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Original Research Article

Association between components of metabolic syndrome with chronic kidney disease in Benin City, Nigeria

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ABSTRACT

Background: The metabolic syndrome (MetS) is a constellation of risk factors of metabolic origin that promote the development of cardiovascular disease. More recently, an association with chronic kidney disease (CKD) is being reported. However, most of these studies are non-indigenous. The aim of the study was to determine the association between components of MetS and CKD in a Nigerian population.
Methods: Patients with MetS were recruited from a tertiary hospital in Benin City, Nigeria. Blood pressures and body mass indices were measured. Plasma glucose, serum lipids, urea and creatinine and spot urine albumin: creatinine ratio were analyzed. CKD was defined as estimated glomerular filtration rate <60mls/min± urinary ACR ≥30mg/g creatinine.
Results: Obesity, waist/hip ratio, diastolic blood pressure, total cholesterol and LDL-cholesterol were associated with CKD in univariate analysis. Body mass index and diastolic blood pressure were independent predictors of CKD. There was a relationship between the number of MetS traits and CKD.
Conclusions: CKD in patients with MetS may therefore result from a synergistic effect of components of the syndrome. Diastolic blood pressure and obesity may predict CKD in MetS patients. Early detection and treatment of obesity and hypertension may thus be a strategy to target the increasing prevalence of renal disease in MetS.

Keywords: Chronic kidney disease, Metabolic syndrome, Nigeria, Obesity

INTRODUCTION

The metabolic syndrome (MetS) is a state of insulin resistance characterized by obesity, serum lipid profile alterations, hypertension and hyperglycaemia.[1] It is highly prevalent worldwide with reported rates of 20-25% contrary to earlier belief, it is no more rare in Africa. This may be related to changes in lifestyle and diet. In Nigeria, the mean overall prevalence of MetS is 31.7%, 27.9% and 28.1% depending on the criteria for definition.[3]

The importance of MetS lies in the fact that each individual component of the disease entity carries a risk for severe vascular events and the combination may thus have a synergistic effect and therefore portend greater risk of complications.

Although it is widely known that the metabolic syndrome is a major risk factor for the development of cardiovascular disease and type 2 diabetes, its relationship with chronic kidney disease (CKD) is only recently being clarified. This risk is probably also related to the number of components of the syndrome present.[1] Establishing the degree of aetiological link between cluster of components of the syndrome and CKD may revolutionize the approach to management of such patients. Early detection and treatment of metabolic syndrome may be a cost-effective strategy to target the

increasing prevalence of CKD and end-stage renal disease (ESRD).[4] Therefore, subjects with MetS are candidates for CKD screening via dipstix proteinuria, spot urine for albumin or protein creatinine ratio (ACR or PCR), microalbuminuria testing and serum creatinine measurements. Also, patients presenting with one obvious component of the syndrome could be screened for the others. According to some researchers, an intensified multifactorial approach in MetS patients may be a promising strategy in CKD prevention.[5]

Reports on relationship between MetS and CKD are sparse in developing countries like Nigeria. Much more studies have been done in developed countries. The aim of the study was therefore to determine the association between components of the metabolic syndrome and CKD among Nigerian patients.

METHODS

The study was carried out in the University of Benin Teaching Hospital (UBTH). UBTH is a tertiary health care centre located in Benin City, the capital of Edo state, in the southern part of Nigeria. It is a referral centre for most neighbouring states.

Patients that consecutively presented in the diabetic and hypertensive clinic of UBTH with features of MetS according to the updated National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria were recruited for the study from September 2010 to May 2011. According to the NCEP ATPIII, the criteria for MetS is met in the presence of at least three of the following characteristics listed below [6]

- Abdominal (central) obesity, defined as waist circumference in men $\geq$102cm and in women $\geq$88cm
- Serum triglycerides $\geq$150mg/dl or drug treatment for elevated triglycerides
- Serum HDL cholesterol $\leq$40mg/dl (1.0mmol/l) in men and $\leq$50mg/dl (1.3mmol/l) in women or drug treatment for low high-density lipoprotein - cholesterol (HDL-C).
- Blood pressure $\geq$130/85mmHg or drug treatment for elevated blood pressure
- Fasting plasma glucose (FPG) $\geq$100mg/dl (5.6mmol/l) or drug treatment for elevated blood glucose.

Patients with other risk factors of CKD, febrile patients and those with evidence of urinary tract infection were excluded from the study. Informed consent was obtained from the participants after a thorough explanation of the procedure to them.

The sample size was determined using the formula[7]

$N=Z^2pq/d^2$

Where N = minimum sample size, Z = normal standard deviate at 95% confidence Interval = 1.96, P = prevalence, q = 1-p, d = precision set at 0.05

In a study of a group of Nigerians with metabolic syndrome by Ulasi et al, the overall prevalence of metabolic syndrome was found to be 15.9%.[8] Applying this as "p" in the Fischer's formula gives a sample size of 205.

However, to make allowances for attrition, 230 patients with metabolic syndrome were enrolled. An evaluation of these patients using socio-demographic data and clinical history was done. Questionnaires were interviewer-administered to all patients who satisfied the inclusion criteria. The following data were obtained: age, sex, marital status, ethnicity, religion, history of hypertension, diabetes, dyslipidemia and family history of hypertension and diabetes. For tobacco intake, history was significant for 'current smokers' who were those that had smoked within the last one month as defined in the data of the National Comorbidity Survey (NCS) of the United States.[9]

Blood pressure (BP) was taken using the Accoson mercury sphygmomanometer. The patient was rested for at least 5 minutes in a sitting position with the arm rested on a table such that the middle of the right arm was about the level of the heart. Korotkoff 1 was taken as the systolic blood pressure (SBP) and Korotkoff 5 as the diastolic blood pressure(DBP). BP was recorded to the nearest 2mmHg.[10] In accordance with the NCEP criteria, SBP of $\geq$130mmHg was considered 'elevated' while lesser values were 'normal' while for DBP, levels of <85mmHg were 'normal' while higher values were 'elevated' Height was measured to the nearest 0.1cm while weight was recorded to the nearest 0.1kg. Body mass index (BMI) was obtained by the Quetelet formula

$BMI = weight / height^2$ in kg/m^2

Waist circumference was measured at a level midway between the lower rib margin and the iliac crest with the tape around the body in a horizontal position to the nearest 0.1cm. Waist circumferences of $\geq$88.0cm and $\geq$102.0cm were considered as 'increased' for women and men respectively while lesser values were considered normal according to the NCEP criteria. With the measuring tape positioned along the widest diameter of the hips, the hip circumference was measured and read to the nearest 0.1cm. Waist/hip ratio was obtained by dividing the waist circumference by the hip circumference. Values of $\geq$0.8 and $\geq$0.9 were considered as increased for men and women respectively and lesser values considered normal.[11]

Five mls of venous blood was obtained from each subject after an overnight fast. Three mls was dispensed in to lithium heparin bottle while 2 mls was put into a plain bottle. The blood samples were spun at 300 revolutions

per minute. The plasma obtained in the lithium heparin bottle was used for the analysis of plasma creatinine and urea while the specimen in the plain bottle was used for assay of lipids. The samples were stored at -20^0 Celsius until analysis. Plasma creatinine was assayed using the modified Jaffe's method while the Urease-Berthelot's colorimetric method was employed for urea assay.[12,13] Total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were assayed by the cholesterol enzymatic endpoint method and the HDL precipitant method respectively.[14,15] Serum triglycerides was determined by the glycerol phosphate oxidase method while serum low density lipoprotein cholesterol (LDL-C) was calculated with the Friedewald formula (LDL = TC-TG/5-HDL).[16,17] Total cholesterol was considered high if a value of ≥200mg/dl was obtained and normal if the value was less.[18] For HDL-C, values of less than 50mg/dl for females and 40mg/dl for males were considered low while higher values were normal.[19] High LDL-C were values ≥100mg/dl while lesser values were normal.[19] For serum triglycerides, high values were those ≥150mg/dl while lesser values were normal.[19] Patients were considered to have dyslipidemia if they had one, two, three or all of the following: elevation of total cholesterol (≥200mg/dl) LDL-cholesterol (≥100mg/dl) triglycerides (≥150mg/dl) and low HDL-cholesterol (<40mg/dl).

The abbreviated version of the Modification of Diet in Renal Disease (MDRD) equation was used in estimating the glomerular filtration rate (GFR) viz: eGFR= 186.3x (serum creatinine) exp [-1.154] age exp [0.203] x [0.724 if female] x (1.21 if African.[20] Spot urine albumin: creatinine ratio was also done for the patients. Urinary albumin was assayed with immunoturbidmetry while urinary creatinine assay was done using the modified Jaffe's method.[12] The ratio of urinary albumin to creatinine was calculated for each patient and expressed in mg/g creatinine. Patients were considered to have chronic kidney disease if the estimated glomerular filtration eGFR <60mls/min±ACR ≥30mg/g creatinine. FPG was done using an accucheck glucometer. Normal FPG levels were values less than 100mg/dl while higher values were considered elevated.[19]

Data was analyzed using the Statistical Package for Social Sciences (SPSS) Inc. Chicago version 17.0 continuous variables were presented as mean and standard deviation while categorical variables were presented as frequencies and percentages. Differences between groups were compared using chi-square test for discrete variables. Where expected frequencies were less than 5, Fisher's exact test was applied. Association between variables and CKD was also tested using univariate regression analysis and odds ratio.

The significance of the MetS-related variables which were associated with CKD in univariate analysis was examined using multivariate logistic regression analysis. Confidence interval was at the 95% limit and p values of <0.05 were accepted as being statistically significant.

RESULTS

A total of five hundred and thirty hypertensives and diabetics were screened. Out of this, two hundred and thirty (43.4%) met the criteria for diagnosis of MetS. One hundred and sixty-two of those that met the criteria were females while sixty-eight were males. However, eight patients could not complete the study making a total of 222 patients in the population actually studied.

The mean age of the patients was 60.0±11.4 years with a range of 29-91years. They were all Nigerians. Binis accounted for a majority of cases (54.5%). Other ethnic groups represented included Esan (15.8%), Delta Ibo (8.6%), Urhobo (3.6%), Etsako (3.6%), Ika (2.7%) and other minority groups (11.2%). A total of 203(91.4%) patients were either known hypertensives or had BP ≥130/85 on presentation. The clinical and biochemical characteristics of the participants are shown in Table 1.

Table 1: Clinical and biochemical characteristics of the MetS subjects.

Characteristic	Values
Clinical	**Frequency (%)**
Presence of elevated blood pressure	203 (91.4)
Presence of elevated blood sugar	190 (85.6)
Presence of dyslipidemia	148 (66.7)
History of stroke	10 (4.5%)
History of ischemic heart disease	23 (10.4)
Family history of hypertension	49 (22.1)
Family history of diabetes	40 (18.0)
Current smokers	19 (8.6)
Significant alcohol intake	34 (15.3)
Clinical	**Mean ± SD**
Duration of diagnosis of hypertension	6.6±7.5yrs
Duration of diagnosis of diabetes	5.1±5.7 yrs
Body mass index	29.3±4.9kg/m^2
Waist circumference	98.0±11.8cm
Waist hip ratio	0.92±0.07
Systolic BP	135.1±18.7mmHg
Diastolic BP	82.9±11.6mmHg
Biochemical	**Mean ± SD**
Plasma creatinine	1.0±0.6mg/dl
GFR	87.7±40.0mls/min
FPG	129.3±57.9 mg/dl
Total cholesterol	193.8±56.2 mg/dl
LDL- cholesterol	124.6±48.9 mg/dl
HDL- cholesterol	48.2±18.0 mg/dl
Triglycerides	123.2±54.0 mg/dl
Urinary ACR	29.7±11.2mg/g cr$^-$
ACR = Albumin creatinine ratio	

Eleven (5.0%) of the patients had all five traits for diagnosis of the metabolic syndrome. Fifty nine (26.6%) had four traits in varying combinations while 152 (68.5%) of all patients had only three traits also in varying combinations. The largest combination of traits (29.3%) was in patients with hypertension/elevated blood pressure, diabetes mellitus/elevated fasting plasma glucose and increased waist circumference (Table 2).

Table 2: The various combinations of MetS traits in the patients.

Number of traits	Combination of trait	Frequency N	Percentage
3	H, D, W	65	29.3
3	H, D, h	43	19.3
3	H, W, h	12	5.4
3	H, D, T	7	3.1
3	H, W, T	7	3.1
3	D, H, T	6	2.7
3	H, h, T	3	1.4
3	D, W, h	6	2.7
3	D, W, T	3	1.4
4	H, D, W, h	43	19.4
4	H, D, W, T	9	4.0
4	H, W, h, T	4	1.8
4	H, D, h, T	3	1.4
5	H, D, W, h, T	11	5.0
Total		222	100

H = hypertension / elevated blood pressure, D = diabetes mellitus/ elevated \blood sugar. W= increased waist circumference, h = low HDL cholesterol, T = high triglyceride

Thirty three individuals with CKD and one hundred and twenty four patients without CKD had systolic BP elevation. There was no difference in elevation of systolic BP between the CKD group and the group without CKD. (p=0.666). On the other hand, diastolic blood pressure elevation was significantly more prevalent in the CKD group (p = 0.008).

Twenty six MetS patients in the CKD group and seventy three individuals in the group without CKD were obese. This difference was statistically significant with more obese individuals being in the CKD group (p=0.046). Similarly, there were also more MetS with' increased WHR' in the CKD group compared with the group without CKD (p = 0.02).

The proportion of MetS participants with high total TC and high LDL-C were significantly more in the patients with CKD compared with those without CKD (p=0.003 and 0.002 respectively). However, this was not the case with the other lipid fractions where there were no significant differences between the groups (p>0.05).

The proportion of metabolic syndrome patients with CKD was 15.8%, 27.1% and 45.5% in those with 3, 4 and 5 traits respectively; with a graded increase with additional MetS traits. This difference was observed to be statistically significant (Table 3).

Table 3: Relationship between number of MetS traits and CKD.

	Chronic kidney disease		
No. of traits	Yes	No	Total
3	24 (53.3%)	128 (72.3%)	152 (68.4%)
4	16 (35.6%)	43 (24.3%)	59 (26.6%)
5	5 (11.1%)	6 (3.4%)	11 (5.0%)
Total	45 (100.0%)	177 (100.0%)	222 (100.0%)

$X^2 = 7.612$, p = 0.019

Table 4: Regression analysis of clinical and laboratory MetS-related variables with CKD.

	Univariate Regression		Multivariate Regression	
Variables	**P**	**OR**	**P**	**OR**
Elevated SBP	0.666	1.175 (0.564 - 2.451)	-	-
Elevated DBP	0.009	2.437 (1.253- 4.741)	0.009	2.578 (1.268 – 5.243)
Elevated FPG	0.831	1.078 (0.539 - 2.155)	-	-
High TC	0.003	2.770 (1.410 - 5.442)		
High LDL-C	0.527	1.254 (0.622 – 2.530)	0.146	1.895 (0.801 – 4.488)
LDL-C_{150}	0.002	2.902 (1.468 – 5.740)		
High TG	0.457	1.330 (0.627 - 2.821)	0.064	2.369 (0.951 – 5.902)
Low HDL	0.668	0.654 (0.598 - 2.230)	-	-
Obesity	0.048	1.950 (1.005 - 3.783)	0.043	0.458 (0.216 – 0.974)
Increased WC	0.158	1.821(0.793 - 4.180)	-	-
Increased WHR	0.041	2.809(1.045 to 7.549)	0.454	1.509(0.514-4.428)

SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, WC = waist circumference, WHR = waist hip ratio, TC =total cholesterol, LDL-C= LDLcholesterol,HDL-C= HDL cholesterol, TG= triglycerides

The variables associated with CKD in univariate regression included diastolic BP, TC >200mg/dl, BMI >30kg/m^2, increased waist hip ratio as well as LDL-C values >150mg/dl (p = 0.002) but not LDL-C>100mg/dl. Out of the MetS-related variables which were significantly associated with CKD in univariate analysis, the only independent predictors of CKD in multivariate analysis were elevated diastolic BP (p = 0.009) and obesity (BMI) >30kg/m^2 (p = 0.043) (Table 4).

DISCUSSION

The number of females with metabolic syndrome exceeded the males in the study. This does not translate to female sex predilection in MetS since this study was a hospital-based study where patients were recruited among those presenting with certain morbidities. The greatest proportion of the MetS patients had only 3 traits. Severe metabolic syndrome (with 4 or 5 traits) was present in 70 (31.5%) patients while those with 5 traits made up only about 5% of the total. This distribution is not much different from existing data in literature.[21,22]

The determinants of CKD in the metabolic syndrome patients were elevated diastolic blood pressure and obesity. Similarly, Hsu et al reported that over weight and obesity were among the most potent risk factors for ESRD in a large cohort study in that study, the hazard ratio for ESRD increased progressively with increasing weight.[23] These findings are also consistent with data from the Framingham Offspring study which show that higher BMI is a risk factor for development of new onset kidney disease.[24] Similarly, Stengel found an increased risk of CKD for persons with a baseline BMI of >35kg/m^2.[25] Gender differences in this association have also been documented in the literature. Iseki and colleagues reported baseline BMI predicted future ESRD risk for men but not for women in a Japanese cohort.[26] However, the proportion of persons with high BMI, as compared with this study was relatively few, even though the sample size was much larger. The study design was also different: Our study was a cross-sectional study while that of Iseki and colleagues was a cohort study. Central obesity (increased waist hip ratio) was also associated with CKD but however was not an independent predictor of CKD in this study. Noori et al however found waist circumference to be a more important determinant of CKD than BMI and waist hip ratio.[27] The differences may be related to study population, sample size as well as the study design. Noori's study was not restricted to MetS patients and was a cohort study that involved a much larger number of participants. Racial differences may also be contributory.

There was a significant relationship between the number of components of MetS and CKD defined as GFR<60mls/min: The prevalence of CKD was highest in those with all traits and least in those with only three components. Similar observations have been reported severally in literature.[22,28,29] According to Lea of the Emory University, the individual components of the MetS do not seem to have much effect on kidney disease progression but when taken together, the syndrome does seem to have a significant impact.[30] There may thus be a synergistic effect among the various components in their association with CKD.

Diastolic BP level was strongly associated with CKD in this study. Hypertension has long been identified among the leading causes of CKD in Nigeria.[31] A clear relationship between ESRD incidence and the level of systolic and diastolic BP was demonstrated in the Multiple Risk Factor Intervention Trial (MRFIT).[32] However, in this study, this association was not noticed for systolic blood pressure elevation. The reason for this is unclear. Diastolic BP was once believed to be the most relevant hemodynamic parameter as a predictor of prognosis in hypertensive patients but over the years, systolic BP elevation has become increasingly important based on some epidemiological studies.[33,34] Almost four-fifths of the patients in this study had elevated systolic blood pressure. This is not surprising, considering that most of our patients were middle aged and elderly. Systolic BP is well known to rise with age.[35]

Fasting plasma glucose level was not associated with CKD. One must interprete this result with caution. Most of the diabetic patients were already on medications which could cause acute changes in blood glucose and may therefore not be a good index of level of glucose control. Also, glycated haemoglobin (Hb) levels may be a better index of glycemic control and thus may be a more useful determinant of microvascular complications of DM (including renal disease) than plasma glucose per se. In the atherosclerosis risk in communities study, the association between fasting blood glucose and the risk of cardiovascular disease or death from any cause was not significant in models with adjustments for co-variates including glycated Hb but the converse was true for glycated hemoglobin.[36] However, glycated Hb was not assayed in this study.

The presence of dyslipidemia was associated with CKD in this study. There was an association between total cholesterol and CKD as well as between LDL-cholesterol and CKD in univariate analysis. Patients with TC >200mg/dl and LDL-C >150mg/dl were more likely to have CKD. However, this association did not hold in multivariate analysis possibly due to interplay of other variables. The association between LDL-C and CKD was not significant even in univariate analysis when the traditional cut-off value for normality (100mg/dl) was used. This may be explained by the fact that most of the patients had LDL-C above this value as evidenced by the mean value, resulting in skewed distribution. It is also possible that LDL-C may not have any effect on kidney

function at this level. Dyslipidemia has been hypothesized to cause kidney damage and to play an important role in the progression of renal failure.[37] Several studies have also shown that dyslipidemia may be a risk factor for renal disease. Data from the Physicians Health Survey indicated that elevated total cholesterol levels, high non-HDL cholesterol levels and LDL/HDL cholesterol ratios were all associated with an increased risk of serum creatinine elevation.[38] In the atherosclerosis Risk in communities study, high triglyceride and low HDL cholesterol levels were associated with an increased risk for developing renal dysfunction.[39]

Our study however showed no association between triglycerides/ CKD and HDL-C/CKD. Conversely, the World Health Organization multinational study of vascular disease in diabetes, which included 959 type 1 and 3558 type 2 diabetic patients with a mean follow-up of 8.4 years, failed to show an association of serum cholesterol with development of renal failure. Serum triglycerides were associated with appearance of renal failure only in type 2 diabetic patients.[40] One must remember that the patient population differed from ours as theirs included patients without MetS patients. Thus, hyperlipidemia may be a risk factor for renal disease in these subjects.

CONCLUSION

In summary, it is obvious from this study that CKD in metabolic syndrome may result from a synergistic effect of all the components of metabolic syndrome. Elevated diastolic blood pressure and obesity may be independently associated with CKD patients. Body mass index may be a more important determinant of CKD than waist hip ratio or waist circumference in this sub-set of patients. The study had some limitations. Screening for CKD and albuminuria were not repeated for the patients after an interval to accurately establish diagnosis. Due to the cross-sectional design of the study, causality cannot be established in real terms. Also, the study was hospital based and not population based, limiting to some extent, the generalisability of the findings.

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