ABSTRACT:
Diabetes is equivalent to CVD risk. It is most important and pertinent to evaluate all diabetics for CVD risk. Assessment of various CVD risk factors in the diabetic subject should be done systematically. Various measures to prevent these risks in the diabetic patients have to be undertaken to reduce the mortality in them. Individual risk factors have to be treated to achieve the target goals besides antplatelet therapy especially aspirin. Role of “polypill” containing Metformin, Aspirin, ACE inhibitor & statin in an asymptomatic diabetic with high CVD risk is interesting and may possibly prove effective in (CVD) Prevention. All these issues are discussed in the light of evidence – based Medicine.

INTRODUCTION:
In recent years with the explosion of knowledge and the sound pathophysiological basis, the distinction between the Type 2 Diabetes (T2DM) and the Cardiovascular disease (CVD) has been blurred; and the central importance of CVD prevention is becoming an integral part of DM management. T2DM carries an equivalent CV risk to that of nondiabetic individual who has already experienced a coronary event (1). There is also a mounting evidence that people with coronary heart disease (CHD) often have undiagnosed T2DM or glucose intolerance (IGT or IFG) which is indicative of an early stage in the pathophysiology of T2DM. DECODE study (2) has shown that even before diabetes is detected, the person may be predisposed to CVD and these prediabetic levels of blood sugar predict mortality. The spectrum of glucose tolerance ranges from normal glucose to IFG or IGT to overt T2DM. A substantial body of evidence supports the concept that increase risk of morbidity and mortality due to CVD is associated with abnormalities in glucose metabolism across the entire continuum of glucose tolerance ranging from normal to clinical diabetes (1, 3, 4). Compared with patients without DM, patients with DM have a 2-4 fold greater risk of death from myocardial infarction (MI) or stroke (5,6). Further it has also been shown that diabetes diminishes the cardioprotective effect in women (7). Even with same lipid profile or number of CVD risk factors as seen in patients without DM, those with DM have a higher case fatality rate from CHD. In a meta – analysis of 95783 people encompassing 22500 person – years of observation, Coutinho et al (8) showed that the progressive relationship between FPG and CVD risk begins at a FPG level of 75mg / dl.

CVD RISK FACTORS IN DM:
1. Abnormal Glycemia (Dysglycemia):
All forms of DM, as defined by fasting or post – oral load glucose levels above a standardized normal range, are well known to be associated with increased risk of microvascular complications such as nephropathy, retinopathy, and neuropathy (DCCT) (9) as well as cardiovascular complications such as CHD (MI) cardiac failure, peripheral artery disease (PAD) & stroke (10, 11). Interventions designed to intensively reduce mean glucose level i.e. HbA1C level have shown to dramatically protect against microvascular complications of DM (DCCT (9) and to a large extent (although non significant) cardiovascular events like MI (UKPDS) (10). Three recent trials namely ACCORD(12), ADVANCE(13) & VADT(14) however have cast a shadow of doubt about the efficacy of very aggressive control of blood glucose(HbA1c target levels set at around or below 6) in improving the cardiovascular benefits. While ACCORD & VADT studies have shown that there was increased mortality in the intensive arm compared with the standard arm, the ADVANCE study showed no overall or cardiovascular benefits in the intensive compared with the standard control arms.

Effects of sustained hyperglycemia lead to endothelial dysfunction and atherosclerosis through several steps including glucotoxicity, lipid oxidation, AGE production, decreased nitric oxide (NO) production and increased endothelium and basement membrane thickening. Recent work in T1DM has suggested that high glucose may contribute directly to atherosclerosis since a follow – up report to the landmark DCCT study showed that intensively treated group had reduced intima – media thickness(IMT) on carotid ultra – sonography compared to conventionally treated group suggesting less progression of vascular disease (15).
2. Visceral obesity & waist circumference:

Visceral (or abdominal) obesity correlates more strongly than the lower body obesity with insulin resistance (IR) (16). Besides, visceral fat correlates more strongly than subcutaneous fat with IR although both play a role (17).

Abnormal obesity is associated with increased levels of plasma fatty acids that result in increased accumulation of triglycerides in muscle and liver. Net effects are:

a. Increased IR in muscle
b. Altered hepatic fat accumulation and altered metabolism.

c. Dyslipidemia
d. Increased proinflammatory adipokines which again give rise to IR.
e. Decrease in Adiponectin levels leading to endothelial dysfunction & vasculitis, ultimately, increased risk of atherosclerotic vascular disease (ASCVD).

Waist circumference is a good indicator of visceral fat. Visceral obesity as measured by waist circumference therefore, assumes an essential component of the metabolic syndrome (MS) as defined by International Diabetes Federation (IDF) as well as by AHA/NHLBI (18).

Waist circumference of >90cm in men and >80cm in women are the South Asian (Indian) limits as defined in IDF criteria. Hypertension (>130 or >80 mmHg), dyslipidemia (TGS & HDL - C) and hyperglycemia (IFG, IGT or diabetes) are other criteria. Thus, measurement of waist circumference is an integral part of CV risk assessment in T2DM, more important than BMI.

3. Atherogenic dyslipidemia:

Increased number of small, dense LDL particles, low levels of HDL cholesterol and high levels of triglycerides are found in T2DM and MS. This atherogenic lipoprotein profile contributes to 2 – 4 fold excess risk of CVD in diabetics (19). HDLC is atheroprotective and low HDLC is independent risk factor for CHD risk even when the LDL is normal or low (20). In a 13 – year follow up study of CHD patients, it was shown that survival probability goes on decreasing as the levels of small, dense LDL particles increase (21). Annual CHD mortality goes on rising with increasing levels of triglycerides as shown in Paris Prospective Study (22). Dyslipidemia, therefore is an important marker of future CVD events in a diabetic patient.

4. Hypertension (HTN):

HTN and DM frequently coexist more than by chance. HTN exaggerates ASCVD in DM and increases the risk of microvascular complications. UKPDS (23) has shown that there is 15% increase in CAD per 10mmHg rise in SBP. In obese patients, BP is sensitive to Na – intake and this sensitivity is related to fasting insulin levels. The anti – natriuretic effect of insulin, together with its ability to activate the sympathetic nervous system and to drive abnormal vascular function contributes to the development of HTN Moreover, both hyperglycemia and insulin activate the RAAS by enhancing the expression of angiotensinogen, angiotensin II and AT1 receptor which contributes to increase in BP in patients with IR/DM. ADA recommends that BP should be measured at every routine visit by DM patient. Patients found to have SBP of >130 mmHg or DBP of >80 mmHg should have BP confirmed on a separate day (ADA 2007) (24) and if so treatment should be aimed at bringing down the SBP to <130 mmHg & DBP to < 80mmHg. HTN is therefore, a modifiable risk factor for both micro and macrovascular complication of DM. Unfortunately HTN is often underdiagnosed and inadequately treated in DM subjects. It is worth knowing that for any given level of BP, DM patients have more tissue damage than nondiabetic. The mechanisms of tissue damage by HTN in DM subjects include decreased vascular compliance, increased BP variability, reduced decline in nocturnal BP, microalbuminuria and ultimately endothelial stress and damage.

5. Proinflammatory & Prothrombotic state:

Chronic subclinical inflammation characterized by elevated cytokines (TNF – alpha & IL – 6) and acute phase reactants (C – reactive protein (CRP) and fibrinogen) is part of MS and recent studies suggest that immunity and inflammation play a role in the development of IR and T2DM. For instance, in Women’s Health study (25) it was shown that an event – free survival probability is reduced significantly over the different levels of CRP over the years of follow – up in apparently healthy women at all levels of severity of M S.

Prothrombotic state characterized by increased levels of plasminogen activator inhibitor (PAI – 1) and fibrinogen which result in impaired fibrinolysis is found in IR and T2DM. PAI – 1 is one of the fibrimolytic proteins expressed by adipose tissue especially the visceral fat and is believed to play a causal role in CVD. Diabetes should therefore be considered as a prothrombotic state resulting in increased blood viscosity, reduced blood flow in the microcirculation and several defects of coagulation and fibrilosis.

6. Smoking & CV risk:

This is a highly reversible, strong CVD risk factor in both diabetics & nondiabetic patients. Accelerated atherogenesis, increased platelet aggregation and other clotting abnormalities which may result in vascular occlusion are the effects of chronic smoking.

7. Non-alcoholic fatty liver disease (NAFLD) & Nonalcoholic steatohepatitis (NASH):

In both these conditions, there is increased prevalence of
obesity, MS, IR & T2DM, and both have the potential to end up in cirrhosis of liver.

8. Age, gender and family history:
These are important irrepressible risk factors for CVD in diabetics as well as nondiabetics. Indian phenotype is prone for T2DM, HTN and CHD. Low birth weight (<2.5kg) and weight at one year (<8kg) are important predictors of DM, CHD and HTN in adult life. Increasing age, male gender and family history of premature CHD are well known risk factors for CHD. Gender differences are gone once the person is a diabetic.

9. Sedentary lifestyle and physical inactivity:
They are modifiable risk factors. The risk CHD in physically inactive people is almost twice that of physically active people and regular exercise may protect against death from CHD. Physical exercise and other life style modifications including dietary changes are well known in the prevention of DM as shown in Diabetes Prevention Programme (26, 23).

10. Microalbuminuria: (24)
Persistent urinary excretion of albumin in the range of 30-299 mg/24hours is microalbumunia which is shown to be the earliest stage of diabetic nephropathy in T1DM and a marker for the development of nephropathy in T2DM. Microalbuminuria is now a well established marker of increased CVD risk. Diabetic nephropathy occurs in 20-40% of patients with DM and is the leading single cause of end – stage renal disease (ESRD). The analysis of a spot sample of urine for the albumin to creatinine ratio is the standard recommendation; but the urine for albumin only by immunoassay or a dipstick test specific for microalbumin (MICRAL) can also be done. Microalbumunia is a manifestation of diffuse endothelial cell injury and indicates progressive endothelial dysfunction which is a starting point for atherosclerosis.

ASSESSMENT OF CVD RISK FACTORS IN A DM SUBJECT:

1. Medical History:
   1. Duration and control of DM; Drugs used.
   2. HTN: Duration and control; Drug used.
   3. Previous MI or any revascularization procedure done or stroke.
   4. Parental h/o DM, obesity, premature CHD, HTN.
   5. H/o physical activity (daily), exercise, alcohol intake.
   6. H/o chest pain, angina, leg pain on walking, (claudication)
   7. H/o smoking.
   8. H/o psychological stress in daily life.

   LV Hypertrophy, retinopathy, nephrotic syndrome (massive oedema)
   Waist circumference; absent peripheral pulses
   Femoral & Carotid bruits
   CHD Risk assessment (Framingham score) (26) and if the score is >15.

3. Risk Factor screening:
   BP: SBP, DBP, Positional changes in DBP & SBP, pulse pressure (PP).
   Lipid Profile: HDL, LDL, TG, Total Chol; LP(a)
   HbA1C & Blood sugar (Fasting, 2Hr PG).
   High sensitivity CRP.
   Serum, Creatinine
   Albuminuria: Gross albuminuria, Microalbuminuria (spot specimen).

4. Cardiovascular evaluation:
   12 lead ECG & chest X Ray
   2D & Doppler Echocardiography
   Stress ECG (TMT); systolic Time Intervals measurements; stress echo (post TMT). Holter Monitoring
   Ambulatory BP monitoring
   Cardiovascular autonomic neuropathy (CAN)
   Ankle – Brachial BP index
   Carotid artery doppler and ultrasound to assess IMT & athero plaques.

OUR STUDIES IN CV RISK ASSESSMENT IN DM:

1. Cardiovascular Autonomic neuropathy: (CAN)
In our study of 25 diabetic subjects (T2DM: 17; T1DM:8) (27) with varying duration & control of diabetes, the various tests of CAN were applied and the findings showed that CAN was present in some form or the other in as many as 64% of cases. Valsalva ratio, postural hypotension, BP response to handgrip and cold presor test emerged to be the decisive tests to evaluate CAN (see table 1 & Table2).

2. Silent Myocardial Ischemia: (SMI)
To evaluate the existence of SMI, 40 T2DM subjects, asymptomatic for CAD underwent Treadmill Testing (TMT) as per Bruce Protocol. They had varying duration of diabetes and all of them had normal resting ECG. 16 out of 40 subjects had positive TMT without any angina (i.e. SMI) (28) (see Table 3). The study concluded that TMT is needed in the routine CV evaluation of T2DM (29).
3. **Echo Doppler Studies:**

Doppler echocardiography for evaluating subclinical LV dysfunction in T2DM was undertaken in 30 asymptomatic normotensive subjects who had normal ECG. 17 had LV diastolic dysfunction and 5 of them had both systolic and diastolic abnormalities by echo – doppler criteria (30). Long duration and poor control of diabetes were evident in these cases. Left ventricular hypertrophy (LVH) was seen in quite a few cases whose BP was normal (Fig. echo 1, 2). Such cases probably represent the cases of diabetic heart disease or diabetic cardiomyopathy which may end up in heart failure. Their epicardial coronary arteries are normal.

### Table 1: DM / CAN: Incidence of Abnormal response to Various tests in our series (N:25) of DM (IDDM : 8; NIDDM : 17), (27) Reference values (Ewing et al 1982) (38)

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
<th>Our series/Abnormal Pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva ratio</td>
<td>&gt;1.21</td>
<td>&lt;1.10</td>
</tr>
<tr>
<td>HR variation on deep breathing (R – R int.)</td>
<td>&gt;15 beats/min.</td>
<td>&lt;10 beats/min</td>
</tr>
<tr>
<td>Immediate HR response to standing (30:15 ratio)</td>
<td>&gt;1.04</td>
<td>&lt;1.00</td>
</tr>
<tr>
<td>SBP response to Standing (Postural Fall)</td>
<td>&lt;10 mmHg</td>
<td>&gt;30 mmHg</td>
</tr>
<tr>
<td>DBP response to sustained handgrip (DBP rise)</td>
<td>&gt;16 mmHg</td>
<td>&lt;10 mmHg</td>
</tr>
<tr>
<td>Cold Pressor test (DBP rise)</td>
<td>&gt;8 mmHg</td>
<td>&lt;8 mmHg</td>
</tr>
<tr>
<td>HR rise to Inj. atropine</td>
<td>Rise</td>
<td>No change</td>
</tr>
</tbody>
</table>

### Table 2: DM / CAN: Decisive tests (Positive in 4 of our 25 cases)

- Valsalva ratio <1.10
- Postural Hypotensin >30 mmHg Fall (SBP)
- Failure of DBP to rise on sustained handgrip <10 mmHg rise
- Failure of DBP to rise on cold pressor <8 mmHg rise

### Table 3: Asymptomatic T2DM patients: Exercise (TMT) ECG data. (Ref: 25)

<table>
<thead>
<tr>
<th>Patient data</th>
<th>TMT positive group “A” N: 24</th>
<th>TMT Negative “B” group N: 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Duration (Minutes)</td>
<td>8.72±1.92</td>
<td>9.84±1.34</td>
</tr>
<tr>
<td>Resting Heart Rate/min</td>
<td>77±7</td>
<td>82±8</td>
</tr>
<tr>
<td>Maximum Heart Rate/ min</td>
<td>159±16</td>
<td>174±10</td>
</tr>
<tr>
<td>Percentage of THR achieved</td>
<td>94±7</td>
<td>101±6</td>
</tr>
<tr>
<td>METs achieved</td>
<td>9.9±1.83</td>
<td>11.32±1.74</td>
</tr>
<tr>
<td>SBP maximum (mmHg)</td>
<td>171±19</td>
<td>172±24</td>
</tr>
<tr>
<td>DBP maximum (mmHg)</td>
<td>88±7</td>
<td>90±5</td>
</tr>
</tbody>
</table>
Other Tests:
Among other noninvasive techniques used earlier to doppler echocardiography include (a) Systolic Time Intervals (STIs) estimation (b) apex cardiography. We studied STIs in 29 young diabetics (mostly T1DM) with varying duration and control of diabetes by simultaneously recording the ECG, the phono at base, and carotid artery pulse at 100mm speed on a 3-channel recorder (Fukuda) (31). Pre-ejection period (PEP) and PEP/LVE Ejection Time ratio were significantly increased in DM subjects compared to controls. This might indicate subclinical diabetic heart disease (32).

All go to show that there is a need to cardiac testing in asymptomatic DM subjects and the present day indications are shown in the table 4.

PREVENTION OF CV RISK IN DM:
1. Lifestyle changes are the mainstay in the prevention of diabetes and the CVD risk accompanying diabetes. The physical exercise done regularly and daily with strict adherence to diabetic diet has been shown to increase the insulin sensitivity and reduce the fasting insulin levels in T2DM subjects in IRAS study (33). The impact of 10kg weight loss in obese diabetics is remarkable: 30% decrease in diabetes-related mortality, improvements in BP, lipid profile and glycemia and overall improvement in psychological and physical well being. There is a net 20% decrease in 5-year mortality (34). Cessation of smoking and moderation in alcohol intake are extremely important in CVD prevention in DM subjects.

2. Glycemic Control: The UKPDS (32) has shown the benefits of intensive control (HbA1C 7%) compared to conventional (HbA1C 7.9%). The relative risk (RR %) of microvascular endpoints was brought down by 25%, myocardial infarction (MI) by 16% and any diabetes – related endpoint by 12% in the intensive control group compared to conventional control. DCCT (9) has already shown the microvascular benefits of intensive glycemic control in T1DM subjects.

3. BP Control: Again, UKPDS has shown the benefits of tight BP control (mean144/82 mmHg) versus conventional BP control group (mean BP 154/87mmHg). The RR in microvascular endpoints was reduced by 37% diabetes – related endpoints by 24%, deaths related to diabetes by 32% and stroke by 44% (23). HOT study data (35) demonstrated the decreasing trend of new CVD cases with tighter control of diastolic BP ranging for <90mmHg to <80mmHg.

4. Lipid Control: The Heart Protection Study (HPS) (36) involving more than 20600 patients with CHD, CVD or diabetes, showed that statin therapy reduced the risk by 24% in major vascular events in high risk patients which included 5963 adults with diabetes at the end of 6yrs follow up. CARDS (37) study demonstrated that statin (atorvastatin) therapy given to the diabetics reduced the CVD event rates by 37% in the 4.75years of follow – up compared to placebo.

Therefore the evidence is accumulating that the tight control of blood glucose, BP and lipids is an integral part of the good and precise diabetes management today. The present day targets to be achieved are as follows:

Table 4: Asymptomatic DM subjects: Indications for Cardiac testing

| 1.  | Routine resting ECG showing ST – T changes.
| 2.  | Sedentary life style and age >55 years.
| 3.  | Abnormal lipid Profile:
| 4.  | BP ≥140/90 mmHg.
| 5.  | Smoking
| 6.  | Family H/o premature CHD.
| 7.  | Microalbuminuria or Macroalbuminuria.
| 8.  | Body Mass Index (BMI) <23
| 9.  | Waist circumference <94cm in men <80cm in women
| 10. | HbA1C <7% (ADA) <6.5% (AACE)
| 11. | BP control: <130/80 mmHg
| 12. | Lipid control: LDL <100 mg/dl <70 mg/dl in high risk patients.
| 13. | HDL >40 mg/dl in men >46 mg/dl in women
| 14. | TG <174 mg/dl
| 15. | TC <174 mg/dl

Prevention of CHD(MI) in DM subjects:
1. Secondary prevention (e.g. post MI):
   - Aspirin 75 – 150mg/day lifelong
   - Tight glycometabolic control
   - ACE inhibitor
   - Betablocker (Non – atenolol group viz: Bisoprolol, metoprolol XL, or Carvediol)
2. Primary prevention of CHD in DM:
   - Periodical check up for CVD risk factors.
   - Aspirin (besides targeting risk factors)
   - Poly pill (Containing Metformin, Aspirin, ACEI, Statin) for comprehensive prevention of CVD in high risk T2DM subjects.
CONCLUSIONS:
The above review based on the evidence provided by the various studies across the world and our small experience supports the concept that diabetes is in reality a syndrome of chronic cardiovascular risk along with basic metabolic abnormalities viz; insulin resistance and defective insulin secretion with a strong genetic / ethnic basis. The review emphasises the need for a comprehensive cardiovascular evaluation in diabetic subjects known to be at increased risk. The various methods to assess the CV risk in diabetes that can be done at the clinician’s office level have been described and are found to pickup the CV disease at the preclinical stage and can well help in the prevention of the risk.

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REFERENCES:-
