Significant Risk Factors for Atherosclerotic Vascular Disease in Diabetes Mellitus as Measured by Carotid Intima Media Thickness

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1 Introduction

Diabetes mellitus especially the type 2 variety is increasingly being seen as a cardiovascular disease that manifests as hyperglycaemia (Yki Jarvinen, 2000). It is therefore not surprising that cardiovascular disease accounts for 80% of mortality in diabetic patients (United Kingdom Prospective Diabetic Study, 2002). Most of the time, these cardiovascular diseases are atherosclerotic by nature (Treatment Options for Type 2 Diabetes Mellitus, 2000). Even before the time of diagnosis as cases of diabetes mellitus, these individuals are known to have established cardiovascular disease (Morrish et al, 1990). Following from this, all studies of cardiovascular disease risk factors in diabetics compared to non-diabetics in any locality show a two-fold burden in the former compared with the latter (Keen et al, 1999).

Intima media thickness is a measure of atherosclerotic vascular disease, considered to capture comprehensively all perturbations caused by several risk factors over time on the arterial walls (Grobbee & Bots, 1994). Though values differ by race, it is a robust measure of sub-clinical development of atherosclerosis (Lazdan et al, 2010). That being the case, any risk factor that correlates significantly with intima media thickness could be considered critical in the development of atherosclerosis; and therefore amenable to treatment to ameliorate cardiovascular disease morbidity. Traditional and some newer cardiovascular disease risk factors have shown a positive association with intima media thickness in epidemiological studies of patients and the general population (Bolinde et al, 1997; Lee et al, 1998; Bots et al, 1997). A cardiovascular disease risk factor is a term coined by Dr. William Kannel, the first director of the Framingham study; and refers to any condition associated with an increased tendency to developing cardiovascular disease (Black, 1992). They are divided into major (cigarette smoking, elevated blood pressure, elevated total and low density lipoprotein cholesterol, low high density lipoprotein cholesterol, diabetes mellitus and advancing age), predisposing (obesity, abdominal obesity, physical inactivity, family history of premature coronary heart disease, ethnic characteristics and psychosocial factors) and conditional (hypertriglyceridaemia, small low density lipoprotein particles, hyperhomocysteinaemia, increased serum lipoprotein(a), prothrombotic factors, left ventricular hypertrophy, hyperuricaemia, short stature, microalbuminuria, oral contraceptive use, hormone replacement therapy and menopause) (Grundy et al, 1999). We therefore sought to use carotid media intima thickness to determine those modifiable cardiovascular risk factors critical to the development of atherosclerotic vascular disease in a diabetic cohort seen in our healthy facility.

2 Methodology

This was part of a larger study on cardiovascular risk factors and carotid atherosclerosis in non-hypertensive type 2 Diabetes Mellitus in Jos University Teaching Hospital, Jos, Nigeria (Alonge, 2007). The protocol was approved by the hospital ethics committee and each patient provides a written consent to be part of the study after careful explanation by BAA.

Seventy non-hypertensive type 2 Diabetes Mellitus patients were recruited from the Diabetes Clinic of the hospital in a consecutive manner. They were all equal to or above 30 years of age, an age chosen to remove the likelihood of including type 1 (insulin dependent diabetes mellitus) which is more common in the younger age group. They were patients who developed classical symptomatology of dia-
Diabetes mellitus with a fasting plasma glucose (FPG) greater than or equal to 7.0 mmol/l or 2 hour post-prandial glucose (2HPPBG) of greater than or equal to 11.1 mmol/l. Known diabetes mellitus patients whose plasma glucose had been controlled on physician prescribed oral hypoglycaemic or who in the course of treatment came to require insulin for control of plasma glucose (Alberti & Zimmet, 1998).

Other than hypertension (blood pressure greater than or equal to 140/90 mmHg or history of physician prescribed anti-hypertensives) and age less than 30 years, the following also served as exclusion criteria: history of ketosis, treatment with drugs capable of affecting serum lipid profile, pregnancy, puerperium, thyroid diseases, heart disease with or without heart failure, and unwillingness to participate in the study.

At enrolment each participant was interviewed with regard to age (as at last birthday), age at diagnosis, duration of disease, occupation, civil status, educational background, family history of diabetes mellitus, alcohol and tobacco use. Degree of physical activity was also sought. They were then examined physically. Weight was recorded in kilograms (to the nearest 0.1 kg) using a flat scale on a firm horizontal plane with patients clad in light clothing only. Height was measured using a stadiometer (to the nearest centimeter) without food or head gear. Both of these conform to the standard prescription (Dowse & Zimmet, 1992). From the height and weight, Body Mass Index (BMI) was determined as the quotient of weight in kilograms and the square of height in metres. Waist circumference was measured using a dress maker’s tape placed horizontally at the mid-point between the iliac crest and lower costal margin (National Institute of Health, 1998). Using the same tape, placed horizontally at the maximum circumference over the buttocks posteriorly and the symphysis pubis anteriorly, the hip circumference was determined in the same centimeter unit as the waist circumference. The waist to hip ratio (WHR) was determined from the two values, the former as the numerator and the latter as denominator.

Blood pressure was then measured, first on both arms with a five minute rest in-between. The arm with the higher value was used for two subsequent measurements separated by at least five minutes. The average of the last two measurements was used for systolic and blood pressure (SBP) and diastolic blood pressure (DBP). Korotkoff sounds 1 and 5 from standard mercury sphygmomanometry using appropriate sized cuff determined systolic and diastolic blood pressures respectively. Measurements were taken with patients supine and standing. The standing values were used for analysis, since diabetics are prone to orthostatic hypotension; and being ambulant, the erect blood pressures would be more representative. Thereafter, blood samples were taken after an overnight fast and two hours after food in appropriate (fluoride oxalate) bottles. Plasma glucose was measured by the glucose oxidase method (Caraway & Watts, 1998) on both the fasting and post prandial samples. Glycosylated haemoglobin (HbA1c) was determined on the fasting sample using the DCA 2000® ANALYSER. The analysis is based on a latex immune agglutination inhibition methodology. Total cholesterol (TC) and High density lipoprotein cholesterol (HDL – C) were determined on the fasting sample by the same enzymatic end point method (Trinder, 1981) using reagent contained in a kit supplied by Randox Laboratories Ltd. U.K. Serum creatinine (Cr) was determined by the Jaffe method (Spencer, 1986), and uric acid (UA) by the phosphotungstic acid method (Newman & Price).

The patients then underwent echocardiography using SONOS 1500 ultrasound system (Hewlett Packard USA) with a 3.5 mHz transducer except in obese patients when a 2.5 mHz transducer was used. The index of interest here was the left ventricular mass (LVM) which was given automatically by the machine from interventricular septal thickness in diastole, left ventricular posterior wall thickness in diastole and left ventricular internal diameter in diastole. These values were determined in standard fashion.
from a 2D mode guided M mode image of the left ventricle at the level of the chordae tendinae; just beyond the tip of the mitral valve. Finally they underwent carotid ultrasonography using a 7.5 mHz linear array transducer of the SONOS 1500 ultrasound system (Hewlett Packard USA) with the patients in the supine position. Both carotids (left and right) were scanned with the heads tilted to the opposite side and neck slightly extended. The carotid intima medial thickness (CIMT) was defined as the distance between the leading edge of the luminal echo of the leading edge of the adventitia of the media. This measurement was taken at a site of 1.0 cm proximal to the carotid bulb.

3 Statistics

The data set were analysed using STATA 11.2, 2009 statistical software. The analysis of variance (ANOVA) was used to compare the dependent variables (right and left carotid intima media thickness with independent variables as follows: systolic blood pressure, diastolic blood pressure, fasting plasma glucose, 2 hour post-prandial plasma glucose, glycosylated haemoglobin, total cholesterol, high density lipoprotein cholesterol, uric acid, creatinine, left ventricular mass, body mass index and waist/hip ratio. Multivariate analysis was done for blood pressure (SBP and DBP) and fasting plasma glucose. The p values that were less than 0.05 were considered statistically significant.

4 Results

The 70 patients consisted of 36 females and 34 males. Their ages ranged from 30 to 71 years with a mean (SD) of 51.2 (10.63) years. The mean carotid intima thicknesses were largely equal on both sides. The mean (SD) values were 0.94 (0.12) mm and 0.94 (0.16) mm for the right and left sides respectively. Only 5 and 6 people smoked and drank significant amounts of alcohol respectively. These numbers were considered small and not further analysed. The cohort mean (SD) of the other measurements are shown in Table 1.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Mean (SD)</th>
<th>Risk Factor</th>
<th>Mean (SD)</th>
<th>Risk Factor</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/l)</td>
<td>7.93 (4.74)</td>
<td>HDL – C (mmol/l)</td>
<td>1.71 (0.78)</td>
<td>BMI (kg/m2)</td>
<td>27.15 (4.36)</td>
</tr>
<tr>
<td>2hPPG (mmol/l)</td>
<td>12.4 (5.59)</td>
<td>UA (micromol/l)</td>
<td>256.63 (113.75)</td>
<td>WHR</td>
<td>0.94 (0.06)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.03(2.78)</td>
<td>Cr (micromol/l)</td>
<td>96.26 (35.11)</td>
<td>SBP (mmHg)</td>
<td>123.63 (11.07)</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>5.09(1.59)</td>
<td>LVM (g)</td>
<td>153.49 (47.26)</td>
<td>DBP (mmHg)</td>
<td>83.03 (5.00)</td>
</tr>
</tbody>
</table>

FPG– Fasting plasma glucose; 2hPPG – 2 hour post prandial plasma glucose; HbA1c – Glycosylated haemoglobin; TC – Total Cholesterol; HDL – C – High density lipoprotein cholesterol; UA – Serum uric acid; Cr – Serum Creatinine; LVM – Left ventricular mass; BMI – Body mass index; WHR – Waist to hip ratio; SBP – Systolic blood pressure; DBP – Diastolic blood pressure;

Table 1: Mean (SD) values of measured atherosclerotic vascular disease risk factors in the study population.
When subjected to analysis of variance, the following exhibited a statistically significant relationship with carotid intima media thickness on the right: SBP, DBP, FPG, 2hPPG, TC, HbA1c, HDL – C and UA. For the left carotid intima media thickness, there was statistically significant difference as follows: SBP, DBP, LVM, FBS, 2hPPG, TC, HbA1c, and UA. These are detailed in Table 2.

<table>
<thead>
<tr>
<th>RF</th>
<th>Right CIMT</th>
<th></th>
<th></th>
<th></th>
<th>Left CIMT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RS</td>
<td>ARS</td>
<td>P</td>
<td>RS</td>
<td>ARS</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>SBP mmHg</td>
<td>0.9910</td>
<td>0.9838</td>
<td>&lt; 0.001</td>
<td>0.9913</td>
<td>0.9733</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>DBP mmHg</td>
<td>0.9910</td>
<td>0.9838</td>
<td>&lt; 0.0008</td>
<td>0.9913</td>
<td>0.9733</td>
<td>0.0115</td>
<td></td>
</tr>
<tr>
<td>FPG mmol/l</td>
<td>0.9995</td>
<td>0.9968</td>
<td>&lt; 0.001</td>
<td>0.9998</td>
<td>0.9985</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>2hPPG mmol/l</td>
<td>0.9995</td>
<td>0.9968</td>
<td>&lt; 0.001</td>
<td>0.9998</td>
<td>0.9985</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>TC mmol/l</td>
<td>0.9995</td>
<td>0.9968</td>
<td>&lt; 0.001</td>
<td>0.9998</td>
<td>0.9985</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>HbA1c %</td>
<td>0.9995</td>
<td>0.9968</td>
<td>&lt; 0.001</td>
<td>0.9998</td>
<td>0.9995</td>
<td>0.0005</td>
<td></td>
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<tr>
<td>UAm micmol/l</td>
<td>0.9995</td>
<td>0.9968</td>
<td>&lt; 0.001</td>
<td>0.9998</td>
<td>0.9985</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>


Table 2: Significant risk factors for atherosclerosis in Diabetes Mellitus.

It can be surmised from the above that the following are consistent significant risk factors for atherosclerotic vascular disease: SBP, DBP, FPG, 2hPPG, HbA1c, TC and UA.

Multivariate analysis was done for blood pressure indices and one parameter of glucose metabolism namely fasting plasma glucose. A significant positive association was found between SBP and FPG on the one hand (t=56.23, p<0.0001, 95% CI: 132.44 - 143.06); and DBP and FPG on the other (t=56.23, p< 0.0001, 95% CI: 90.64 - 97.23).

5 Discussion

Blood pressure when high is a risk factor for progressive atherosclerosis (Khan, 2006). The risk is linear with blood pressure, and starts as low as systolic blood pressure of 115 mmHg and diastolic blood pressure of 75 mmHg (Kozub, 2010). However some workers posit that there is no indication of a critical value (Kannel & Wilson, 2008). When hypertension co-exists with diabetes mellitus, microvascular and macrovascular complications leading to cardiovascular disease, stroke and end stage renal disease are accelerated (Sampanis & Zamboulis, 2008). As shown in this study even when within normal range, both systolic and diastolic blood pressures are associated significantly with carotid intima media thickness as well as measure of glucose metabolism namely fasting plasma glucose. Blacks have been found to manifest microvascular and macrovascular structural and functional abnormalities including even in the normotensive range of blood pressure (Din-Dziethan et al, 2004); including increased carotid intima media thickness (Heffernan et al 2008). As blood pressure rises the arterial walls respond to this stress by thickening its walls. The pulsatile force of blood flowing at high pressure damages the intima resulting in smooth muscle proliferation (Khan, 2006). For the carotids, these will result in increase in carotid intima
media thickness. The implication of these is that in patients with diabetes mellitus, blood pressure should be as low as possible; provided there is no accompanying hypotensive or ischaemic features. As shown in the United Kingdom Prospective Diabetes Study, hypertensive-diabetic patients had less microvascular and macrovascular end points if blood pressure control was tight (UK Prospective Diabetic Study, 1998). This benefit needs persistent tight control to control as another study (Holman et al, 2008) showed that during a 10 year post-interventional follow up, if there was no attempt to maintain tight control the benefit was lost within two years.

Measures of glycaemic control be it fasting blood sugar, 2 hour post prandial blood sugar or glycosylated haemoglobin were associated significantly with carotid intima media thickness in this study. Most diabetes especially the type 2 variety has as the centerpiece insulin resistance and hyperinsulinaemia. This biochemical state results in impairment of the arterial wall irrespective of vessel size, the result of which is diabetes induced vasculopathy (Utsunomiya, 2012). This vasculopathy is critical to the development of cardiovascular disease risk factors (Reaven, 2011) which most of the time have atherosclerosis as the basis. Hyperglycaemia using a point test as in fasting blood sugar or one that assesses general control over a period like glycosylated haemoglobin are associated with atherosclerotic changes (Keen et al, 1999). In fact as shown in the Hoorn study of carotid artery stenosis which is related to carotid intima media thickness, the odds for developing atherosclerotic changes in the carotid artery is higher in hyperglycaemic states (Beks et al, 1997). Hyperglycaemia does this by inducing endothelial dysfunction, which has been shown to be less with lower glycosylated haemoglobin as a measure of glycaemic state (Jensen-Urstad et al, 1996). This relationship between insulin resistance and reduced function of vessels has also been reported more recently (Kubota et al, 2011), with cellular mechanisms resulting in reduction or elimination of endothelial nitric oxide synthase being culprit. 2 hour post prandial blood sugar even in the absence of abnormal baseline glucose metabolism could induce early atherosclerosis (Cerrielo, 1998). Infact recent perspectives see it as a greater independent cardiovascular disease risk factor than fasting hyperglycaemia (Hanefeld et al, 1996). Post prandial hyperglycaemia is said to predispose to atherosclerosis and cardiovascular disease by inducing endothelial dysfunction, low grade inflammation and oxidative stress; a phenomenon described as “vascular failure” (Node & Inoue, 2009). Specifically, 2 hour post prandial blood sugar has been shown in the Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study been shown to demonstrate a continuous graded and direct relationship with cardiovascular death (DECODE Study Group, 2003). Compared to either fasting blood sugar or glycosylated haemoglobin, it has been shown to be a better predictor of cardiovascular risk (Tominga et al, 1999). This risk is said to start from 80 mg/dl (4.4 mmol/l) and by 140 mg/dl (7.8 mmol/l), the risk for cardiovascular disease has already gone up by about 58% (Node & Inoue, 2009).

Cholesterol was another significant risk factor that emerged from this study. Total cholesterol was high and high density lipoprotein cholesterol low. In the process of atherosclerosis, the first step appears to be endothelial dysfunction. Once this injury is established, monocytes are attracted. They adhere and migrate into the intima where they get activated and form foam cells. If cholesterol (especially low density lipoprotein cholesterol) get into the sub-intimal space, they get oxidized with release of products of lipid oxidation, free radicals and toxic products. Inflammatory cells are attracted and a state of chronic low grade inflammation is established. With this comes attraction of smooth muscle cells which proliferate and get deposited in the intima resulting in atherosclerotic plaque (Khan, 2006; Gilles, 2001). Oxidation of lipoproteins is enhanced in the presence of hyperglycaemia and hypertriglyceridaemia (Dinneen &
Gestein, 1997). The latter is high in diabetes mellitus largely due to reduction in lipoprotein lipase activity (Gugliano et al, 1996). Low high density lipoprotein was also significantly associated with increased carotid intima media thickness in this study. Low high density lipoprotein cholesterol is typical of diabetic dyslipidaemia (Treatment Options for Type 2 Diabetes Mellitus, 2000). This is because in the presence of hyperglycaemia, they are easily glycated increasing their clearance from circulation (Lyons, 1992).

Serum uric acid also had a significant association with carotid intima media thickness. Hyperuricaemia is an independent risk factor for cardiovascular disease (Lawrence Edwards, 2009). It could do this by its linkage with a wide variety of metabolic and vascular risk factors (Rich, 2000)as also shown in a study (Bo et al, 2001) where uric acid correlated with triglycerides, body mass index, systolic blood pressure, albumin excretion rate, C-peptide, creatinine clearance, high density lipoprotein cholesterol and glycosylated haemoglobin. Uric acid can stimulate vascular smooth muscle cell proliferation and endothelial dysfunction independent of hypertension (Beck, 1986). This in itself with increase in vascular intima media thickness will be further aggravated when hypertension, diabetes mellitus and dyslipidaemia are co-existing.

The association between carotid intima media thickness and left ventricular mass was significant only for one side; the left. There was however such tendency on the right, only that it did not attain statistical significance. Left ventricular mass is related to left ventricular hypertrophy which has been found to correlate positively with carotid intima media thickness (Sorof et al, 2003); leading the authors to suggest that the same adaptive process was operating in the myocardium and vascular media. All the factors that result in increased left ventricular mass, manifesting in the metabolic syndrome also initiate or worsen atherosclerosis. Hence it would be no surprise finding left ventricular mass as a significant association with atherosclerosis especially in diabetics.

In conclusion, when the skill and facilities are available, carotid intima media thickness can point to certain significant risk factors driving the process of athero-thrombosis. Targeting them by life style medicine and pharmacotherapy would then reduce the morbidity and mortality that would ordinarily accompany the disease in question. It is important to point out certain limitations in this work. Deliberate efforts were not made to exclude diabetics with pulmonary disease, obstructive sleep apnoea and systemic inflammatory diseases which could influence CIMT values. Pulmonary disease and systemic inflammatory diseases fuel atherosclerosis by background chronic inflammation and endothelial dysfunction. Obstructive sleep apnoea syndrome (Ciccone et al, 2012), gives rise to increased CIMT by a variety of mechanisms deriving from its pathophysiology namely hypoxia, hypercapnia, micro-arousals, sympathetic hyperactivity, oxidative stress, systemic inflammation and hypercoagulability.

References


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