Metabolic Syndrome in Subjects with Type-2 Diabetes Mellitus

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Background: Each component of metabolic syndrome (MS) conveys increased cardiovascular disease risk, but as a combination they become much more powerful. Vigorous early management of the syndrome may have a significant impact on the prevention of both diabetes and cardiovascular disease.

Aim: This study aims to determine the frequency of occurrence of MS and its relation to cardiovascular events among patients with type-2 diabetic mellitus.

Methods: The study group consisted of 218 type-2 diabetic patients. These were screened for hypertension, hyperlipidemia, obesity, microalbuminuria, and cardiovascular events.

Results: There were 128 (58.7%) males and 90 (41.3%) females. The mean age was 53.4 ± 6.3 years and a mean body mass index (BMI) of 25.5 ± 5.4 (males—23.4 ± 4.2; females—26.2 ± 5.7). MS was present in 55 (25.2%) of the study population. Systemic hypertension was the most common component of MS seen in 84 (38.5%) patients. The mean serum total cholesterol was 168.6 ± 25.8 mg% (men 153 ± 23; women 169 ± 19; $p>0.05$). Eight female and 12 male patients had serum total cholesterol ≥200 mg%. Dyslipidemia occurs more commonly in males than females. Obesity was more common in female patients than in males. Out of 128 male type-2 patients with diabetes seen, 111 (86.7%) were without microalbuminuria. The corresponding figure among the females was 90% (81 out of 90 patients).

Conclusions: The study demonstrated that MS was present in 25.2% of the study population. The syndrome and its different components were positively associated with a higher risk of stroke, peripheral vascular disease, and occurrence of microalbuminuria, $p<0.001$. Ischemic heart disease occurs rarely in the population. A long-term, targeted, intensive intervention involving multiple cardiovascular risk factors is recommended to reduce the risk of both cardiovascular and microvascular events among patients with type-2 diabetic mellitus.

Key words: cardiovascular risks ■ metabolic syndrome ■ diabetes

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INTRODUCTION

The clustering of cardiovascular disease risk components found in persons with abnormal glucose tolerance (impaired glucose tolerance or diabetes mellitus) has been labeled variously as Syndrome X,[1] the Insulin Resistance Syndrome,[2] the Deadly Quartet,[3] or metabolic syndrome (MS).[2] The World Health Organization (WHO),[4] has defined the syndrome to include a combination of impaired glucose regulation or diabetes, insulin resistance, raised arterial blood pressure, raised plasma triglycerides and/or low HDL-cholesterol, central obesity and/or BMI >30 kg m^{-2} and microalbuminuria. Each component of the cluster conveys increased cardiovascular disease risk, but as a combination they become much more powerful.[3] This means that the management of persons with MS should focus not only on blood glucose control but also include strategies for reduction of the other cardiovascular disease risk factors.[5] There is evidence that insulin resistance may be the common etiological factor for the individual components of the syndrome.[2,6] Vigorous early management of the syndrome may have a significant impact on the prevention of both diabetes and cardiovascular disease.[7]

Early detection of microalbuminuria requires the use of radioimmunoassay and dipsticks, such as Micral 1-Test immunoassay (Boehringer Mannheim, Mannheim, Germany), that are expensive and not always readily available in developing countries, such as Nigeria. Recently, some workers have shown that a combined negative sulfosalicylic acid test (SAT) result and a negative result on chemstrips, such as Albustic test (AT), virtually exclude microalbuminuria.[8]

The aim of this study is to determine the frequency of MS at the Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria and its relation to cardiovascular morbidity and mortality.

PATIENTS AND METHODS

A total of 218 subsamples of consecutive patients with type-2 diabetes seen between September 1999

and August 2001, in both the medical outpatient department and the medical wards of the Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Nigeria were studied.

Type-2 diabetic subjects were those who: 1) were treated with oral hypoglycemic agents only; 2) were treated with oral hypoglycemic agents only but required insulin during an acute illness; 3) whose diabetic state has been controlled on diet but previously on oral hypoglycemic agents; 4) have diabetes onset after the age of 40 years and a body mass index (BMI) above normal (≥25 kg/m^2 in females and ≥27 kg/m^2 in males).

Clinical parameters, including age, sex, duration of diabetes mellitus, drug therapy, BMI, and presence of hypertension, were recorded. BMI was calculated as the ratio of weight (kilograms) to standing height (meters) squared (kg/m^2); participants with a BMI 30 kg m^{-2} were classified as obese. To calculate waist-to-hip ratio (WHR), waist girth was measured at the umbilicus, and hip girth was measured as the largest diameter around the gluteal muscles. Blood pressure was measured by standard mercury sphygmomanometer after five minutes in supine position and recorded to the nearest 2 mmHg. Cuff size 20–31 cm was used in patients with an upper-arm circumference less than 32 cm, and cuff size 28–36 cm was used in patients with an upper-arm circumference above 32 cm. Systolic and diastolic blood pressures were taken as the appearance and disappearance of the Korotkoff sounds (phases I & V, respectively). Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg. Patients already on antihypertensives were taken as hypertensive. Occurrence of ischemic heart disease and stroke were taken from clinical history and previous documents or as an acute event and mortality recorded. Peripheral vascular disease was defined as an ankle-to-brachial systolic pressure ratio of less than 0.9 in either leg. Appropriate cuff sizes were used to measure ankle blood pressure over the posterior tibial vessels. Stroke was defined as the sudden or rapid onset of focal or global neurologic symptoms lasting more than 24 hours or leading to death and of vascular cause.

Early-morning urine specimen was taken from all eligible subjects. Each urine sample was divided into two parts: protein was *first* tested for in one part using the AT strip and then using the SAT. AT strips were used according to the manufacturer's instructions and results recorded as negative, trace, or 1 + positive. In the urine protein precipitation test with SAT, five drops of 20% sulfosalicylic acid were added to 3 mls of urine in one test tube, and that tube was compared with a tube of untreated urine held against a dark background. Tubes were to be observed immediately by two independent observers, and a result was assumed positive if both observers agreed after the addition of sulfosalicylic acid; turbidity was taken to indicate proteinuria. Combined negative results from these two tests (SAT and AT), were taken as excluding microalbuminuria.

Laboratory parameters, including plasma cholesterol and triglycerides, fasting, and two hours postprandial blood sugars, were estimated. Patients were diagnosed as having MS according to the WHO criteria:

- Central obesity (males: WHR >0.90; females: WHR >0.85) and/or BMI >30 kg m^{-2};

Table 1. Clinical Characteristics of Type-2 Diabetic Subjects with and without Metabolic Syndrome X

	Total Number Subjects with Type-2 Diabetes	Type-2 Diabetic Patients with Syndrome X	Type-2 Diabetic Patients without Syndrome X	p-Value
Number of patients (%)	218 (100)	55 (25.2)	163 (74.8)	<0.05
Age (years)	52 ± 5.8	53.4 ± 6.3	52 ± 5.8	>0.05
Duration of diabetes (years)	8.5 ± 7.1	9.4 ± 4.1	5.5 ± 3.2	<0.05
Waist–hip ratio >0.85 (%)	132 (60.6)	89 (54.9)	43 (53.8)	>0.05
Body mass index >25(Kg/m^2) (%)	108 (49.5%)	28 (50.9)	80 (49.1)	>0.05
Hypertension (%)	84 (38.5%)	29 (52.7%)	55 (33.7%)	<0.05
Mean SBP (mmHg)	147.5 ± 15.5	168 ± 13.5	125 ± 10.5	<0.05
Mean DBP (mmHg)	93 ± 9.5	105 ± 7.4	75 ± 8.3	<0.05
Fasting blood sugar (mmol/L)	5.4 ± 1.2	6.3 ± 1.8	5.0 ± 1.6	<0.05
Total cholesterol (mg%)	168.6 ± 25.8	162 ± 12.3	155 ± 18.6	<0.05
Serum total cholesterol >200 mg (%)	20 (9.2)	16 (29.1)	4 (2.5)	<0.05
Microalbuminuria (%)	26 (11.9)	17 (30.9)	9 (5.5)	<0.05

SBP: systolic blood pressure; DBP: diastolic blood pressure

- Dyslipidemia—raised plasma triglycerides (≥1.7 mmol l^{-1}; 150 mg dl^{-1}) and/or low HDL-cholesterol (<0.9 mmol l^{-1}, 35 mg dl^{-1} men; <1.0 mmol l^{-1}, 39 mg dl^{-1} women);
- Hypertension defined as systolic blood pressure of ≥140 mmHg and or diastolic blood pressure of ≥90 mmHg. Patients already on antihypertensives were taken as hypertensive;
- Microalbuminuria (urinary albumin excretion rate >20 μg min^{-1} or albumin:creatinine ratio >30 mg g^{-1}).

A subject with type-2 diabetes is taken as having MS if two of the criteria are fulfilled.[9] Quantitative data was expressed as mean ± SD. Students' t- and Chi-squared tests were used to assess the difference between the various subject groups. Statistical significance was placed at $p \leq 0.05$.

RESULTS

A total of 218 subjects with type-2 diabetes were studied. The mean age of all the patients was 52 ± 5.8 years (range 36–62 years), consisting of 128 (58.7%) males and 90 (41.3%) females. The mean duration of disease was 8.5 ± 7.1 years. The mean fasting blood glucose and two-hour postprandial blood glucose levels in the population were 5.4 ± 1.2mmol/l (range 4.3–6.2 mmol/l) and 7.9 ± 0.3mmol/l (range 7.4–8.5 mmol/l) respectively. The mean WHR was 0.97 and 0.96 in male and female subjects, respectively. The mean BMI was 25.5 ± 5.4 (males—23.4 ± 4.2; females—26.2 ± 5.7). Table 1 shows the baseline data of the subjects with and without MS.

Systemic hypertension was the commonest component of the syndrome seen in 84 (38.5%) subjects: more in females (48—37.5% males vs. 36–40% female subjects). The mean systolic blood pressure was 150 ± 16 mmHg in men and 145 ± 15 mmHg in women. The mean diastolic blood pressures were 94 ± 9 mmHg and 92 ± 10 mmHg, respectively, male vs. female.

Dyslipidemia occurs more commonly in males than females. Eight female subjects and 12 male subjects had serum total cholesterol ≥200 mg%. The mean serum total cholesterol for the entire group was 168.6 ± 25.8 mg% (men 153 ± 23; women 169 ± 19; $p>0.05$). Generally, the obese had significantly higher levels of serum total cholesterol than the nonobese.

Obesity was more common in female subjects than in males. In the population, 23 (10.6%), 87 (39.9%), 82 (37.6%), and 26 (11.9%) were underweight (BMI<20.0), of normal weight (BMI=20.1–25.0), overweight (BMI=25.1–29.9) and obese (BMI>30.0), respectively.

Out of 128 male type-2 diabetic patients, 111 (86.7%) subjects tested negative to both SAT and AT, thus being without microalbuminuria. The corresponding figure among the females is 90% (81 out of 90 subjects).

Table 2 shows the frequency of occurrence of MS in subjects with type-2 diabetes studied. MS was present in 25.2% (55 out of 218 subjects) of the study population. Combinations of the different components of MS were more frequent in males, except that the combination of obesity and hypertension was more common in females, $p<0.05$.

Table 3 shows the cardiovascular events in type-2 diabetic subjects with and without MS. The syndrome and its different components were positively associated with a higher risk of stroke, peripheral vascular disease, and occurrence of microalbuminuria, $p<0.001$. Ischemic heart disease occurs rarely in the population.

DISCUSSION

Multiple risk factors are associated with cardiovascular disease in subjects with diabetes, including hypertension, hyperlipidemia, obesity, and microalbuminuria,[10] which are the key components of MS. They have a risk of death from cardiovascular causes that is two- to six times that among persons without diabetes. Among white Americans, the age-adjusted prevalence of coronary heart disease (CHD) is twice as high among those with type-2 diabetes as among those without diabetes.[11]

People with MS are at increased risk for developing diabetes mellitus and cardiovascular disease, as well as increased mortality from cardiovascular disease and all causes. Because the implications of MS for healthcare are substantial, it is essential to estab-

Table 2. Frequency of Occurrence of Metabolic Syndrome in Type-2 Diabetic Subjects Studied

	Males (n=128)	Females (n=90)	p-value
Hypertension	48 (37.5%)	36 (40%)	<0.05
Obesity	11 (8.6%)	13 (14.4%)	<0.05
Hyperlipidemia	23 (18%)	11 (12.2%)	<0.05
Microalbuminuria	17 (13.3%)	9 (10%)	<0.05
Metabolic syndrome	32 (25%)	23 (25.6%)	>0.05

lish the prevalence of this condition in Nigeria. Whereas the global epidemic of type-2 diabetes is now well-characterized, data on the occurrence of MS in populations are limited.[12] The lack of an accepted internationally agreed definition has impeded epidemiological work on the prevalence and antecedents of this syndrome. Two definitions of MS have been proposed—one by the WHO,[9] and one in the U.S. Third Report of the National Cholesterol Education Program, Adult Treatment Panel, 2001 (NCEP–ATP III).[13] MS as defined by the NCEP was three or more of the following: fasting plasma glucose of at least 110 mg/dL (6.1 mmol/L), serum triglycerides of at least 150 mg/dL (1.7 mmol/L), serum HDL cholesterol less than 40 mg/dL (1.04 mmol/L), blood pressure of at least 130/85 mm Hg, or waist girth of more than 102 cm. However, there is only moderate agreement between the two definitions of MS, p=0.53, 0.46–0.60).[12] There is a need for a single internationally agreed definition of MS.

When the high proportion of subjects with MS in this study (25.2%) is considered, one would expect a lot of cardiovascular events, but the study revealed only 12 (5.5%) cases of stroke, occurring more commonly among subjects with MS, seven (58.3%) vs. five (41.7%). There was no documented case of CHD. This is in keeping with observations in Nigeria and black Africa of low incidence of CHD.[14-16] The general low values of cholesterol might be a contributing factor to this low prevalence. Peripheral vascular disease is the only cardiovascular event with a relatively high prevalence among this population with a frequency of 21.6% (47 out of 218 patients). This may be difficult to explain since the presence of the same cardiovascular risk factors predispose to the other known cardiovascular events.

The prevalence of MS (using the WHO definition) in Ireland was 21%.[17] The prevalence was higher in men (24.6%) than in women (17.8%). From the available data from "the Botnia study" (using the WHO definition) and involving families of Finland and Sweden descent, the prevalence was 84% and 78% (male:female) in subjects with type-2 diabetes.[18] In all subjects, a history of CHD, MI (myocardial infarction), and stroke was more common in those with MS than it was in those without MS (P<0.001). In the United States, the prevalence of MS was 21.8% using the ATP III definition.[13] Mexican Americans had the highest prevalence of MS (31.9%). The prevalence was similar for men (24.0%) and women (23.4%). The average figure of 25.2% that was obtained in this study is comparable to that in Ireland and the United States but significantly lower than the prevalence in Mexican Americans, Finland, Sweden, and Saudi Arabia. This study showed that in Nigeria, the prevalence is similar in men and in women. Similar documented studies in Africa are lacking.

Hypertension is the most frequently occurring component of MS in these subjects with type-2 diabetes, occurring in 38.5% (84 out of 218 subjects). This is significantly more than the Nigerian national average of 11.2%.[19] The average figure of 38.5% is however comparable to the prevalence rates of 10–55% quoted for diabetic patients across the continent of Africa.[20]

This study primarily investigated the prevalence of MS and its relation to cardiovascular morbidity and mortality. It has been documented that MS is a promoter of renal disease progression.[21] It is recommended that in these patients, hypertension should be managed aggressively with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, which have been shown to decrease proteinuria, lower blood pressure, and slow down the progression of renal diseases. The control of hypertension, dyslipidemia, proteinuria, obesity—among others—are intervention strategies for preventing progression of renal diseases.[21]

The study has demonstrated that MS occurs commonly among our local subjects with type-2 diabetes with an increased risk of occurrence of peripheral vascular disease and stroke. A long-term, targeted, intensive intervention involving multiple cardiovascular risk factors is recommended to reduce the risk of both cardiovascular and microvascular events as already documented among Caucasians.[22]

Table 3. Cardiovascular Events in Type-2 Diabetic Subjects with and without Metabolic Syndrome

Events	Total Type-2 Diabetic Subjects (n=218)	Type-2 Diabetic Subjects without the Metabolic Syndrome	Type-2 Diabetic Subjects with the Metabolic Syndrome
Peripheral vascular disease (%)	47 (21.6)	15 (31.9)	32 (68.1)
Stroke (%)	12 (5.5)	5 (41.7)	7 (58.3)
Coronary heart disease (%)	0 (0)	0 (0)	0 (0)
p<0.001			

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