

# Diabetes Mellitus And Cardiovascular Risk

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## Citation

C Unachukwu, S Ofori. *Diabetes Mellitus And Cardiovascular Risk*. The Internet Journal of Endocrinology. 2012 Volume 7 Number 1.

## Abstract

**BACKGROUND:** Diabetes mellitus is the most common chronic metabolic disorder in Nigeria. The prevalence is increasing worldwide and the condition is a major risk factor for cardiovascular disease which is the primary cause of death in people with diabetes. **OBJECTIVE:** To investigate the risk factors and pathogenesis of cardiovascular disease in individuals with type 2 diabetes mellitus and methods to reduce their cardiovascular disease burden. **METHODS:** The sources of information were based on a Medline search using key words including: diabetes, cardiovascular disease, risk factors, Africa, prevalence, pathophysiology and healthcare. The World Health Organization (WHO), International Diabetes Federation (IDF) and World Bank websites were also explored for relevant information. **RESULTS:** Individuals with diabetes mellitus are at an increased risk for cardiovascular disease and diabetes is currently considered to be a cardiovascular risk equivalent. Cardiovascular disease is the most common cause of death among persons with diabetes mellitus. Women with diabetes have an even greater risk of heart disease compared to those of similar age who do not have diabetes. Traditional risk factors, such as obesity, dyslipidemia, and hypertension, only partially account for this excess risk. Endothelial dysfunction and increased oxidative stress are present in diabetic individuals and are pathogenetic mechanisms for atherosclerosis in diabetes. Insulin resistance plays a critical role in the development of cardiovascular disease in diabetic individuals. Diabetic cardiomyopathy with ventricular dysfunction contributes to poorer outcomes when diabetic persons suffer an acute coronary event. Lifestyle interventions such as weight control, regular exercise and smoking cessation are important in the prevention of type 2 diabetes and have a considerable impact on preventing cardiovascular disease in diabetic individuals. Achieving target glycemic, lipid and blood pressure levels with pharmacotherapy is essential. Blood pressure goals are lower in the diabetic as compared to non diabetic hypertensive individuals and the use of drugs that suppress the renin-angiotensin and sympathetic nervous systems is preferable. Also the use of low-dose aspirin can add to these benefits. **CONCLUSION:** Diabetic individuals have additional non-traditional risk factors that increase their overall risk for cardiovascular events. Prevention of type 2 diabetes is an important step towards decreasing the prevalence of cardiovascular disease. Risk factor reduction in people with diabetes by lifestyle intervention, proper education of the patient and effective drug therapy is essential.

## INTRODUCTION

The World Health Organization (WHO) defines diabetes mellitus (DM) as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. <sup>1</sup>

DM is a chronic condition that has the potential to have significant adverse effects on the quality of life of the patient as a result of its microvascular and macrovascular complications. The microvascular events include retinopathy, nephropathy and neuropathy. While these markedly increase the morbidity of persons with DM, it is the macrovascular complications (cardiovascular disease) that account for the increased mortality in this population. <sup>2</sup>

It is recognized that people with diabetes have an increased

prevalence of cardiovascular diseases and diabetes can be said to be a condition of premature cardiovascular complications in the setting of chronic hyperglycemia. <sup>3</sup>

Cardiovascular disease (refers to disease of the heart and circulatory system) is the leading cause of death in people with DM yet much of the population remains unaware of the risk and this is compounded by the fact that many diabetic individuals are unaware that they suffer from the metabolic disorder. Chronic hyperglycemia can cause arteries to narrow and/or lose elasticity and a high cholesterol level which is a common metabolic abnormality in these patients, can clog arteries. <sup>3</sup>

DM is considered a cardiovascular risk equivalent <sup>4</sup> and this implies that a person with DM is at the same risk level as a non-diabetic person with a previous myocardial infarction

(MI). The Copenhagen Heart Study<sup>5</sup>, which was a large follow up study of cardiovascular risk factors in the general population showed that of all the risk factors, diabetes mellitus was associated with the highest relative risk for coronary heart disease in both sexes and was most pronounced in women. The relative risk of incidence of MI or stroke was increased 2-3 fold in those with type 2 DM and risk of death increased 2 fold independent of other risk factors.<sup>5</sup>

A recent study<sup>6</sup> has shown that young people with type 1 diabetes have a unique form of insulin resistance not associated with obesity or abnormal lipid levels but are also at increased risk for cardiovascular complications. Although current cardiovascular risk prediction models may not be applicable for type 1 DM as risk factors including younger age at diabetes onset and presence of diabetes complications are not considered.<sup>7</sup>

In Sub-Saharan Africa, delay in seeking medical attention and therefore diagnosing diabetes leads to a high incidence of microvascular complications even at time of diagnosis. This is further compounded by poor glycemic and often blood pressure control. Wokoma et al.<sup>8</sup> in a study that assessed the glycemic control using glycosylated hemoglobin levels in adult Nigerians with diabetes found that the HbA1c levels in their study population ranged from 7.5-13% with a mean of 8.58± 2.7%. Furthermore 60% of their study population had HbA1c more than 10%. With the rising prevalence of diabetes in the area, the excess burden of consequent cardiovascular disease is a major concern for the healthcare system that is currently overburdened with the issues of infectious diseases especially the HIV/AIDS pandemic.

### EPIDEMIOLOGY OF DIABETES MELLITUS AND CARDIOVASCULAR DISEASE

A 2011 Centers for Disease Control and Prevention (CDC) report<sup>9</sup> estimates that nearly 26 million Americans that is, approximately 8.3% of the population have DM. Worldwide, at least 171 million people currently have diabetes and the International Diabetes Federation (IDF) projects that by 2025, three hundred and eighty million people will be living with DM. Africa is expected to contribute significantly to this rise. The IDF estimated that there were 12.1 million people living with diabetes in Africa in 2010 with a projected rise to 23.9 million by 2030.<sup>10</sup> The rising prevalence of non-communicable diseases especially diabetes mellitus in Africa as well as rising mortality from

diabetes and its complications prompted the IDF African Region in 2009 to launch its action plan to tackle this escalating threat.<sup>10</sup>

In Nigeria, the national standardized prevalence rate of diabetes was estimated to be 2.2% in 1997.<sup>11</sup> In 2003 a community based study done in Port-Harcourt, Nigeria, found the crude prevalence of DM to be 6.8%.<sup>12</sup> DM remains a major cause of death worldwide and the IDF estimated that DM would account for 6% of all deaths in the 20-79 age groups in 2010 in Africa<sup>10</sup>. Unachukwu and associates in a study in Nigeria found that the case fatality rate among patients with diabetes was high accounting for 11.1% of total medical deaths. Though majority of these deaths were from acute metabolic complications, cerebrovascular disease caused 10% of the diabetic deaths.<sup>13</sup>

Type 2 DM is predominantly a disease of adults, however its incidence is increasing more rapidly in adolescents and young adults than in other age groups. The disease is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups and the obese.<sup>14</sup>

Cardiovascular disease prevalence increases with age and the incidence in the general population is higher for men than pre-menopausal women presumably due to the protective effects of the sex hormones oestrogen and/or progesterone.<sup>15</sup> However it has been found that diabetes is associated with a relatively greater risk for CVD in women than in men, negating the normal gender differences in the prevalence of CVD.<sup>16</sup> A follow up study of the Framingham population showed that when adjusted for other risk factors, the risk rate for increased mortality was 2.4 times greater for diabetic men and 3.5 times greater for diabetic women.<sup>17</sup> Women with diabetes also have poorer prognosis after a myocardial infarction (MI), have higher risk of death from CVD than men, and typically receive less aggressive treatment to achieve treatment goals.<sup>18</sup>

CVD is a major complication of diabetes and the leading cause of early death among people with diabetes- about 50 percent of people with diabetes die from heart disease and stroke.<sup>19</sup> In the US there has been a significant decline in mortality associated with heart disease in the general population in the last several decades but this trend is much less in the diabetic population.<sup>20</sup> It has been found that on the average the life span of a diabetic individual is shortened by about 5-10 years and most of this excess mortality is due to cardiovascular disease.<sup>19</sup>

Cardiovascular disease previously considered rare in Africa is becoming increasingly prevalent probably owing to the adoption of western lifestyle and diabetes mellitus is a major contributor.<sup>21</sup> In a prospective study conducted in Ghana 11.3% of the study population had coronary artery disease making it the fifth most common cardiovascular disease and 22.5% of these patients had diabetes.<sup>22</sup> A retrospective study in Nigeria showed that non communicable diseases accounted for 56.2% of all medical admissions and hypertension and DM were the major non-communicable disease indications for medical admission.<sup>23</sup>

Stroke is one of the leading causes of death and physical disability worldwide and diabetes is a recognized risk factor for ischemic stroke.<sup>24</sup> Diabetes increases the risk of stroke by up to four fold and in patients presenting with a stroke the prevalence of diabetes is three times that of matched controls.<sup>25</sup> A study in Benin City Nigeria revealed that diabetes mellitus independently conferred a 3.23 times greater risk for stroke and this was further enhanced when the patient also had hypertension.<sup>26</sup> Similarly Kolawole and Ajayi in their study found that diabetic patients had an overall higher mortality rate and in those who had concomitant hypertension, 50% of the deaths were stroke related.<sup>27</sup> In Jos Nigeria, Ugoya et al.<sup>28</sup> found that diabetic patients had a slightly higher prevalence of stroke than non diabetic controls (6.7% vs. 5%). Diabetes increases risk for stroke in young people,<sup>24</sup> people of African descent,<sup>29</sup> and women.<sup>30</sup> In a 20 year follow up of subjects in the Renfrew/Paisley study,<sup>31</sup> (a large population based study in Scotland) it was found that patients with diabetes also tend to have worse outcomes -recurrent strokes, stroke-related dementia, and mortality- after a stroke than non diabetic individuals.

### RISK FACTORS FOR CARDIOVASCULAR DISEASE IN DM

A continuous relationship exists between glycaemic control and the incidence and progression of microvascular complications but the relationship between glucose concentrations and macro- vascular events is less powerful than for microvascular disease.<sup>32</sup>

The traditional risk factors that are associated with cardiovascular disease in the general population including obesity, physical inactivity, hypertension, and dyslipidemia are prevalent in the diabetic population. Persons with diabetes tend to have a clustering of these risk factors in what is termed the metabolic syndrome hence multiplying their overall risk. Wokoma et al.<sup>33</sup> in Nigeria found that

49.9% of adult Nigerians with type 2 diabetes had significant dyslipidemia necessitating intervention by the NCEP ATP III criteria. Also there was positive correlation of dyslipidemia with indices of poor metabolic control including obesity, high mean fasting glucose and HbA1c levels. Similarly Okeahialam et al.<sup>34</sup> in a more recent study found that diabetic patients had a greater burden of cardiovascular disease risk factors especially dyslipidaemias, increased waist circumference, cigarette smoking, alcohol abuse, and physical inactivity, than the non diabetic individuals in the study population. Recognition of DM as a cardiometabolic disorder has therefore made it imperative that simultaneous management of these cardiometabolic risk factors be rigorously attended to in order to improve cardiovascular outcomes.

Hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease.<sup>35</sup> Hypertension amplifies the already high cardiovascular disease risk in diabetes. Up to 75% of CVD in diabetes may be attributable to hypertension.<sup>35</sup> This has led to the recommendations for more aggressive treatment (i.e., reducing blood pressure to <130/85 mm Hg) in persons with coexistent diabetes and hypertension.<sup>35</sup>

Obesity increases the risk of cardiovascular disease in adults and has been strongly associated with insulin resistance in normoglycemic persons and in individuals with type 2 diabetes.<sup>36</sup> Apart from the degree of obesity the risk is also dependent on the distribution of body fat as it has been found that visceral adiposity is more closely linked to cardiovascular disease than peripheral adiposity.<sup>37</sup> Visceral adipocytes are more lipolytically active and release increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that cause resistance of the body to the actions of insulin resulting in increased production of this hormone by the pancreas and ensuing hyperinsulinemia.<sup>38</sup> Insulin resistance in obesity and type 2 diabetes is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output.<sup>39</sup> Through this mechanism of insulin resistance, obesity has been found to increase the risk of hypertension<sup>40</sup> and dyslipidemia<sup>41</sup> in diabetic individuals thus multiplying their overall cardiovascular risk.

Microalbuminuria is defined as a urinary albumin excretion rate between 20 and 200 µg/min. Microalbuminuria is a marker of endothelial dysfunction and increased oxidative

stress which predispose to atherosclerosis. It is an independent risk factor for the development of CVD and is associated with a doubling of the risk of early death, mainly from coronary heart disease.<sup>42</sup> It is associated with insulin resistance, atherogenic dyslipidemia, central obesity, and the absence of nocturnal drop in both systolic and diastolic pressures<sup>43</sup> and is a part of the metabolic cardiovascular syndrome associated with hypertension.<sup>44</sup>

The age at which an individual transitions to a high risk for cardiovascular disease is a way to demonstrate the powerful risk imparted by the presence of DM. The transition to a high risk category (10 year event rate of more than 20%) occurs at a younger age for men and women with DM than for non diabetic persons. Patients with type 2 DM have a high rate of coronary artery disease as determined by the presence of coronary artery calcification on electron beam CT scanning and by inducible silent ischemia on stress imaging.<sup>45</sup> Diabetic patients with coronary artery disease tend to have worse ischemic events than non diabetic people with coronary heart disease and this may be attributed to sympathetic denervation and prolongation of angina perceptual threshold (the time from onset of 0.1 mV of ST segment depression to onset of angina during treadmill exercise) that has been found during exercise testing, predisposing diabetic patients to silent myocardial ischemia.<sup>46</sup> A study done at a diabetes clinic in northern Nigeria that 20% of the diabetic patients had resting electrocardiographic evidence of ischemic heart disease though all of them were asymptomatic and similar to other studies it was found that hypercholesterolemia and female gender were the most frequent factors associated with ischemic heart disease.<sup>47</sup>

Prediabetic patients also have an increased risk for cardiovascular disease<sup>48</sup> and there is a graded increase in cardiovascular risk with increasing degrees of glucose intolerance below the definition of overt DM, evidence of which led to the so-called “ticking clock” hypothesis.<sup>49</sup> In an 8-year follow-up of the San Antonio Heart Study,<sup>50</sup> subjects who converted to diabetes during the follow-up had higher baseline levels of total and LDL cholesterol, triglycerides, and blood pressure and lower levels of HDL than those who remained nondiabetic, even after adjustment for obesity. The enhanced atherogenic risk profile in the prediabetic state may contribute to the subsequent increased risk of CVD.

### **PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE IN DM**

Cardiovascular disease in DM can broadly be classified into

2 groups<sup>51</sup> : DM cardiomyopathy and atherosclerotic vascular disease (leading to coronary heart disease (CHD), stroke and intermittent claudication).

Diabetic cardiomyopathy refers to a disease process which affects the myocardium in diabetic patients causing a wide range of structural abnormalities eventually leading to left ventricular hypertrophy and diastolic and systolic dysfunction or a combination of these.<sup>52</sup> The cardiomyopathy associated with diabetes is a unique myopathic state that appears to be independent of macrovascular/microvascular disease and contributes significantly to CVD morbidity and mortality in diabetic patients, especially those with coexistent hypertension or coronary artery disease with resulting synergistic adverse effects. A variety of morphological changes including thickening of capillary basement membrane, myocyte atrophy and hypertrophy and myofibril depletion not distinguishable from other forms of cardiomyopathy, have been found in endomyocardial biopsy and autopsy samples from diabetic patients. However a striking feature of diabetic cardiomyopathy is myocardial and interstitial fibrosis even in the absence of clinically detectable disease and a direct consequence of this is diastolic dysfunction.<sup>53</sup> The myopathy not only impairs myocardial performance but also renders the myocardium more susceptible to and less able to recover from ischemic insults increasing the incidence of post myocardial infarction congestive heart failure in these patients as compared to non diabetics.<sup>51</sup> It has been reported that the immediate and long-term post MI mortality is increased 1.5–2 fold among diabetic patients as compared to non diabetic individuals.<sup>54</sup> Diabetic cardiomyopathy can be subclinical or apparent depending on the presence of symptoms and signs. There appears to be a long subclinical course in most patients before the development of symptoms.<sup>52</sup>

The pathogenesis of atherosclerosis in DM is multifactorial and very complex and begins years to decades prior to diagnosis. More than 50% of newly diagnosed type 2 diabetics have coronary artery disease and the risk of atherosclerotic events is two to four folds greater in those with diabetes than those without.<sup>55</sup> About 80% of all deaths from diabetes can be attributed to atherosclerosis, of which three-quarters are from coronary heart disease and the remainder from either cerebrovascular or peripheral vascular events.<sup>51</sup> Once coronary disease is manifest, the risk of further vascular events is greatly increased.<sup>55</sup>

There are several determinants of atherosclerotic disease in DM. In diabetic patients the balance between thrombosis and fibrinolysis is affected in various ways. Factors that predispose to thrombosis include platelet hyperaggregability, increased concentration of procoagulants and reduced concentration and activity of antithrombotic factors. On the other hand, factors predisposing to attenuation of fibrinolysis include reduced tissue plasminogen activator activity, increased plasminogen activator inhibitor type 1 (PAI-1) and reduced concentration of alpha 2 antiplasmin. These increase thrombus formation and accelerate plaque formation.<sup>56</sup> DM patients also tend to have lipid-rich atherosclerotic plaques that have more inflammatory cell types and inflammatory markers than in non diabetic patients and these plaques are more vulnerable to rupture than those found in non diabetic patients.<sup>57</sup>

Endothelial dysfunction which may be defined as changes in the concentration of the chemical messengers produced by the endothelial cell and/or by blunting of the nitric oxide-dependent vasodilatory response to acetylcholine or hyperemia is thought to be the initial lesion of atherosclerosis.<sup>58</sup> The endothelium controls the tone of the underlying vascular smooth muscle through the production of vasodilator mediators. The endothelium-derived relaxing factors (EDRF) comprise nitric oxide (NO), and prostacyclin. Experimental studies have shown that when endothelial cells are exposed to a diabetic environment there is attenuation in the ability of nitric oxide synthase to generate nitric oxide.<sup>59</sup> Several mechanisms of endothelial dysfunction include impaired signal transduction or substrate availability, impaired release of EDRF, increased destruction of EDRF, enhanced release of endothelium-derived constricting factors and decreased sensitivity of the vascular smooth muscle to EDRF. The principal mediators of hyperglycaemia-induced endothelial dysfunction may be activation of protein kinase C, increased activity of the polyol pathway, non-enzymatic glycation and oxidative stress.<sup>60</sup> Endothelial dysfunction eventually leads to loss of vasodilatation, platelet aggregation, vascular remodeling, inflammation and smooth muscle growth.

There exists a complex interplay between obesity, dyslipidemia, insulin resistance and endothelial dysfunction in DM that significantly increases cardiovascular risk. Free fatty acids are classically increased in the plasma of obese patients, people with DM and in individuals with the metabolic syndrome and Steinberg et al<sup>61</sup> have demonstrated that FFA directly induces endothelial dysfunction. The

endothelial cell is very susceptible to damage by oxidative stress. The diabetic state is also typified by an increased tendency for oxidative stress and high levels of oxidized lipoproteins especially the so-called small, dense low density lipoprotein cholesterol (LDL-C).<sup>62</sup> Apart from the independent contribution of LDL cholesterol, the presence of atherogenic dyslipidemia in diabetic patients often called diabetic dyslipidemia is characterized by 3 lipoprotein abnormalities: elevated very-low-density lipoproteins (VLDL), small LDL particles, and low high-density-lipoprotein (HDL) cholesterol. These represent a set of lipoprotein abnormalities besides elevated LDL cholesterol that promote atherosclerosis.<sup>63</sup> High levels of fatty acids and hyperglycemia have both been shown to induce an increased level of oxidation of phospholipids as well as proteins. Oxidative stress causes reduced available nitric oxide.

Plasma homocysteine is a relatively recently recognized risk factor for cardiovascular disease. It is frequently increased in diabetic patients and is a predictor of cardiovascular mortality.<sup>64</sup> It may cause damage to endothelial cells. Elevated levels have been linked to diets low in folate and some rare genetic defects. Also plasma homocysteine levels correlate with albumin excretion rate. In the HOORN study,<sup>64</sup> 80% of patients with DM and hyperhomocysteinemia had nephropathy. However uncertainty still remains about the strength of the relation between homocysteine and CHD.

Chronic hyperglycemia leads to nonenzymatic glycation of proteins and macromolecules.<sup>65</sup> Advanced glycation end products result from initial non enzymatic reactions of glucose with proteins and nucleic acids followed by irreversible cross linking of these macromolecules. They are implicated in the morphological changes that occur in the diabetic heart.<sup>51</sup> They may play a role in initiation and progression of macro- and microvascular complications and tissue changes associated with ageing. AGEs involving plasma proteins and lipoproteins, extracellular proteins, cytoplasmic proteins and nucleic acids disrupt molecular structures, alter enzyme action, affect degradation and removal of age related molecules, and reduce receptor recognition of ligands. AGE modified apolipoprotein B can lead to hyperlipoproteinemia, reduce LDL clearance, facilitate LDL deposition in vessel walls and promote atherosclerosis.<sup>66</sup> The accumulation of AGE-modified extracellular matrix results in loss of elasticity of vessel walls that could interfere with myocardial function and this may explain the observation that diabetic patients can

develop congestive heart failure in the absence of hypertension or increased ventricular wall thickness.<sup>51</sup>

The increased plaque vulnerability, AGE mediated vascular remodeling, increased production of cytokines like interleukin 1 (IL-1), tumor necrosis factor (TNF), oxidative stress and increased endothelin all contribute to altered vessel structure and function and ultimately atherosclerosis which is the pathologic basis of cardiovascular disease in DM<sup>65</sup>.

### REDUCING THE CVD RISK IN DM

The DCCT<sup>67</sup> clearly showed the benefit of optimum glycemic control in reducing the risk of microvascular complications in type 1 DM but the evidence for glycemic control in reducing macrovascular complications is less clear. Treatment of hypertension and all components of any dyslipidaemia are important to delay the progression of macrovascular disease. Every patient diagnosed with diabetes should therefore have a cardiovascular risk assessment done according to established guidelines.<sup>4</sup>

A combination of dietary and lifestyle modifications including exercise, losing weight to maintain a normal body mass index, smoking cessation and moderate alcohol consumption must be implemented. Lowering lipid levels to target according to the ATP III recommendations<sup>4</sup> can be achieved with lipid lowering agents like the statins (which are HMG CoA reductase inhibitors) and should be added for those patients who fail to achieve the goal on diet and lifestyle changes alone. Diabetic patients usually will require simultaneous commencement of lipid lowering drugs because they need intensive lowering of LDL cholesterol as they are considered to be at a very high risk of cardiovascular disease.<sup>4</sup>

It has been shown that pharmacological therapy can reduce the frequency of progression to type 2 DM in prediabetic patients with insulin resistance.<sup>68</sup> The UKPDS trial showed that tight glycemic control reduced the incidence of microvascular complications but the relative benefit on CVD risk reduction was conferred in a far more powerful fashion by intensive blood pressure reduction rather than by tight glucose control alone.<sup>69</sup> However it was also found that each absolute 1% rise in HbA1c increased the incidence of coronary heart disease by 11% suggesting that tight glycemic control may in fact reduce the incidence of coronary heart disease. The study also found that the use of metformin, an insulin sensitizing agent improved insulin resistance and reduced macrovascular events. Regardless of

the pharmacologic agent used to achieve glycemic control, the goal is to maintain as near normal levels of HbA1c as possible.

The choice of anti-hypertensive agents to use in diabetic patients are varied but several trials<sup>70</sup> have shown clear benefit from the use of angiotensin converting enzyme inhibitors (ACEI) as drugs of first choice in lowering blood pressure. The clinical benefits of ACEIs go beyond lowering of BP as they also reduce the progression of renal disease and cardiovascular disease. The Hypertension Optimal Treatment (HOT) randomized trial<sup>71</sup> showed the benefit of aggressive lowering of blood pressure in diabetic patients and these patients frequently require 3 or more drugs to achieve a “tight control” of blood pressure to <130/80. Whereas previous studies<sup>72</sup> and guidelines<sup>73</sup> discouraged the use of  $\beta$ -blockers and low dose diuretics to lower blood pressure in DM, more recent randomized prospective trials have not shown an increase in the development of diabetes with  $\beta$ -blocker or low-dose diuretic treatment of hypertension.<sup>74</sup> Part of the reduction in cardiac events with  $\beta$ -blockers in patients with diabetes and coronary artery disease may be due to a particular benefit in those with autonomic dysfunction.  $\beta$ -blockers are more effective than other antianginal drugs in reducing silent ischemia, and they increase heart-rate variability after myocardial infarction.

The American diabetes association recommends the use of antiplatelet agents such as low dose aspirin in primary and secondary prevention of cardiovascular disease in the absence of any contraindication.<sup>75</sup> In the HOT trial, aspirin significantly reduced cardiovascular events by 15% and myocardial infarction by 36% in hypertensive patients.<sup>73</sup> This may provide further evidence of its efficacy in diabetic patients with hypertension.

Though evidence exists that diabetes is associated with increased oxidative stress, studies carried out so far offer no proof that taking antioxidants supplements such as vitamin E or C, or beta-carotene, has any beneficial role in preventing cardiovascular disease. Similarly, reducing homocysteine levels through folic acid and other vitamin supplements has not yet been proven to be beneficial. Consumption of a balanced, nutritious, fiber-rich diet that includes naturally available nutrients from fruits and vegetables in adequate amounts and increasing intake of omega 3 fatty acids is more important.<sup>76</sup>

### CONCLUSION

Having diabetes mellitus is as bad as having a previous

myocardial infarction. Death in patients with DM is usually due to an acute coronary event and these are more extensive than in those without DM. Insulin resistance plays a vital role in the pathogenesis of the increased risk. The complex interplay of risk factors in type 2 DM make it necessary to apply a holistic approach to the management of this chronic disorder.

In Sub-Saharan Africa where income per capita is low and the health system funding is not adequate, the proverbial “prevention is better than a cure” holds true. It has been shown that about 75% of patients with diabetes identified in community surveys in sub-Saharan Africa are unaware that they have diabetes thus they often have complications at the time of diagnosis.<sup>77</sup> The cost of widespread routine screening of the general population is prohibitive but public education via mass communication media can raise public awareness of this burgeoning epidemic. Diet and lifestyle changes are vital in reducing cardiovascular risk. There are slight differences in blood pressure and lipid target levels in diabetes as compared to the general population and these are a reflection of the increased risk that people with diabetes face. Managing diabetes especially in low resource settings must therefore move beyond the traditional primary focus on attainment of glycemic goals to encompass the modification of the multiple risk factors present. Also recognizing that cardiovascular risk is present in the pre-diabetic subgroup, efforts have to be made by health care workers to recognize individuals in this subgroup like first degree relatives of patients with type 2 diabetes and institute life style changes that would ultimately help reduce the incidence of CVD in this high risk population. CVD and type 2 diabetes may be prevented or at least postponed by lifestyle changes that maintain normal weight and physical activity. A comprehensive care plan should therefore include modification of all cardiovascular risk factors. Thus, modification of life habits should be at the heart of the public health strategy for reducing rates of type 2 diabetes and its cardiovascular complications.

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