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SERUM URIC ACID LEVELS IN METABOLIC SYNDROME ASSOCIATED WITH DIABETES, HYPERTENSION, CHRONIC KIDNEY DISEASE AND APPARENT HEALTH.

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ABSTRACT
Aim. Serum uric acid (SUA), though not one of the factors for the diagnosis of metabolic syndrome (MS), has been reported to be consistently elevated in MS. The later predisposes to cardiovascular events and type 2 diabetes. This work evaluated the levels of SUA in MS associated with diabetes, hypertension, chronic kidney disease and apparent health. **Method.** Data from previous study were analyzed and sensitivity and specificity of SUA and its correlation with factors of MS were determined. **Results.** The mean (±SD) of SUA (µl/l) recorded in the study groups were 357.8 (94.75), 429 (118.7), 389 (123.2) and 356 (88.07) ($p<0.01$) for DM, HTN, CKD and AHS respectively. Two hundred and eighty nine subjects (53.5%) had ≥3 risk factors and were diagnosed with MS. SUA correlated significantly only with waist circumference in all the test groups. The per cent incidence of MS in the respective groups is 77.2, 49.2, 37.3 and 38.5 for DM, HTN, CKD and AHS respectively. Hyperuricaemia (>400µmol/l) was recorded in 111 of all the MS subjects, (38.4%). This gave per cent incidence of hyperuricaemia in the groups as 30.9, 58.2, 38.7 and 32.7 respectively. The sensitivity and specificity of SUA as a biomarker of MS in the study population were 37.7% and 51.6% and in the groups they were 28.7% and 66.7%; 60.9% and 52.7%; 38.7% and 65.4%; 32.6% and 34.9% respectively, (Table 3). **Conclusion.** SUA may not serve as a good marker for the MS in the study population. The increase in SUA reported by other workers has not been a consistent finding in this study and it may be due to dietary differences between the reported society and the present study population. The question of whether raised SUA is a cause or consequence of MS still remains unresolved.

KEYWORDS: metabolic syndrome. Uric acid, hyperuricaemia.

INTRODUCTION
Metabolic syndrome (MS) is a constellation of metabolic abnormalities that occur together in the same individual more often than might be expected by chance (Zimmet, 2003). The abnormalities are associated with cardiovascular disease and type 2 diabetes and include insulin resistance/ hyperinsulinaemia, dyslipidaemia of the high-triglyceride, low high density lipoprotein cholesterol type, hypertension, central obesity and glucose intolerance, microalbuminuria (NCEP, 2002; Flegal *et al*, 2002; Alexander *et al*, 2003). Uric acid is the product of purine catabolism. It has extracellular antioxidant capacity but intracellular pro-oxidant capacity (Billiet et al, 2014). Hyperuricaemia is not one of the factors for the diagnosis of metabolic syndrome according to existing criteria but there have been reports of consistent hyperuricaemia in metabolic syndrome. Serum uric acid (SUA) has been reported to show correlation with BMI, blood pressure and serum triglyceride levels (positive) and with high density lipoprotein cholesterol (negative) and these are factors of metabolic syndrome, (Ishizaka et al, 2005; Silva et al, 2015; NECP, 2001). Silva et al, (2015) and Puin and Martinez, (2008), also reported an increase in the prevalence of MS with increase in the level of serum SUA and an increase in serum uric acid levels as the number of risk factors increases. A stronger association between MS and SUA was reported in females than males, (Chiou et al, 2010). It is not known if increased uric acid concentration in the serum of patients with metabolic syndrome is a cause or consequence of the disease (Heinig et al., 2006, de Oliveira et al., 2012). Takahiko et al (2006) reported a causal relationship between SUA with MS. Uric acid may decreases the

availability of nitric oxide which results in less vasodilatation and more reactive oxygen species. It also can stimulate monocytes to produce TNF-α and all these will create the pro-inflammatory state found in MS (Lanaspa, et al 2011). Fructose, which can cause metabolic syndrome in rats, also raises uric acid and lowering uric acid in fructose-fed rats prevents features of the metabolic syndrome. The main causes for higher plasma UA are either lower excretion, higher synthesis or both. The dietary factor in hyperuricaemia has not been clarified but fructose-rich food of industrialized societies can dispose to increase in SUA level and renal impairment. The energy-dependent fructokinase reaction is not under negative control. Fructose phosphorylation in the liver results in ATP breakdown ultimately reflected in an increased uric acid synthesis. Hyperuricaemia can also be a consequence of the MS. Hyperinsulinaemia often seen in MS enhances proximal tubular reabsorption of sodium which will decrease uric acid excretion. Since diet can be a factor in both MS and hyperuricaemia, there is need to investigate the reported hyperuricaemia of MS in a typical Nigerian population and this has not been done.

MATERIALS AND METHODS

Data generated in earlier studies, (Ogbu, I.S.I. 2009; *Incidence of the metabolic syndrome among hospital-based patients in the University of Nigeria Teaching Hospital and apparently healthy people in Enugu metropolis* an PhD thesis submitted to the University of Calabar, Nigeria) were analyzed. It was a cross sectional study done between March and July, 2007 and involved a total of 540 subjects as in Table 1. Ethical clearance was obtained from the Ethics Committee of the University of Nigeria Teaching Hospital, Ituku/Ozalla, Enugu State. Informed consent was obtained from each candidate before recruitment into the study.

Plasma glucose was determined by the method of Trinder, (14), serum TG by the method of Buccolo and David (15). HDL-C was estimated in the serum supernatant after precipitating β-apoprotein containing lipoproteins using the method of Allain et al, (16). SUA was estimated by the method of Tamaoku *et al*, 1982. Cromatest$^{(R)}$ mono-reagent test kits were used for all biochemical determinations. Analyses of data were done with GraphPad Prism Version 2 statistical programme. The National Cholesterol Education Programme/Adult Treatment Panel 111 criteria, which required only the presence of any three of the following: Waist Circumference, Men > 102 cm, Women > 88 cm, Fasting triglycerides ≥ 1.7 mmol/l (≥150mg/dl), Blood pressure ≥ 130/85 mmHg HDL cholesterol Men ≤ 1.0 mmol/l; (40 mg/dl), Women ≤ 1.3 mmol/l; (50 mg/dl), Fasting blood glucose ≥ 5.6 mmol/l; (100mg/dl) were adopted in the diagnosis of MS (NCEP, 2001) and SUA levels >400µmol/l was regarded as hyperuricaemia.

TABLE 1. Number and gender distribution of subjects used for the study.

Subject Groups.	MALES.	FEMALES.	TOTAL.
Diabetics (DM).	105	78	183
Hypertensives (HTN).	76	60	136
Chronic Kidney Disease Subjects	43	41	84
(CKD) Apparently Healthy Subjects (AHS)	68	69	137
Total Number of Subjects	292	248	**540**

RESULTS

The mean (±SD) of SUA (µl/l) recorded in the study groups were 357.8 (94.75), 429 (118.7), 389 (123.2) and 356 (88.07) ($p<0.01$) for DM, HTN, CKD and AHS respectively. Two hundred and eighty nine subjects (53.5%) had ≥3 risk factors and were diagnosed with MS. SUA correlated significantly only with waist circumference in all the test groups. The per cent incidence of MS in the respective groups is 77.2, 49.2, 37.3 and 38.5 for DM, HTN, CKD and AHS respectively. Hyperuricaemia (>400µmol/l) was recorded in 111 of all the MS subjects, (38.4%). This gave per cent incidence of hyperuricaemia in the groups as 30.9, 58.2, 38.7 and 32.7 respectively, (Table 2).

TABLE 2. Number of subjects with hyperuricaemia (>400µl/l) and/or metabolic syndrome in the study population.

	DM	HTN	CKD	AHS	All
No of subjects	183	136	84	137	540
No positive for MS	139(75.9%)	67(49.2%)	31(36.9%)	52(37.9%)	289(53.5%)
No of MS with hyperuricaemia	43	39	12	17	111
% MS with hyperuricaemia	30.9	58.2	38.7	32.7	38.4

The sensitivity and specificity of SUA as a biomarker of MS in the study population were 37.7% and 51.6% and in the groups they were 28.7% and 66.7%; 60.9% and 52.7%; 38.7% and 65.4%; 32.6% and 34.9% respectively, (Table 3).

Table 3: sensitivity and specificity of SUA as biomarker of MS in the test groups

Index	DM	HTN	CKD	AHS	ALL
Sensitivity,%	28.7	60.9	38.7	32.6	37.7
Specificity,%	66.7	52.7	65.4	34.9	51.6

There were significant differences ($p<0.0001$, $F = 7.931$) between the SUA levels of the male and female test subjects only in the diabetes group and between the female diabetes subjects and female hypertensive subjects. When the performance indices of SUA were determined according to sex, sensitivity was found to be low (<50%) for male and female diabetes and apparently healthy subjects as well as for male HTN and CKD subjects but not for the female HTN and CKD subjects.

DISCUSSIONS

The mean SUA levels in the study population was below 400µl/l and among the groups only HTN subjects recorded mean level >400µl/l. Values >600µl/l occurred equally (50/50) among those with and those without the MS. This is reflected in its poor sensitivity as a biomarker. SUA concentrations varied widely within the groups. The moderate performance of SUA as biomarker of MS in hypertension is due to its performance in the female subjects only. Its usefulness as a biomarker for MS in the population is doubtful especially considering its poor performance among apparently healthy subjects with the MS. However, Yuan et al (2015), opined that an excess circulating SUA even within the normal range is always co- morbid with MS. The numbers of test subjects with hyperuricaemia were almost the same in the HTN and AHS groups (55% and 50%) yet the percentage of these subjects with MS differed considerably, 29 and 14 respectively. The hyperuricaemia in the study group may be predominantly dietary in origin since AHS and HTN subjects may not be as restricted in their diet as diabetes and CKD subjects. Diuretics taken by hypertensive subjects can also account for the raised SUA levels in the disorder. The hyperinsulinaemic theory may be relevant here also and its renal effect more pronounced in HTN than in any other group in this study especially in female subjects.

Values >600µl/l accounts for only a negligible fraction, 10.3%, of the results. The diabetes group with the highest prevalence of MS (75.9%) in this study did not record the highest prevalence of hyperuricaemia (30.9%) rather CKD with the least prevalence of MS, (36.9%) recorded a higher prevalence of hyperuricaemia, (38.7%). Hyperuricaemia, therefore, is unlikely to be a cause of MS but it can be its consequence depending on other dietary factors in the study population. The subjects studied may not be as exposed to fructose-containing drinks/medicaments as their counterparts in developed countries and this may be a factor in the low uric acid levels recorded in this study.

CONCLUSION

SUA may not serve as a good marker for the MS in the study population. The increase in SUA reported by other workers has not been a consistent finding in this study and it may be due to dietary differences between the reported society and the present study population. The question of whether raised SUA is a cause or consequence of MS still remains unresolved.

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