

Metabolic Syndrome in Chronic Kidney Disease: Prevalence and Risk-Factors Analyses

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ABSTRACT: **Background:** Metabolic syndrome (MS) has been recognised as a risk factor for chronic kidney disease (CKD). **Methods:** To determine the prevalence of (MS) and adequacy of the National Cholesterol Education Programme/ Adult Treatment Panel III (ATP III) criteria for the diagnosis of MS in Nigerians with CKD, 168 CKD outpatients, (men 86), aged ≥ 35 years recruited from the Nephrology Outpatient Clinics of the University of Nigeria Teaching Hospital, Enugu south-eastern Nigeria, were evaluated. In addition to waist circumference (WC) and blood pressure measurements, fasting plasma glucose and lipid profile were determined by standard laboratory methods. **Results:** MS prevalence of 40.5% was recorded with more men (46.5%), than women (34%) having the syndrome. Sex-specific and significant differences were recorded in fasting plasma glucose (FPG) and serum triglycerides (TG) ($p < 0.05$) but not in waist circumference (WC) of the subjects. WC cut-off point of ≥ 93 cm recorded higher sensitivity (61.3%), positive predictive value (61.3%) and odd ratio (5.4) than 41.2%, 56% and 2.5% respectively given by the ATP III cut-off point of >102 cm. Fasting triglyceridaemia, hypertension and low high density lipoprotein-cholesterol (HDL-C) formed a cluster in majority of the subjects. **Conclusions:** The prevalence of the MS in CKD was moderately high with the male patients recording higher values than the females. The ATP III criteria, especially the WC may need adjustments to make them suitable for the diagnosis of MS in Nigerians with CKD. Suggested criteria for MS diagnosis in the study population are as follows: excess WC ≥ 93 cm for men and women; fasting hypertriglyceridaemia ≥ 1.70 mmol/l; raised blood pressure $\geq 130/85$ mmHg, low HDL-C (men ≤ 1.0 mmol/l, women ≤ 1.3 mmol/l) and FPG ≥ 5.6 mmol/l. More research is needed to fine-tune the diagnostic potentials of HDL-C and FPG for the CKD patients.

Key words: Metabolic syndrome, Obesity, Insulin resistance, Glucose intolerance, Dyslipidaemia

Introduction

Metabolic syndrome (MS), a recognised risk factor for chronic kidney disease (CKD) (1-3) is characterized by truncal obesity, elevated blood pressure (BP), dyslipidaemia, hyperglycaemia and insulin resistance (IR) (4-7). Several mechanisms have been proposed for MS related CKD. These include development of systemic and glomerular hypertension due to decreased renal flow and increased sodium reabsorption, renal dysfunction (8-11) as a result of cytokine induced endothelial dysfunction and oxidative stress (12), glomerular hyperfiltration caused by hyperglycaemia, stimulation of sympathetic nervous and rennin-angiotensin-aldosterone systems by insulin resistance (13) and inhibition of vasodilation via reduced nitric oxide bioavailability (14) as well as direct injury to kidney cells (15) by hyperuricaemia associated with MS (14).

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Studies suggest different pattern of clustering of the risk factors of MS in individuals from different ethnic groupings (16-18). For instance, ethnic-specific values have been advocated and defined for Chinese, Japanese and South Asians (19) based on this fact (20). Effects of obesity may vary as a function of ethnicity necessitating the development of ethnic-specific values to identify individuals at greatest risk (21). In this study, we determined the prevalence of the MS and the adequacy of the ATP III criteria in the diagnosis of the syndrome in CKD patients of Nigerian origin.

Materials and Method

One hundred and sixty eight, CKD outpatients, (men 86), aged 35 years and above {when the syndrome was said to be more prevalent (22)}, who attended the Nephrology Outpatient Clinics of the University of Nigeria Teaching Hospital, Enugu south-eastern Nigeria, participated in the study. They had glomerular filtration rate less than 60 ml/min for more than 3 months (23). The Ethics Committee of the Hospital approved the study protocol and informed consent was obtained from all the subjects before data and sample collections. Exclusion criteria consisted of secondary hypertension, clinical or laboratory evidence of congestive heart failure, coronary artery disease, history of cerebro-vascular accident, valvular heart disease, diabetes or acute kidney injury.

Waist circumference was measured to the nearest 0.5cm at a level midway between the lowest rib and the iliac crest using measuring tape. Fasting blood samples, (5ml), were collected from patients between 8 am and 11 am each day using standard methods (24). Two millilitre of blood sample was put into fluoride oxalate tube and spun at 3000g for 5 minutes and the plasma was used for glucose estimation. The rest of the sample was put into a plain sample tube and allowed to clot at room temperature. They were similarly spun and the serum harvested and used for the determination of triglycerides and high density lipoprotein cholesterol. Plasma glucose was determined by the method of Trinder (25), while serum triglycerides by the method of Buccolo and David (26). High density lipoprotein cholesterol was estimated in the serum supernatant after precipitating β -apoprotein containing lipoproteins using the method of Allain et al. (27). Cromatest^(R) mono-reagent test kits were used for biochemical determinations.

Analyses of data were done with GraphPad Prism version 2 statistical programme. Odd ratio (OR), sensitivity, specificity, positive predictive value (PPV) and prevalence were calculated using standard formulae (28).

Definitions

Metabolic syndrome diagnosis was made using the National Cholesterol Education Programme/ Adult Treatment Panel III, (NCEP/ATP III), criteria (6). Metabolic syndrome was diagnosed in the presence of any three or more of the following factors: excess waist circumference, men (>102cm), women (>88cm); raised fasting triglycerides ($\geq 1.70\text{mmol/l}$), raised blood pressure ($\geq 130/85\text{mmHg}$), low HDL-C men ($\leq 1.0\text{mmol/l}$), women ($\leq 1.3\text{mmol/l}$) and fasting blood glucose $\geq 5.6\text{mmol/l}$.

Results and Discussion

A total of 68 CKD patients had three or more abnormal predictors and therefore fulfilled the condition for the diagnosis of the MS giving a prevalence of 40.5%. More men, 40 (46.5%), than women, 28 (34%), had the syndrome. The men had more unfavourable parameters than the women, (Table 1). Only FPG and TG differed significantly between the male and female subjects (Table 1).

Table 1: Comparison of parameters between male and female chronic kidney disease patients.

Parameters	All patients (n = 168)	Male patients (n = 86)	Female patients (n = 82)	p-values (male vs. female)
FPG (mmol/L)	5.5 ± 1.9	5.9 ± 2.5	5.1 ± 0.6	0.04*
TG (mmol/L)	2.1 ± 0.7	2.4 ± 0.8	1.8 ± 0.4	0.01*
HDL (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	0.18
DBP (mmHg)	89 ± 16	91 ± 16	88 ± 15	0.32
SBP (mmHg)	149 ± 27	150 ± 25	148 ± 29	0.27
WC (cm)	88.7 ± 8.9	89.5 ± 9.0	88.0 ± 8.9	0.16

* p < 0.05.

FPG: fasting plasma glucose; **TG:** Triglyceride; **HDL:** High density lipoprotein; **DBP:** diastolic blood pressure; **SBP:** Systolic blood pressure.

There were no sex-specific significant differences between the WC and HDL-C of the subjects. This seems to negate the use of separate cut-off points for these parameters in the diagnosis of the MS as in published reports. More of the subjects, 122 (72.6%) had raised systolic blood pressure (SBP), than raised diastolic blood pressure 80 (47.6%). However this has no influence on the prevalence of MS since the elevation of one or both of them is regarded as positive.

Less than one third of the patients had abnormal FPG, HDL-C and WC. The ATP III cut-off point for blood pressure ($\geq 130/85$ mmHg) gave high value for sensitivity, 94%, low specificity (38%), PPV of 50.8% and OR of 9.8 in the general patient's population. Its specificity among the men and women respectively was also low while the sensitivity was high; (100% among the male patients). This would suggest that the cut-off point was too low. Substituting $\geq 140/90$ mmHg in place of $\geq 130/85$ mmHg in the general patient's population gave lower values for sensitivity 79.4%; specificity, 44%, PPV of 49.1% and OR of 3 but the same prevalence value (Table 2).

These were not remarkable improvements on the values given by the ATP III cut-off point. The slight improvement in specificity, from 38% to 44%, was not significant in view of the fact that the same prevalence value was recorded. The later figures 140/90mmHg is used routinely in the locality²⁹⁻³². However, since they did not provide significant improvement as cut-off point for blood pressure, the ATP III cut –off point may yet be used for the population.

Similarly the ATP III cut-off point (>102 cm and >88 cm) for WC of men and women respectively, gave low sensitivity, 41.2%; moderate specificity 78%, average PPV of 56% and low OR, 2.5. These were improved when ≥ 90 cm was substituted for >102 cm, to give 91.7%, 37.5%, 52.4% and 6.6 for sensitivity, specificity, PPV and OR respectively but the prevalence was raised from 40.5% to 42.9%. Even better improvements were obtained by substituting ≥ 93 cm; 61.3%, 77.4%, 61.3% and 5.4 respectively. The prevalence was even lowered from 40.5% to 36.9% (Table 2). Similar trends were observed in the male and female groups (Table 2).

The substituted value, ≥ 93 cm is nearer the mean value obtained for WC in the study, 88.9cm, and the International Diabetes Federation cut-off point of 94cm. Since no sex-specific significant difference was observed in WC, the same cut-off point may be used for men and women. It has previously been shown that the effects of obesity may vary as a function of ethnicity necessitating the development of ethnic-specific values to identify individuals at greatest risk (21). In a recent joint statement issued by six organizations involved in the study of MS, WC was assigned no specific figure but was said to be population- and country-specific (30). Ethnic-specific values for WC have been advocated and defined for Chinese, Japanese and South Asians (19) based on this fact (20). The cut-off point, ≥ 93 cm may therefore be preferred for the study population. The World Health Organization (WHO) and American Association of Clinical Endocrinologists (AACE), did not include WC as a measure of obesity. They have, instead, body mass index and or waist-hip ratio. Regrettably, these were not evaluated in this study.

Table 2: Calculated indices using the ATP III and suggested cut points for male, female and general patients population ¹

	>102	WC (cm) ≥ 90	≥ 93	BP 130/85 (mmHg)	BP 140/90 (mmHg)	FPG (5.6 mmol/L)	TG > 1.7 (mmol/L)	HDL < 1.0 (mmol/L)
Male								
Sensitivity (%)	10	91.3	45	100	95	75	95	45
Specificity (%)	100	40	78.3	39	39.1	87	39	95.6
PPV (%)	100	63.4	58.8	58.8	57.6	83.3	57.6	90
OR (n)	2.6	7.0	2.9	12.9	12.2	20	12.2	18
Prevalence (%)	46.5	53.5	46.5	46.5	46.5	46.5	46.5	46.5
Female								
Sensitivity (%)	85.7	92.2	91	85.7		28.5	78.6	71
Specificity (%)	59	35.7	76.7	333		88.9	85.2	85
PPV (%)	53	40	58.8	40		57	73.3	71.4
OR (n)	8.7	6.7	32.9	3		3.2	21	14
Prevalence (%)	34	31.7	26.8	34	34	34	34	34
All								
Sensitivity (%)	41.2	91.7	61.3	94	79.4	55.9	88.2	55.9
Specificity (%)	78	35.7	77.4	38	44	88	64	90
PPV (%)	56	52.4	61.3	50.8	491	76	62.5	79.2
OR (n)	2.5	6.6	5.4	9.8	3	9.3	13.3	11.5
Prevalence (%)	40.5	42.9	36.9	40.5	40.5	40.5	40.5	40.5

OR: Odd ratio; **PPV:** Positive predictive value. ¹ All values in percentage except OR.

The ATP III cut-off point for FBG gave more than average figures for sensitivity 56%, specificity, 88%, PPV, 76% and OR of 9.3 in male plus female patients group (Table 2). It gave equally acceptable figures among the male patients, 75%, 87%, 83.3% and 20 respectively (Table 2), but low sensitivity among the female patients (28.5%) (Table 2). The parameter qualifies as a predictor of MS in the males-plus-females and males-only groups but not in the females-only group where it gave low sensitivity. Sex-specific reference values have not been suggested for plasma glucose. Therefore, the only inference from this result may be that hyperglycaemia may not be a good predictor of the MS in CKD women as in men. This is supported by the low incidence (19.5%) of hyperglycaemia among the female patients.

The ATP III cut-off point for TG and HDL-C seemed right for all the groups with sensitivity 88.2% and 55.9% specificity 64% and 90% PPV 62.5% and 79.2% OR 13.3 and 11.5 respectively in the general population (Table 2). Much better figures were obtained among the female patients, 78.6% and 71%, 85.2% and 85%, 73.3 and 71.4%, 21 and 14 respectively. TG and HDL-C gave a low specificity, 39%, and low sensitivity, 45% respectively among the male patients (Tables 2). Attempts to adjust the cut-off point to improve the specificity among the male patients did not yield better results and it may be inferred that serum triglycerides may not be a good predictor of the syndrome in the male CKD patients just as hyperglycaemia may not be good enough for the female patients.

HDL-C may qualify as a good predictor of the MS in chronic kidney disease in spite of the low prevalence of abnormal results, 29.3%, in the study population. However, 83.3% of these abnormal results were associated with MS and this reflects in its high specificity, 90%. It displayed adequate OR, sensitivity and specificity especially among the female patients as shown above. In male patients, HDL-C had low sensitivity and very high specificity (Table 2). This goes to suggest that the ATP III cut-off point for this parameter for the male patients was too high. The WHO criteria contains lower cut-off points for men and women, < 0.88mmol/l and < 0.98mmol/l respectively. Data generated in this study contained no values as low as these cut-off points. Therefore they are unsuitable for the study population.

Conclusions

The prevalence of the MS in CKD was moderately high with the male patients recording higher values than the female. Analyses of risk factors showed the inadequacy of the ATP III criteria for predicting MS in the study population and clustering of Low HDL-C, raised FPG, WC and TG as predictors. The usefulness or otherwise of these predictors, as indicated by their sensitivity, specificity, PPV and/or OR, varied with the group, males-plus-

females, males only or females only, being considered. Suggested criteria for MS diagnosis in the study population are as follows: excess WC ≥ 93 cm for men and women; fasting hypertriglyceridaemia ≥ 1.70 mmol/l; raised blood pressure $\geq 130/85$ mmHg, low HDL-C (men ≤ 1.0 mmol/l, women ≤ 1.3 mmol/l) and FPG ≥ 5.6 mmol/l. More research is needed to fine-tune the diagnostic potentials of HDL-C and FPG for the CKD patients. More work is required to improve the predictive potential of low HDL-C and FPG in the study population.

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