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## Research Article

# Pattern of Risk Factors Clustering Among Diabetes, Hypertension, Chronic Kidney Disease and Apparently Healthy Subjects with the Metabolic Syndrome

<sup>1</sup>Okeke, Nduka Jude, <sup>2</sup>I.S.I. Ogbu, <sup>3</sup>Felix Edegbe, <sup>4</sup>Eze Clementina N. and <sup>5</sup>Obi Ihuoma A.

<sup>1</sup>Department of Chemical Pathology, Faculty of Clinical Medicine, Ebonyi State University, Abakalilki, Ebonyi State, Nigeria

<sup>2</sup>Department of Medical Laboratory Science, Evangel University. Akaeze, Ebonyi State, Nigeria

<sup>3</sup>Department of Histopathology, Faculty of Clinical Medicine, Ebonyi State University, Abakalilki, Ebonyi State, Nigeria

<sup>4</sup>Basic School of Midwifery, Alex Ekwueme University Teaching Hospital, Abakalilki, Ebonyi State, Nigeria

<sup>5</sup>Department of Nursing Services, Ebonyi State University, Abakalilki, Ebonyi State, Nigeria

## Abstract

**Background and Objective:** Metabolic syndrome (MS) is a health condition associated with several factors including central obesity, glucose intolerance, dyslipidaemia, (low HDL-C, hypertriglyceridaemia) and elevated blood pressure. The aim of this study was to determine the pattern of clustering of these factors in diabetes, hypertension (HBP), chronic kidney disease, (CKD) and apparently healthy subjects, (AH), with the MS. **Materials and Methods:** A cross-sectional study was carried out. A total of 531 subjects including 174 diabetics, 136 hypertensive, 84 with CKD and 137 apparently healthy (37-72 years of age) participated in this study. Fasting plasma glucose level and lipids were analyzed while waist circumference and blood pressure was measured using standard procedures. MS was diagnosed according to the National Cholesterol Education/Adult Treatment Panel 111, (ATP 111), criteria. Graphs and logical binary regression were utilized to assess the validity of each parameter and metabolic syndrome. **Results:** Frequency of MS in this study were 68, 47, 35 and 26% for diabetes, hypertension, CKD and AH subjects respectively. Among the subjects with the MS, 52, 71, 65.5 and 78.8% of DM, HBP, CKD and AH subjects had three factors; correspondingly 39.7, 27.4, 34.5 and 21.2% had four factors and 8.2, 1.6, 0, 0 had five factors. Central obesity was diagnosed in 96, 76, 60 and 61%; hyperglycaemia was diagnosed in 100, 65, 76 and 77%; hypertriglyceridaemia was diagnosed in 82, 73, 54 and 43%; low HDL-C in 88, 85, 65 and 52% while elevated blood pressure was diagnosed in 84, 100, 43 and 36% of the DM, HBP, CKD and AH subjects with the MS respectively. **Conclusion:** Results suggested that MS could be caused by the central obesity and since waist circumference can easily and accurately be measured, it is an easier and definite method of screening for the MS in the population.

**Key words:** Metabolic syndrome, diabetes, obesity, dyslipidaemia, chronic kidney disease

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**Corresponding Author:** Okeke, Nduka. Jude, Department of Chemical Pathology, Faculty of Clinical Medicine, Ebonyi State University, Abakaliki, Nigeria

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**Competing Interest:** The authors have declared that no competing interest exists.

**Data Availability:** All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Metabolic syndrome (MS) is a combination of medical disorders that increase the risk of developing cardiovascular disease and type 2 diabetes mellitus (T2DM). The disorders include central obesity, glucose intolerance, atherogenic dyslipidaemia of high triglyceride, low high density lipoprotein cholesterol and elevated blood pressure among others. The presence of three out of five risk factors is diagnostic of MS<sup>1</sup>. The 5 risk factors include central obesity/excess waist circumference, (men >102 cm, women >88 cm), elevated fasting blood glucose ( $\geq 5.6$  mmol L<sup>-1</sup>), elevated serum triglyceride [ $\geq 1.7$  mmol L<sup>-1</sup>, low HDL-C (men  $\leq 1.0$  mmol L<sup>-1</sup>, women  $\leq 1.3$  mmol L<sup>-1</sup>)] and elevated blood pressure, ( $\geq 130/85$  mm Hg<sup>2</sup>) (Table 1).

MS promotes 2-fold increased risk for cardiovascular disease and a 5-fold risk of developing T2DM compared with those without the syndrome. It also increases risk of fatty liver disease, cancer and stroke<sup>3</sup>. The prevalence of MS in most western countries is between 20 and 30% of the adult population and in some populations or segments of the population is even higher but in developing world, the prevalence is lower but with increasing affluence, dietary changes and aging of the population, the prevalence undoubtedly will be elevated<sup>4</sup>. In a previous study conducted on rural community in Nigeria, prevalence of metabolic syndrome was found to be 12.1% but another study conducted on teachers in semi urban town showed a prevalence rate of 20% hence showing a parallel rise with worldwide value<sup>5,6</sup>. The global spread of metabolic syndrome are the end result from the years of taking "a modern diet" (high calorie-low fiber fast food) high in refined carbohydrate such as breads, starches and sugars, as well as decreased physical activity occasioned by lack of exercise, sedentary lifestyles and mechanized transportation. In view of enormity of potential health implication of MS, early screen is important therefore, the clustering of risk factors assessment in the early detection, monitoring/follow up of individuals who are at great risk of developing MS is pertinent when we consider the cost implication for developing country in assessing all the risk

factors before a diagnosis is made. Most worked one on MS have been on diagnosis, prevalence but none on screening. This study, therefore, assessed the pattern of clustering of these risk factors among diabetes, hypertension, chronic kidney disease (CKD) and apparently healthy (AH) subjects with the MS in Enugu Eastern Nigeria, with a view of advocating possible risk factor that should be used in screening for MS.

## MATERIALS AND METHODS

**Experimental design:** This cross-sectional study was carried out at the department of chemical pathology and internal medicine. Data from a previous report (The Frequency of Metabolic Syndrome among Hospital-based Patients in the University of Nigeria Teaching Hospital and Apparently Healthy People in Enugu Metropolis, PhD thesis by I.S. I Ogbu, University of Calabar Nigeria) were analyzed. The study population (total 531) was made up of 174 (men 96, women 78) diabetics, 136 (men 76, women 60) hypertensive, 84 (men 43, women 41) patients with chronic kidney disease (CKD) and 137 (men 68, women 69) apparently healthy subjects. The patients were attending respective outpatient clinics of the University of Nigeria Teaching Hospital, Enugu while the apparently healthy subjects were mostly hospital workers who were not on any drug therapy at the time of sample collection. Ethical Clearance was obtained from the Ethical Committee of the University of Nigeria Teaching Hospital. Informed consent was obtained from participants after detailed explanation of the study protocol before commencement of the study.

**Materials and research Tools:** Trained laboratory assistants and a trained qualified nurses were employed to assist the researchers in collection of blood and waist circumference/blood pressure measurement respectively. Waist circumference and blood pressure were measured using tape (in cm) and Accuson sphygmomanometer (in mmHg) respectively. EDTA bottles for plasma lipid estimation and

Table 1: National cholesterol education program adult treatment panel III (2002) for diagnosis of metabolic syndrome

No.	Risk factors	Cutoff values
1	Central obesity/excess waist circumference	Male >102 cm, Female >88 cm
2	Fasting blood glucose	$\geq 5.6$ mmol L <sup>-1</sup>
3	serum triglyceride	$\geq 1.7$ mmol L <sup>-1</sup>
4	low HDL-C (men $\leq 1.0$ mmol L <sup>-1</sup> )	Male $\leq 1.0$ mmol L <sup>-1</sup> , Female $\leq 1.3$ mmol L <sup>-1</sup>
5	Blood pressure	$\geq 130/85$ mm Hg

fluoride oxalate bottles for glucose estimation were made available. KD780 Semi-autochemistry analyzer was used for measurement of concentration of parameters.

**Data collection and processing:** Waist circumference (cm), of subjects were measured at the umbilicus using ordinary tailor's tapes at end of expiration<sup>7</sup>. Samples were collected after overnight fasting. The site from which the blood sample was taken was disinfected with methylated spirit and dried. Only 10 mL venous blood was collected from the ante-cubital vein. The blood was collected into EDTA bottles for plasma lipid estimation and fluoride oxalate bottles for glucose estimation. These were centrifuged for 10 min at 3000 rpm. Plasma was separated into clean sterile containers and stored at -20°C. Grossly haemolyzed or icteric samples were discarded.

**Parameters measured:** Anthropometric measurement (waist circumference) and blood pressure was measured and recorded side by side. Plasma glucose was measured using the glucose oxidase method<sup>8</sup>, The plasma triglyceride was measured using the enzymatic method<sup>9</sup>. HDL-C was estimated in the plasma supernatant after precipitating β-apoprotein containing lipoproteins using the precipitation technique<sup>10</sup>. Analytical accuracy and precision was ensured by simultaneous analysis of commercially prepared control sera obtained from Randox Laboratories Ltd, Finsbury House, 23 Finsbury Circus, London with each batch of sample analysed. MS was diagnosed according to the National Cholesterol Education/Adult Treatment Panel 111, (ATP 111), criteria<sup>2</sup>.

**Statistical analysis:** Data were analyzed using statistical software program GraphPad Prism Version 2. Result of analysis of patients and apparently healthy subjects were grouped separately and prevalence rates were calculated. The data were further segregated into diseases (diabetes, hypertension and renal failure) and prevalence rates were calculated. Logical binary regression was performed to assess the validity of each parameter and metabolic syndrome.

## RESULTS

**The rate of occurrence of MS among the different classes of patients:** The result showed that among the subjects with the MS, 52% of DM, 71% of HBP, 65.5% of CKD and 78.8% of AH subjects had three risk factors while correspondingly 39.7% of DM, 27.4% of HBP, 34.5% of CKD and 21.2% of AH had four risk factors. Negligible numbers (8.2, 1.6, 0 and 0% respectively)

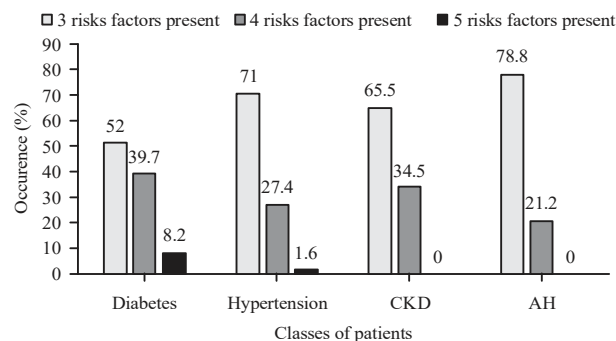


Fig. 1: Percentage occurrence of number of risk factors among different classes of patients  
CKD: Chronic kidney disease, AH: Apparent healthy

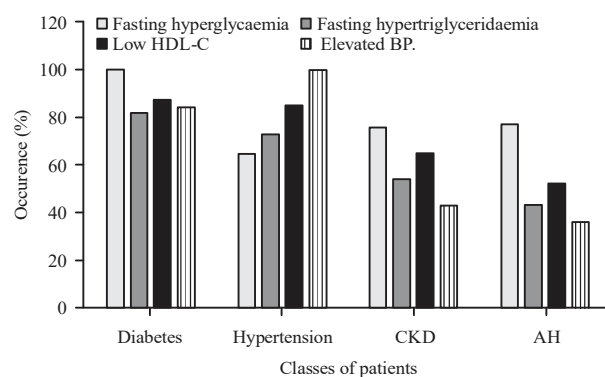


Fig. 2: Percentage of occurrence of different risk factors among the different classes of patients  
CKD: Chronic kidney disease, AH: Apparent healthy

had five risk factors (Fig. 1). The frequency of MS in this study were 68% for DM, 47% for HBP, 35% for CKD and 26% for AH subjects. Also, truncal obesity (excess WC) was diagnosed in 96% of the DM, 76% of the HBP, 60% of the CKD and 61% of the AH subjects with the MS. Corresponding figures for hyperglycaemia were 100, 65, 76 and 77%, for hypertriglyceridaemia; 82, 73, 54 and 43%; for low HDL-C corresponding figures were 88, 85, 65 and 52% while for HBP the figures were 84, 100, 43 and 36%, respectively (Fig. 1).

Meanwhile, apart from hyperglycaemia in DM and elevated blood pressure in hypertension which were expectedly constant (100%), the 3 most prevalent risk factors for DM subjects were excess WC, low HDL-C and elevated blood pressure; for subjects with hypertension the risk factors were: low HDL-C, excess WC and hypertriglyceridaemia; for subjects with CKD: hyperglycaemia, Low HDL-C and excess WC and for AH subjects the risk factors were hyperglycaemia, excess WC and low HDL-C, (Fig. 2). From Fig. 3, it is obvious

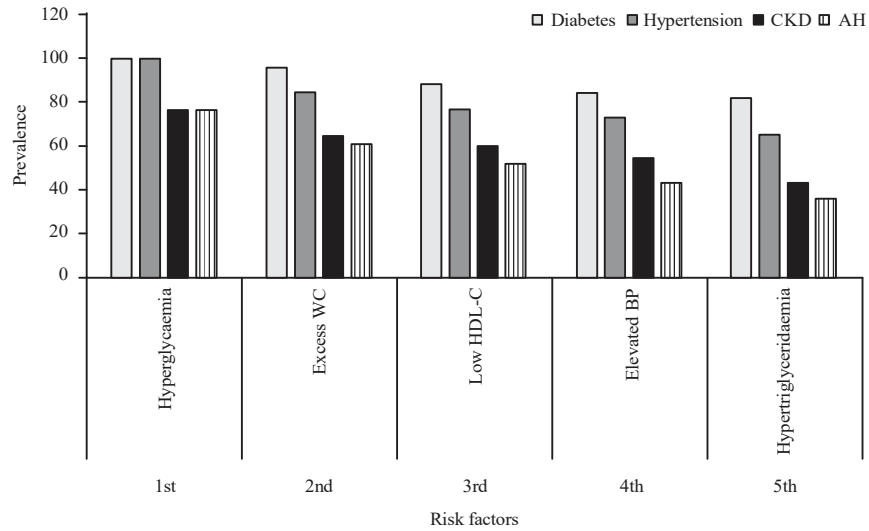


Fig. 3: Order of occurrence of the risk factor of MS among the different groups of patients

CKD: Chronic kidney disease, AH: Apparently healthy

Table 2: Omnibus tests of model coefficients

		Chi-square	df	Significance
Step 1	Step	143.004	7	0.000
	Block	143.004	7	0.000
	Model	143.004	7	0.000

Table 3: Model summary for diabetic

Step	-2 Log likelihood	Cox and Snell R <sup>2</sup>	Nagelkerke R <sup>2</sup>
1	293.975 <sup>a</sup>	0.360	0.484

<sup>a</sup>Estimation terminated at iteration number 7 because parameter estimates changed by less than 0.001

that the order of prevalence of risk factors in all the subjects was excess WC (74.5%), hyperglycaemia (71%), low HDL-C (70.1%), hypertriglyceridaemia (63%) and finally elevated blood pressure (54%) (Hyperglycaemia and elevated blood pressure in DM and hypertension respectively were not counted). None of the risk factors was absent in any of the group but their prevalence varied considerably (Fig. 3).

**Effect of the parameters on the outcome of MS among diabetic participants:** The logical binomial regression model was used to determine the effect of WC, blood pressure, fasting blood glucose (FBG), triglyceride (TG) and high density lipoprotein (HDL-C) on the occurrence of MS among diabetic patients. The binary logistic model showed that 79.7% cases were diagnosed with metabolic syndrome (Table 2-4). Results showed that increase in FBG and low HDL-C is significantly ( $p < 0.00$ ) associated with the incidence of metabolic syndrome among the diabetic patients but

Table 4: Classification Table<sup>a</sup>

		Predicted			
		-----			
		Diabetic	Percentage		
-----Observed-----		-----			
		No	Yes	Correct	
Step 1	Diabetic	No	110	27	80.3
		Yes	38	145	79.2
Overall percentage					79.7

<sup>a</sup>The cutoff value is 0.500

increase in blood pressure was not significantly associated with occurrence of metabolic syndrome among the diabetic patients (Table 5).

**Incidence of metabolic syndrome among patients diagnosed with hypertension:** The logical binomial regression model was used to determine the effect of WC, blood pressure, FBG, triglyceride (TG), high density lipoprotein (HDL-C) on the incidence of MS among patients diagnosed with hypertension. The binary logical regression model showed that 68.1% cases were diagnosed with metabolic syndrome (Table 6-8). It also revealed that increase in FBG and HDL-C is significantly ( $p < 0.005$ ) associated with increased likelihood of having metabolic syndrome (Table 9-11).

**Incidence of metabolic syndrome among patients diagnosed with renal failure:** The logical binomial regression model was used to determine the association of WC, SPB, DBP, FBG, TG and HDL-C with MS among patients

Table 5: Variables in the equation

		B	S.E.	Wald	df	Significance	Exp (B)	95% C.I. for EXP(B)	
								Lower	Upper
Step 1 <sup>a</sup>	WC	0.013	0.010	1.729	1	0.188	1.014	0.993	1.034
	SPB	-0.001	0.007	0.022	1	0.883	0.999	0.986	1.013
	DBP	-0.003	0.012	0.041	1	0.840	0.997	0.973	1.022
	FBG	0.557	0.090	38.389	1	0.000	1.745	1.463	2.081
	TG	0.020	0.103	0.036	1	0.849	1.020	0.833	1.248
	HDL-C	-0.731	0.245	8.905	1	0.003	0.482	0.298	0.778
	Gender(1)	0.343	0.299	1.319	1	0.251	1.409	0.785	2.530
	Constant	-3.061	1.254	5.960	1	0.015	0.047		

<sup>a</sup>Variable(s) entered on step 1: WC, SPB, DBP, FBG, TG, HDL-C, Gender

Table 6: Omnibus tests of model coefficients

		Chi-square	df	Significance
Step 1	Step	65.642	7	0.000
	Block	65.642	7	0.000
	Model	65.642	7	0.000

Table 7: Model summary

Step	-2 Log likelihood	Cox and snell R <sup>2</sup>	Nagelkerke R <sup>2</sup>
1	312.813 <sup>a</sup>	0.214	0.285

<sup>a</sup>Estimation terminated at iteration number 6 because parameter estimates changed by less than 0.001

diagnosed with renal failure. Overall 75.6% cases were diagnosed with metabolic syndrome (Table 12). Results showed that increase in FBG is significantly ( $p < 0.005$ ) associated with the occurrence of metabolic syndrome as shown in Table 13.

## DISCUSSION

In the study population, excess WC and low HDL-C, are more likely to define the MS followed by hyperglycemia than any other risk factors. Excess WC and low HDL-C were consistently the 2nd and/or 3rd most prevalent risk factors in the four groups of subjects. In previous reports, excess WC has been shown to be a better index of obesity than the traditional body mass index (BMI)<sup>11</sup>. The importance of this fact in the screening for the MS in the general population is obvious. Apparently healthy individuals with excess WC were invariably found to have the MS. Moreover, abdominal obesity is the first sensitive predictor of MS that appears in an individual before the appearance of other risk factors.

The higher the WC, the more the number of risk factors present in a group. Diabetics and hypertensive subjects with higher percentage of excess WC also have greater numbers of the risk factors (5 and 4). Good correlation between WC and lipid profile (TG and HDL-C) was also observed in the population. WC is a measure of visceral adiposity. Visceral fat is of the white type and is resistant to the anti-lipolytic action of insulin<sup>11</sup>. Lipolysis, therefore, occurs freely in subjects with

Table 8: Classification Table<sup>a</sup>

		Predicted			
		Diabetic		Percentage	
	-----Observed-----	No	Yes	Correct	
Step 1	Hypertensive	No	101	36.0	73.7
		Yes	51	85.0	62.5
Overall Percentage			68.1		

<sup>a</sup>The cutoff value is 0.500

excess WC releasing TG into the circulation and depleting serum HDL-C. This aggravates glucose control in the subject more so as adipose tissue secretes cytokines such as TNF- $\alpha$  and interleukins that oppose the action of insulin and are also pro-inflammatory<sup>12</sup>. Therefore, the three most prevalent risk factors found in this study were excess WC, hyperglycemia and low HDL-C. Low HDL-C could be pathogenically related with excess WC playing some sort of causative role especially in hypertension and apparently healthy subjects. Nevertheless, hyperglycemia may have additional causative influence since it occurred more often than excess WC in AH since type 2 diabetes mellitus is a multifactorial disease and hyperglycemia is related to a decrease in glucose peripheral uptake and to an increase in hepatic glucose production, due to reduced insulin secretion and insulin sensitivity. It results from aging of the population and from "western" lifestyle, with progressive increase in mean body weight, due to excess in energy intake, decreased energy expenses and low physical activity level<sup>13</sup>. About 4 out of every 5 apparently healthy subject with the MS will exhibit 3 (hyperglycaemia, obesity and low HDL-C) out of the 5 MS criteria. The blood glucose of apparently healthy subjects with MS is usually in the pre-diabetes range and can easily be ignored as well as HDL-C as against WC that is easy to measure accurately. This is an important consideration in screening for the MS in the general population even though hyperglycemia occurred more often than excess WC. The procedure for screening for the MS in the general population should, therefore, be to first diagnose obesity and then follow it up with the determinations of blood glucose

Table 9: Variables in the equation

							95% C.I. for EXP(B)		
		B	S.E.	Wald	df	Significance	Exp(B)	Lower	Upper
Step 1 <sup>a</sup>	WC	0.009	0.010	0.958	1	0.328	1.010	0.991	1.029
	SPB	0.006	0.008	0.529	1	0.467	1.006	0.991	1.021
	DBP	0.000	0.013	0.001	1	0.973	1.000	0.975	1.027
	FBG	0.609	0.142	18.256	1	0.000	1.838	1.390	2.430
	TG	-0.124	0.169	0.538	1	0.463	0.883	0.634	1.231
	HDL-C	-0.822	0.229	12.938	1	0.000	0.440	0.281	0.688
	Gender(1)	0.041	0.286	0.021	1	0.885	1.042	0.595	1.826
	Constant	-3.265	1.370	5.681	1	0.017	0.038		

<sup>a</sup>Variable(s) entered on step 1: WC, SPB, DBP, FBG, TG, HDLP, gender

Table 10: Omnibus tests of model coefficients

		Chi-square	df	Significance
Step 1	Step	78.319	7	0.000
	Block	78.319	7	0.000
	Model	78.319	7	0.000

Table 11: Model summary

Step	-2 Log likelihood	Cox and snell R <sup>2</sup>	Nagelkerke R <sup>2</sup>
1	215.217 <sup>a</sup>	0.298	0.406

<sup>a</sup>Estimation terminated at iteration number 6 because parameter estimates changed by less than 0.001

Table 12: Classification table<sup>a</sup>

		Predicted		Percentage Correct
		Diabetic	Non-diabetic	
Observed	No			
	Yes			
Step 1	Renal failure	No	Yes	85.4
		117	20.0	
		34	50.0	59.5
Overall percentage				75.6

<sup>a</sup>The cut value is 0.500

Table 13: Variables in the equation

							95% C.I. for EXP(B)		
		B	S.E.	Wald	df	Significance	Exp(B)	Lower	Upper
Step 1 <sup>a</sup>	WC	-0.018	0.011	2.806	1	0.094	0.982	0.962	1.003
	SPB	0.014	0.010	1.835	1	0.176	1.014	0.994	1.035
	DBP	0.038	0.021	3.211	1	0.073	1.038	0.996	1.082
	FBG	1.352	0.236	32.740	1	0.000	3.863	2.432	6.138
	TG	-0.077	0.141	0.304	1	0.582	0.925	0.702	1.219
	HDL-C	-0.287	0.306	0.877	1	0.349	0.751	0.412	1.368
	Gender(1)	-0.008	0.344	0.001	1	0.982	0.992	0.506	1.946
	Constant	-10.051	2.078	23.383	1	0.000	0.000		

<sup>a</sup>Variables entered on step 1: WC, SPB, DBP, FBG, TG, HDL-C, gender

and HDL-C. The fourth risk factor which may be either elevated serum triglycerides or elevated blood pressure has only 2 in 5 chances of occurrence and therefore cannot be a sensitive marker of MS in the healthy population.

The relatively low percentage of CKD-MS subjects with excess WC may be due to the severity of the condition in comparison with the other health conditions. The percentage of the apparently healthy subjects with the MS and hypertriglyceridemia in this study is low which tends to lend

support to the so called "lipid paradox" which states that the serum TG of people of African origin with the MS could be deceptively low<sup>13</sup>. There has been no explanation to this but it could be due to mis-diagnosis of MS in the healthy population.

Four out of every five diabetics exhibited the 5 diagnostic risk factors of hyperglycaemia, hypertriglyceridaemia, hypertension, low HDL-C and obesity. It may, therefore, be safe to say that every diabetic subject has the MS. This agrees

with the alternative name of the MS, Insulin Resistance Syndrome<sup>14,15</sup>. It has been noted that MS with normal glucose tolerance is a candidate for future diabetes<sup>16</sup>.

### **CONCLUSION**

All individuals with excess waist circumference have high risk of MS. Since WC can easily be measured, therefore, it is an easier and accurate method of screening for the MS in the general population in a resource-limited setting like Nigeria.

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