older, especially those that are overweight (i.e., BMI of 25 or higher), be screened for Prediabetes.
- Screening should also be considered in individuals younger than 45 if they are overweight and have one or more additional risk factors.
- If testing is positive for Prediabetes, a follow up test should be performed on a subsequent day to confirm the diagnosis.
- People with diagnosed Prediabetes should receive regular retesting every one to two years to monitor for type-2 diabetes. Individuals with a normal screening result can be retested every three years.

**Criteria for the Diagnosis of Diabetes\*. (Normoglycemia, IFG or IGT Diabetes)<sup>17</sup>**

FPG < 100 mg/dl (5.6 mmol/L) = Normal fasting glucose;
FPG < 100 -125 mg/dl (5.6-6.9 mmol/L) = (IFG-impaired fasting glucose);
FPG ≥ 126 mg/dl (7.0 mmol/L) = Provisional diagnosis of Diabetes (the diagnosis must be confirmed, as described below).
2-h PG† < 140 mg/dl 2-h + Normal glucose tolerance test
2-PG 140 -199 mg/dl (7.8-11.1 mmol/L) = Impaired Glucose Tolerance (IGT)
2-h PG > 200 mg/dl (11.1 mmol/L) = Provisional diagnosis of Diabetes (the diagnosis must be confirmed, as below).

**Table 4 : Classification of Glucose Tolerance States<sup>3</sup>**

State	FPG level (mg/dl)	2-h plasma glucose in OGTT (mg/dl)*
IFG	100 to 125	< 200
Isolated IFG	100 to 125	< 140
IGT	< 126	140 to 199
Isolated IGT	< 100	140 to 199
Combined IFG/IGT	100 to 125	140 to 199
NGT	< 100	< 140

\*Standard 75-g OGTT.

**Symptoms of diabetes and casual plasma glucose concentration ≥ 200 mg/dl**

\*In the absence of unequivocal hyperglycemia, a diagnosis of diabetes must be confirmed, on a subsequent day, by measurement of FPG, 2-h PG, or random plasma glucose (if symptoms are present). The FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as no caloric intake for at least 8 h. †This test requires the use of a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. 2-h PG, 2-h post load glucose.

Patients with IFG and/or IGT are now referred to as having “pre-diabetes”<sup>17</sup> indicating the relatively high risk for development of diabetes in these patients. In the absence of pregnancy, IFG and IGT are not clinical entities in their own right but rather risk factors for future diabetes as well as cardiovascular disease. They can be observed as intermediate stages in any of the disease processes. IFG and IGT are associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride and low/or low-HDL type, and hypertension. It is worth mentioning that medical nutrition therapy aimed at producing 5-10% loss of body weight; exercise, and certain pharmacological agents have variably demonstrated to prevent or

delay the development of diabetes in people with IGT, the potential impact of such interventions to reduce cardiovascular risk has not been examined to date. Note that many individuals with IGT are euglycemic in their daily lives. Individuals with IFG or IGT may have normal or near normal glycated hemoglobin levels. Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standard OGTT.

### **Preclinical Natural History**<sup>22,33</sup>

#### **Insulin Resistance, Insulin Secretion and the Balance between Alpha ( $\alpha$ ) vs. Beta Cells ( $\beta$ ):**

Insulin resistance tends to be the “backbone” of type 2 diabetes; 80% to 85% of patients with type 2 diabetes have some degree of insulin resistance. There are two things that influence its development: genetic predisposition for insulin resistance, which some persons probably will inherit if family members have diabetes, and lifestyle and diet. If one is obese and sedentary, it contributes to the development of insulin resistance because when one gets obese. If a person is inherited the genetic potential, one need not even have to be obese to have insulin resistance. In fact, about 20% of patients who are at a normal weight or who are even underweight have insulin resistance, and about 20% of overweight patients who are clearly overweight or obese do not have insulin resistance. Obesity is important as a promoter of insulin resistance, but it is not required in order to develop insulin resistance. Typically, someone with genetic potential may also have a sedentary lifestyle, eat a diet that is hyper-caloric, and gain weight. However, someone with a genetic predisposition for abnormal beta-cell function can lose beta cells as time passes, without necessarily having insulin resistance. Finally, a person can eat a diet associated with weight gain, have a sedentary lifestyle and yet not have insulin resistance, and even maintain normal beta-cell function. So being overweight and sedentary does not necessarily mean that a person has insulin resistance, and conversely, a person does not need to have a genetic predisposition for insulin resistance in order

to have abnormal beta-cell function. But assuming that a patient has insulin resistance, the susceptible individual can take one of two pathways: patient either has genetically-programed normal beta cells, or has genetically-programed abnormal beta cells. If patient has normal beta cell function the person will go through life compensating for his hyperinsulinemia but person will always remain normoglycemic.

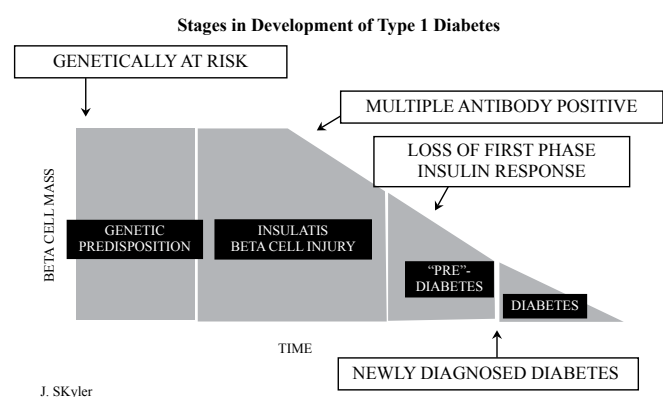
Those patients have the metabolic syndrome, which is a **Prediabetes stage**. *They never develop elevated blood glucose because their beta cells are able to compensate for their insulin resistance.* At this point is to do glucose challenge test, a lot of these patients do not have normal blood glucose; they have IGT. But if the patient's beta cells are programed to function abnormally, they will not be able to compensate for their insulin resistance. They will have relative insulin deficiency, will develop hyperglycemia, and eventually, type 2 diabetes. Interestingly, only about 20% to 25% of patients at risk for diabetes, who have normal beta-cell function will deteriorate into abnormal beta-cell function. This means that about 80% of at-risk population is walking around with normal blood glucose.

The problem is that insulin resistance, IGT, compensatory hyperinsulinemia, and diabetes all accelerate atherogenesis. So just because the glucose is not elevated does not mean that there is no problem. There is a huge problem. The cardiovascular complication rate in IGT or metabolic syndrome is not quite what it is in overt diabetes, but it is still quite a bit higher than in a normal individual. How far a patient goes on this continuum is determined by how healthy their beta cells are, and elevated blood glucose is the last stage of this evolution.

### **Regulation of Insulin Secretion**<sup>22</sup>

There are many things that affect the regulation of insulin secretion. The sulfonylurea drugs and the D-phenylalanine drugs, etc, that all attach themselves to the beta cell and do their work through transporters, etc. That is a complicated

**Figure 1**



mechanism, but the purpose of this illustration is to show that drugs, neurotransmitters, nutrients, and hormones all affect insulin release from the beta cells of the pancreas.

Nutrients are often underappreciated. For example, that glucose affects insulin release. If an individual has a healthy pancreas, the higher the blood glucose, the more insulin is released. Amino acids do that too; they are pretty effective stimulators of insulin secretion. What is sometimes not appreciated is the role of free fatty acids, which are really powerful. When they are elevated, as is common in obesity, there is actually a shutdown of insulin production –called lipo-toxicity–just as there is with glucose elevation. When glucose is elevated chronically, there is a shutdown of insulin production called gluco-toxicity. Many patients have gluco- and lipo-toxicity. All these factors can affect insulin secretion. The newest players are the hormones: glucagon-like peptide-1 (GLP-1) principally, and the next one is gastric inhibitory polypeptide (GIP).

### Islet Alpha- and Beta-cell Hormones Regulate Glucose Homeostasis <sup>18, 22</sup>

The normal healthy subject has many beta cells in the islets that secrete insulin, and much fewer alfa cells in the islets that secrete glucagon. In type 2 diabetes it is a different situation. The number of beta cells is reduced, and they do not secrete as much insulin. The alfa cells do not decrease in

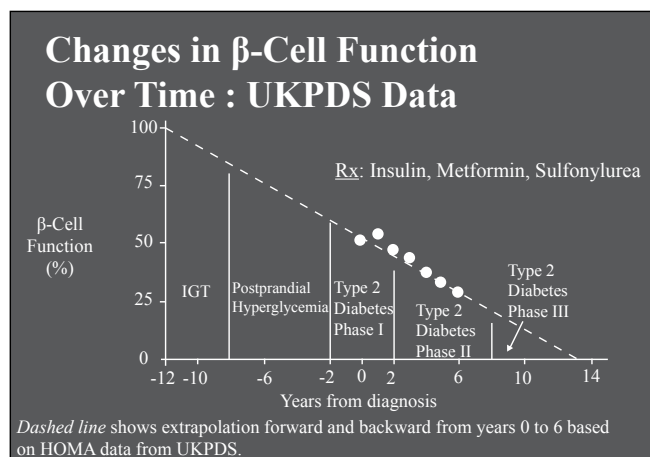
number—the glucagon-producing cells remain about the same—but they become dysfunctional. They start secreting glucagon, when glucagon should be suppressed. When there is type 2 diabetes, there is inappropriate secretion of glucagon from pancreatic alfa cells. There are mechanisms that are responsible for changes in beta-cell function. A normal beta cell adapts to insulin resistance by increasing secretion from each cell and increasing the number of cells (beta-cell mass). But when there is impaired beta-cell adaptation, and the inherited beta-cell weakness component, the susceptible person is destined to have impaired beta cells with decreased insulin secretion from each cell as well as reduced beta-cell mass.

### Changes in Beta-Cell function over time: United Kingdom Prospective Diabetes Study (UKPDS) Data <sup>33</sup>

From the UKPDS, that it has been shown over a very long 12- to 14-year study, beta-cell function failed progressively. By the time diabetes was diagnosed, with fasting blood glucose greater than 126 mg/dL, at least 50% of the functioning beta-cell population has been lost and maybe even 75% or 80%. (Figure 1).

The process begins 10 or 12 years before diagnosis.<sup>22</sup> The blood glucose rises and the beta-cell mass begins to decrease. There is a very straight line that continues until, eventually, persons with type 2 diabetes, if they live long enough, will have almost no insulin production from their beta cells. Most type 2 diabetics need insulin eventually, because all the agents that are available today that are so effective in managing type 2 diabetes depend on the pancreas' ability to make some insulin in order for these agents like Metformin, Sulfonylurea to work. With too little or no physiologic insulin production, exogenous insulin will then need to be administered. This is an important concept. Most type 2 diabetics, if they live long enough, will eventually need insulin either as supplemental or total therapy because their beta cells will continue to fail.

Figure 2



Source<sup>42</sup> Lebovitz H. Changes in beta-cell function over time: UKPDS data, *Diabetes Rev.* 1999;7, 139-53

## Beta-Cell Mass in Normal Patients and Patients with Diabetes & Prediabetes<sup>22</sup>

In fact, autopsy studies show that people with diabetes, whether they are lean or obese, have much reduced beta-cell mass. In the mid-1970s and early 1980, islet cell auto antibodies (ICA), insulin auto antibodies (IAA), and recently, a 64-kd protein were found to be present in the serum of the majority of patients with type 1 diabetes at the time of diagnosis. This form of diabetes, which accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes, type-1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the  $\beta$ -cells of the pancreas. Markers of the immune destruction of the  $\beta$ -cell include islet cell auto-antibodies, auto-antibodies to insulin, auto-antibodies to glutamic acid decarboxylase ( $GAD_{65}$ ), and auto-antibodies to the tyrosine phosphatase IA-2 and IA-2 $\beta$ . One and usually more of these auto-antibodies are present in 85–90% of individuals when fasting hyperglycemia (IFG) is initially detected. Also, the disease has strong HLA associations, with linkage to the DQA and DQB genes, and it is influenced by the DRB genes. These *HLA-DR/DQ* alleles can be either predisposing or protective.

In this form of diabetes, the rate of  $\beta$ -cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life known as “Latent Onset of Diabetes in Adults” (LADA).<sup>22, 23, 33</sup> Autoimmune destruction of  $\beta$ -cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Although patients are rarely obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis. These patients are also prone to other autoimmune disorders such as Graves’ disease, Hashimoto’s thyroiditis, Addison’s disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anemia. Theoretically, it can be fairly predicted that immune markers are reasonably useful in early detection of type 1 diabetes as early as few years too that will help in designing early interventions and prevent Type 1 diabetes.

## Insulin Patterns in Diabetes<sup>22</sup>

Abnormal Acute Insulin Response to Intravenous Glucose in Type 2 Diabetes is seen in some of patients’ cousins, uncles, aunts, and grandparents and some of these relatives will have blunted first-phase insulin release. Their blood glucose levels may be normal but the first-phase insulin release may be blunted. A very strong marker of genetically transmitted diabetes is the loss of first-phase insulin release.

## Clinical significance of Prediabetes & Diabetes risk

### Prediabetes as a model of the metabolic syndrome

There has been in recent time’s confusion about definitions of Prediabetes. Traditionally, Prediabetes referred to studies in which subjects were followed longitudinally and one could actually identify which subjects would later develop diabetes. In



2003, the ADA suggested that certain high-risk groups such as individuals with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) should be identified as having Prediabetes. This is an unfortunate choice of a name, since many or most IGT and particularly IFG subjects will never develop diabetes.<sup>23</sup> Given the natural history of Prediabetes, about 3%–10% of people per year with Prediabetes develop diabetes. Data are particularly well substantiated for IGT. In the Diabetes Prevention Programme<sup>24</sup> with subjects who had IGT, with or without IFG, there was about a 10% annual rate of progression to diabetes in the control group. Overall, Prediabetes confers about a six fold increased risk of diabetes compared with normal glucose tolerance. In most populations studied, the rates of conversion from IFG and IGT to diabetes are similar, with IGT having greater sensitivity but less specificity than IFG in predicting diabetes risk.<sup>25</sup> In an 11-year follow-up study among adults with IGT in Mauritius, 46% developed diabetes, 28% remained unchanged in category, 4% developed IFG, and glucose levels normalized in 24%. Thus, many people with Prediabetes (a quarter or more) may revert long term to having normal glucose tolerance, and after a protracted follow-up, only about 50% of people with IGT or IFG will develop diabetes.

### **Cardiovascular disease risk**

In comparison with adults who have normal glucose tolerance, people with Prediabetes have an increased risk of developing cardiovascular disease (CVD) and cardiovascular and all-cause mortality.<sup>26</sup> There is a two- to threefold increased prospective risk of cardiovascular events, which is most marked in younger adults with Prediabetes. Prediabetes is associated with increased rates of the cardiovascular risk factors found in people with type 2 diabetes. Some data indicate that people with IGT and normal levels of fasting plasma glucose have a greater risk of CVD than those with IFG. In addition, when other known CVD risk factors, such as hypertension and lipid abnormalities, are

adjusted for statistically, IGT, but possibly not IFG, remains as an independent CVD risk factor. An increasing plasma glucose level in IGT is associated with a greater risk of cardiovascular death.

### **Associations with the metabolic syndrome**

The metabolic syndrome (MetS) refers to a clustering in an individual of CVD risk factors and diabetes susceptibility.<sup>26</sup> People with MetS have about a twofold increased risk of developing diabetes and cardiovascular disease, compared with those without the syndrome. Several MetS definitions exist, with two being widely used. Recently, a third definition has been adopted by the International Diabetes Federation.<sup>27</sup> Each definition has impairment of glucose metabolism as an optional criterion, although some consider only IFG. Most adults who have Prediabetes will also have MetS. Whether Prediabetes or MetS best defines diabetes and cardiovascular risk remains to be determined. However, it is not clear whether MetS and Prediabetes represent the same or different clinical entities.<sup>28</sup> The data demonstrated by Diamantopoulos et al<sup>28</sup> showed that MetS and Prediabetes have an overlapping pattern. MetS appears to have a more pronounced effect on early renal dysfunction and increased inflammatory activation, while Prediabetes tends to be associated with early carotid structural changes. These findings may be due to a different pathophysiologic substrate of these clinical phenotypes in terms of insulin resistance and secretion, as well as to the varying prevalence of cardiovascular risk factors.

IGT also accounts for a highly heterogeneous Japanese population,<sup>29</sup> with the condition varying from individual to individual. In this study, findings suggest that IGT subjects with high insulin response and those with low insulin response vary greatly in regard to the number of atherosclerotic risk factors complicated and the frequency with which they are associated with the metabolic syndrome. It is also shown in middle-aged Japanese males that

**Table 5 : Treatment Recommendation for Individuals with IFG, IGT, or Both**<sup>3</sup>

Population	Treatment
IFG or IGT	Lifestyle modification (i.e., 5 to 10% weight loss and moderate intensity physical activity > 30 min/day) in a week
Individuals with IFG and IGT and any of the following:	Lifestyle modification (as above) and/or Metformin*
• < 60 years of age	
• BMI ≥ 35 kg/m <sup>2</sup>	
• Family history of diabetes in first-degree relatives	
• Elevated triglycerides	
• Reduced HDL cholesterol	
• Hypertension	
• A1C > 6.0%	

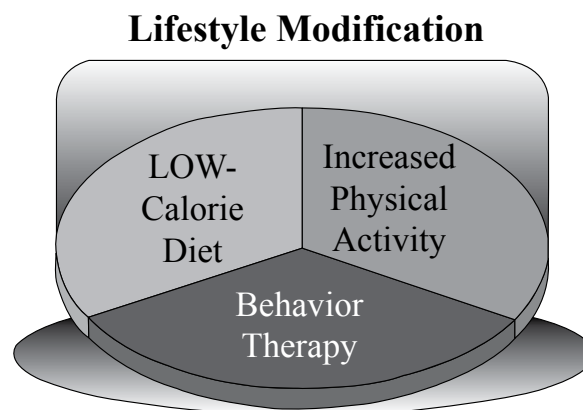
\*Metformin 850 mg twice per day.

of the two forms of IGT, IGT with high insulin response is more closely linked to the pathogenesis of atherosclerotic cardiovascular disease. Impaired glucose tolerance (IGT) represents a Prediabetes state positioned somewhere between normal glucose tolerance and diabetes, which is also assumed to make individuals in this state highly susceptible to atherosclerotic disease.<sup>29</sup>

An observation suggested by sahib et al<sup>30</sup> that insulin resistance may be associated with essential hypertension. There are some thoughts to favour the argument that insulin resistant Individuals are at a higher risk to develop hypertension as compared to insulin sensitive individuals.

### Interventions to prevent Prediabetes<sup>3</sup>

Just as there are different potential definitions of the natural history of IFG and IGT, there are different ways in which the natural history can be altered. The progression to diabetes is a time-dependent phenomenon; one possible alteration is simply to “reset the clock” without changing the rate of the deterioration. It is possible that some interventions will lower glycemia initially but do nothing to change the subsequent rate of rise of

**Figure 3**

Wadden TA, Butryn ML, Byrne KJ. Efficacy of lifestyle modification for long-term weight control. *Obes Res* 2004;12:151S-162S.

glycemia. This mechanism will delay crossing the glycemia threshold that defines diabetes. Prediabetes is a condition that does not fall squarely into the primary or secondary prevention domain, and therefore tends to be inadequately addressed by interventions in either health promotion or disease management. There is substantial evidence to suggest that even at these blood glucose levels, significant risk exists for both micro and, macro vascular complications. Biuso et al<sup>31</sup> introduces a conceptual framework of care for Prediabetes that includes both screening and the provision of up-to-date clinical therapies in conjunction with an evidence-based health coaching intervention. In combination, these modalities represent the most effective means for delaying or even preventing the onset of diabetes in a Prediabetes population.

Research studies have found that lifestyle changes<sup>3,31,34</sup> can prevent or delay the onset of type 2 diabetes among high-risk adults. The three components of lifestyle modification are diet, exercise, and behavior therapy (Table 5 & Figure 4). Several reviews have found that standard lifestyle modification programs conducted in academic medical centers induce a mean weight reduction of approximately 8–10% of initial weight in 16–26 weeks of treatment.<sup>36</sup> These studies included people with IGT and other high-risk characteristics

for developing diabetes. Lifestyle interventions included diet and moderate-intensity physical activity (such as walking for 2 1/2 hours each week). In the Diabetes Prevention Program, a large prevention study of people at high risk for diabetes, the development of diabetes was reduced 58% over 3 years.

In the Diabetes Prevention Program,<sup>8</sup> people treated with the drug Metformin reduced their risk of developing diabetes by 31% over 3 years. Treatment with Metformin was most effective among younger, heavier people (those 25-40 years of age who were 50 to 80 pounds overweight) and less effective among older people and people who were not as overweight. Similarly, in the STOP-NIDDM Trial,<sup>8,24</sup> treatment of people with IGT with the drug Acarbose reduced the risk of developing diabetes by 25% over 3 years. Other medication studies are ongoing. Besides lifestyle, various pharmacological treatments have proven their efficacy to reduce the incidence of type 2 diabetes in high-risk individuals, especially in those with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). Ongoing trials should confirm such a favorable effect with those drugs and may demonstrate a similar protective effect with other pharmacological approaches such as glinides or even basal insulin regimen. Therefore, the distinction between a true preventing effect and simply a masking effect is difficult with glucose-lowering drugs.<sup>34</sup> In addition, as type 2 diabetes is a progressive disease, it is still questionable whether the effect corresponds to a prevention effect or only to a postponing of the development of the disease. Owing to the pathophysiology of the disease, the only way to block the progression to type 2 diabetes is probably to avoid the progressive loss of beta-cell function and/or mass. Whatsoever, these data obtained in large clinical trials bring further argument to support early treatment of diabetes, even at a Prediabetes state, in order to stop the vicious circle leading to an inevitable deterioration of glycemia in predisposed subjects. The demonstration by recent randomized controlled trials that type 2 diabetes mellitus is

preventable has raised hope for the possibility of reducing cardiovascular morbidity and mortality associated with diabetes. Interventions like lifestyle modification and pharmacological therapy are recommended in individuals with Prediabetes to achieve the goal of prevention of diabetes in high-risk population.<sup>35</sup>

## Conclusion

Presentations at the 1st International Congress on "Prediabetes" and the Metabolic Syndrome<sup>14, 16</sup> reported that better definition and intense study of Prediabetes and the metabolic syndrome have led to some important insights in the past decade:

1. Prediabetes and the metabolic syndrome are extremely prevalent;
2. People with Prediabetes and the metabolic syndrome are at high risk for diabetes and CVD;
3. Early detection of IFG / IGT in high risk individuals and interventions to prevent progression to diabetes through Intensive lifestyle changes are effective and should be encouraged; and
4. Effective pharmacologic therapies must also be identified.

## References

1. Diabetes Atlas. 3rd edition, International Diabetes Federation, 2006; 1
2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001; 414:782-87.
3. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired Fasting Glucose and Impaired Glucose Tolerance: Implications for Care, *Diabetes Care*. 2007;30(3):753-59.
4. Alberti GK, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539-53
5. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005; 365:1415-28.
6. Twigg SM, Kamp MC, Davis TM et al. Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association. 2007; 186 (9): 461-5

7. Knowler WC, Barrett-Conner E, Fowler SE, et al. The Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or Metformin. *N Engl J Med* 2002; 346:393-403.
8. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. the STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *Lancet* 2002; 359:2072-7.
9. Torgerson JS, Hauptman J, Boldrin MN, et al. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; 27:151-61.
10. Ramachandran A, Snehalatha C, Mary S, et al: Indian Diabetes Prevention Programme (IDPP): the Indian Diabetes Prevention Programme shows that lifestyle modification and Metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006;49:289-97.
11. Gerstein HC, Yusuf S, Boxch J, Pogue J, et al: DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators: effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet* 2006, 368:1096-105.
12. Vague J. Sexual differentiation. A factor affecting the forms of obesity. *Presse Med.* 1947; 30:339-40.
13. Avogaro P, Crepaldi G, Enzi G, et al. Associazione di iperlipemia, diabete mellito e obesita di medio grado. *Acta Diabetol Lat.* 1967;4:572-90.
14. Crepaldi G. Origin and development of the metabolic syndrome. Program and abstracts of the 1st International Congress on "Prediabetes" and the Metabolic Syndrome; Berlin, Germany. 2005;13-6.
15. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26: 3160-7.
16. Grundy S. Do we need to expand the metabolic syndrome? Program and abstracts of the 1st International Congress on "Prediabetes" and the Metabolic Syndrome; Berlin, Germany. 2005;13-16.
17. ADA Clinical Practice Recommendations. Position Statement. *Diabetes Care.* 2007 S46; 30:1
18. Twigg SM, Kamp MC, Davis TM et al. Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association. 2007; 186 (9): 461-5
19. A Ramachandran. Netaji Oration. Epidemiology of Diabetes in India – Three Decades of Research. *Journal Phy of India.* 2005; 53:35-8
20. Graham AH, McCarthy MI, Mohan V et al. The genetics of non-insulin dependent diabetes mellitus in south-India: An overview. *Ann Med* 1992; 24:491-7.
21. Ramachandran A, Jali MV, Mohan V, et al. High prevalence of diabetes in an urban population in south India. *BMJ.* 1988; 297(6648):587-90
22. Sherry NA, Tsai EB, Herold KC. Natural History of  $\beta$ -Cell Function in Type 1 Diabetes, Section I: Aspects of Pathophysiology, *Diabetes* 2005; 54:S32-S39
23. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2006;29:S43-S48.
24. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or Metformin. *N Engl J Med* 2002; 346: 393-403.
25. Unwin N, Shaw J, Zimmet P, Alberti KG. Impaired glucose tolerance and impaired fasting Glycaemic: the current status on definition and intervention. *Diabet Med* 2002; 19: 708-23.
26. Decode Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001; 161: 397-405.
27. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Taskforce Consensus Group. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; 366: 1059-62.
28. Diamantopoulos EJ, Andreadis EA, Tsourous GI, et al. Metabolic syndrome and Prediabetes identify overlapping but not identical populations. *Exp Clin Endocrinol Diabetes.* 2006 ;114(7):377-83.
29. Mori Y, Hoshino K, Yokota K, et al. Japanese IGT subjects with high insulin response are far more frequently associated with the metabolic syndrome than those with low insulin response. 2006; 29(2):351-5.
30. Sahib AK, Sahu SK, Reddy KN. Prediabetes and hypertension. *J Indian Med Assoc.* 2007; 105(1):25-8.
31. Biuso TJ, Butterworth S, Linden A. A conceptual framework for targeting Prediabetes with lifestyle, clinical and behavioral management interventions. *Dis Manag.* 2007;10(1):6-15
32. Sinha R, Fisch G, Teague B, Tamborlane WV, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med.* 2002;346(11):802-10.
33. Lebovitz H. Changes in beta-cell function over time :UKPDS data, *Diabetes Rev.* 1999;7, 139-53
34. Scheen AJ. Antidiabetic agents in subjects with mild dysglycaemia: prevention or early treatment of type 2 diabetes? *Diabetes Metab.* 2007;33(1):3-12.
35. Zargar AH, Bashir MI. Epidemiological aspects of Prediabetes--review of the current data. *J Indian Med Assoc.* 2005;103(11):591-3
36. Wadden TA, Butryn ML, Byrne KJ. Efficacy of lifestyle modification for long-term weight control. *Obes Res* 2004;12:151S-162S.