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SERUM URIC ACID LEVEL AS AN INDEPENDENT COMPONENT OF THE METABOLIC SYNDROME IN TYPE 2 DIABETIC BLACKS.

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ABSTRACT

Context: No consensus has been achieved on the components included in the definition of Metabolic Syndrome (MS). Uric acid and Gamma glutamyl transpeptidase are however newer markers not included in previous studies.

Objectives: This study was carried out to determine the prevalence of MS in Diabetes Mellitus, the correlation between hyperuricaemia and MS as well as make a case for the inclusion of serum Uric acid level as a new marker for MS.

Methodology: Fasting venous sample from the cubital vein of 77 females and 44 males diagnosed NIDDM patients for enzymatic determination of serum lipids, glucose and uric acid using QCA kits. The demographic records were obtained from the folders. Metabolic syndrome was diagnosed using the WHO criteria

Result: The prevalence of the new component hyperuricaemia among the study subjects was 10.7%. Thirty-eight (31.6%) of the subjects who had high blood pressure, hypertriglyceridemia, low HDL-C and BMI > 30 kg/m^2 diagnostic of MS also had hyperuricaemia as against the 29 (23.9%) subjects who had MS only.
About 23.7% of the 38 subjects who had MS and hyperuricaemia had serum uric acid values above 0.38mmol/l recommended as the cut off value. There was a significant correlation ($r = 0.301$, $p<0.01$) between serum uric acid level, BMI, total cholesterol, LDL-C and HDL-C/TC, among the female subjects while the male subjects showed significant correlation ($p<0.05$) between their BMI and serum HDL-C level only. There was a significant difference ($p<0.001$) in the CHD risk ratio between the male and the female MS subjects.

Conclusion: The correlation between hyperuricaemia and other components of MS as demonstrated in this study may suggest a common etiological factor between the MS components as suggested in other studies. Insulin resistance has been implicated as a common denominator. Thus a further investigation in this direction would be needed.

Keywords: Serum, Uric Acid, Metabolic Syndrome, Diabetes Mellitus. (*Accepted 28 August 2006)*

INTRODUCTION

Uric acid is a by product of the continual process in the body where old cells are broken down and new ones formed. It is the major product of purine metabolism formed from Xanthine by the action of Xanthine oxidase.[1] The serum level of uric acid varies with height, body weight, blood pressure, kidney function (eliminated from the body in urine.) and alcohol intake in adults.[2] It value also increases in women after menopause suggesting an interaction with sex hormones.[3] There is evidence also to suggest an association or correlation between serum uric acid and metabolic syndrome with all its components such as obesity,[4] hypertension,[5] reduced high density lipoprotein (HDL) cholesterol,[6] hypertriglyceridemia,[7] hyperinsulinemia and recently associated with insulin resistance and reduced sensitivity,[8,9] Serum uric acid has been demonstrated to have an independent, significant association with MS, showing a consistence relation to insulin resistance[10]. This relationship persisted when the differences in age, sex, overall obesity, abdominal obesity were taken into account. Facchini et al [9] found that urinary uric acid clearance decreases in proportion to increases in insulin resistance in normal volunteers, leading to an increase in the serum uric acid concentration.In a previous study, a strongest correlation was found between serum lipids and BMI, serum lipids And uric acid level, BMI and uric acid

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level and uric acid and HDL-C levels[11] in non diabetic individuals as predictors of cardiovascular disease (CVD) and diabetes incidence.

Hyperuricaemia has also been shown to be a strong predictor of stroke event in middle-age patient with NIDDM, independently of other cardiovascular risk factors [12]

In non diabetic subjects an elevated level of uric acid has been shown to be an independent predictor of coronary heart disease and that of total mortality[13-16]. In a study, women with the highest uric acid level in their blood were three times more likely to die from heart disease than those with the least. Among men, the risk was 77% higher in men with the highest level compared with those with the least levels.[17] The risk of dying was higher in Blacks than in Whites, with Black women having the highest risk. According to WHO criteria[18], metabolic syndrome is defined as the combination of diabetes, impaired glucose tolerance, impaired fasting glucose, or insulin resistance plus two or more of the following abnormalities: high blood pressure >140/90mmHg, hyperlipidemia-triglyceride concentration >150 mg/dl (1.8 mmol/l) and/or HDL cholesterol <35 mg/dl (0.9 mmol/l) in men and <39 mg/dl (1.0 mmol/l) in women, central obesity: waist-to-hip ratio of >0.90 in men or >0.85 in women and or BMI >30 kg/m^2, micro-albuminuria-urinary albumin excretion rate 20 µg/min or an albumin-to-creatinine ratio 20 mg/g.

However, no consensus concerning the components and cut-off points of the components has been established in recent literatures. Uric acid level greater than 0.38mmol/L and gamma glutamyl transpeptidase greater than 70U/L have been added as newer components.[19]

The prevalence of Diabetes Mellitus/Metabolic syndrome is increasing in this country and control of each component of the syndrome would reduce the incidence[20]. The correlation between hyperuricemia, Diabetes Mellitus and Metabolic Syndrome has not been studied in this environment. This study was carried out to determine the prevalence of MS in type 2 DM, determine the correlation between hyperuricaemia and MS as well as make a case for the inclusion of serum uric acid level as a new marker for MS.

SUBJECTS, MATERIALS AND METHOD

One hundred and twenty one diabetic patients attending the Diabetic clinic of University of Ilorin Teaching hospital without evidence of clinical nephropathy (absence of proteinuria on early morning urinalysis) were recruited randomly into the study after an informed Consent. The clinic attends to between 30 40 patients routinely weekly. All laboratory specimens were drawn in the morning, after a 12-hour fast.

Fasting plasma glucose was determined by the glucose oxidase method[21] while serum lipids and lipoproteins were assayed by enzymatic methods (QCA kit, Spain).[22] Serum HDL cholesterol was also determined by enzymatic method after precipitation of low-density and very-low-density lipoproteins with dextran sulfate $MgCl_2$ (QCA kit, Spain).[23] Elevated levels were defined according to the WHO guidelines as cholesterol (>5.2mmol/L), triglyceride (1.8mmol/L), HDL-C (>0.9mmol/L) and LDL-C (4.65mmol/L) respectively.[18] Serum uric acid was measured with use of an enzymatic method (QCA kit, Spain).[24]

Blood pressure was measured with the patients in a sitting position after a 5-minute rest with use of a mercury sphygmomanometer and read to the nearest 5 mm Hg. Subjects were classified as having hypertension if they had systolic blood pressure of above 140mm Hg or diastolic blood pressure of above 90 mm Hg independent of each other on two clinic visits at three weeks interval. Body mass index (BMI)-Kg/m^2 was derived in the subjects as weight (Kg) divided by the square of height in meter (m^2). BMI of <20 was regarded as under weight, 20-24.9 as normal weight, 25-30 as overweight and >30 as obese.[25]

The WHO criteria on diagnosis and classification of diabetes mellitus, was used in determining MS in our study group.[18] Data analyses were done with the Epi Info ver 6.1 software.

RESULT

Of the 121 diabetic subjects studied, 77 (63.6%) were females while 44 (36.4%) were male. The age range was 37-78 years (mean 57.3+10 years) in both sexes. The mean age of the female subjects was 56.1±9.3years while that of the male was 59.3±10.2 years. The age and sex distribution is as shown on table 1.

As outlined in table 2, Thirty one (25.6%) of the subjects were obese (BMI>30kg/m^2) while 47 (38.9%) were overweight. Among the obese were 17(22%) female while only 14 (31.8%) were males. About forty-two (34.7%) of the subjects was found to have hypercholesterolemia with 37 (48.1%) and 15 (34.1%) of the female and male subjects respectively having hypercholesterolemia.

The overall prevalence of hypertriglyceridemia was 21%, though hypertriglyceridaemia was commoner among the female (23.4 %) than the male (22.7%) subjects. HDL-C below recommended level was observed in 64.9% and 72.7% of the female and male subjects respectively. The mean total subjects respectively. The mean total cholesterol and the LDL-C were higher among the obese compare to the other weight status, while the Mean TG was highest

amongst normal weight subjects (BMI>18.5-24.9kg/m^2).

Thirty-eight (31.6%) of the subjects who had high blood pressure, hypertriglyceridemia, low HDL-C and BMI > 30 kg/m^2 diagnostic of MS also had hyperuricaemia as against the 29 (23.9%) subjects who had MS only. About 23.7% of the 38 subjects who had MS and Hyperuricaemia had serum uric acid values above 0.38mmol/l recommended as the cut off value, while the mean serum uric acid level of the subjects studied was 0.30mmol/L.

There was a significant correlation (r = 0.301, p<0.01) between the BMI and total cholesterol, LDL-C and HDL-C/TC, among the female subjects while the male subjects showed significant correlation (p<0.05) between the BMI and the HDL-C.

The pattern of combination of various components of metabolic syndrome in subjects with serum uric acid level greater than 0.38 is as displayed on table 3. Only

Table 1 **Age and Sex Distribution of the Subjects**

Age Range	Males	Female	Total	%
31-40	5	3	8	6.6
41-50	10	20	30	24.8
51-60	8	29	37	30.6
61-70	16	23	39	32.2
>71	5	2	7	5.8
Total	**44**	**77**	**121**	**100**

Table 2: **Distribution of Body Mass Indices (BMI) in subjects**

BMI Range	Males	(%)	Females	(%)	Total	(%)
>18.5-24.9	17	38.6	26	33.8	43	35.5
25-29.9	13	29.6	34	44.2	47	38.9
>30	14	31.8	17	22.0	31	25.6
Total	**44**	**100**	**77**	**100**	**121**	**100**

Table 3: **Pattern of combination of various components of MS and Uric acid level by sex distribution**

Component	SERUM URIC ACID LEVEL > 0.38mmol/L					
	Total No of subjects MS Components	Male (n)	(%)	Female (n)	(%)	TOTAL (n)	(%)
DM + HBP	28(23.1%)	2	(40)	3	(60)	5	(17.9)
DM +OB	31(25.6%)	7	(77.8)	2	(22.2)	9	(29.0)
DM + HL	25(20.7%)	1	(20.0)	4	(80.0)	5	(20.0)
DM + HU	18(14.8%)	7	(77.8)	2	(22.2)	9	(50.0)
HBP + OB	10(8.3%)	2	(20)	0	(0)	2	(20)
HBP + HL	22(18.2)	3	(100)	0	(0)	3	(13.6)
HL + OB	17(14.1)	2	(0)	2	(100)	2	(11.8)
HBP + HU	6(5)	1	(16.7)	5	(83.3)	6	(100)
HL + HU	7(57.9)	5	(71.4)	2	(28.6)	7	(100)
OB + HU	9(7.4)	7	(77.8)	2	(22.2)	9	(100)
DM+HL+HBP+OB	29(23.9%)	7	(77.8)	2	(22.2)	9	(31.1)
DM+HL+HBP+OB+HU	38(31.4%)	7	(77.8)	2	(2.2)	9	(23.7)

KEY

DM - Diabetes Mellitus HBP -Hypertension HU -Hyperuricaemia
HL -Hyperlipidemia OB -Obesity

Table 4 **Characteristics of Serum Uric Acid in MS subjects**

Variables	High uric acid (N=8) >=0.38mmol/L	Low uric acid (n=30) <0.38mmol/Lp value	p value
Age (yrs)	60.2±7.6	56.5±9.2	p<0.05
Body mass index (kg/m^2)	29.8±1.1	30.1±4.0	p>0.8
Total triglyceride (mmol/L)	1.98±0.2	1.3±0.5	p=0.1
Total cholesterol (mmol/L)	3.8±0.7	5.7±1.8	p=0.9
HDL cholesterol (mmol/L)	0.7±0.2	0.8±0.3	p=0.7
LDL cholesterol (mmol/L)	2.0±0.3	3.4±0.3	p<0.05
Plasma glucose (mmol/L)	6.9±3.7	8.9±4.3	p=0.1
Systolic blood pressure (mmHg)	140.0±10.7	141.3±16.1	p<0.05
Diastolic blood pressure (mmHg)	87.5±8.0	87.3±10	p=1

five (20%)out the twenty-five (65.8%) of the 38 MS subjects That had HDL-C level > 0.8 mmol/L, had serum uric acid level above cut off level. A total of 55.3% of the MS subjects were hypercholesterolaemic, but only 1(4.8%) was found to have uric acid level above 0.38mmol/L. The characteristics of the serum Uric acid in the MS subjects is as indicated in table 4

DISCUSSION

There are many definitions of metabolic syndrome (MS) because there is no consensus concerning the components of MS that has been international agreed or established in recent literatures[25]. However, according to WHO criteria[18], metabolic syndrome is defined as the combination of diabetes, impaired glucose tolerance, impaired fasting glucose, or insulin resistance plus two or more of the following abnormalities: High blood pressure, hyperlipidemia, central obesity, waist-to-hip ratio >0.90, BMI >30 kg/m^2, and microalbuminuria.The global prevalence of MS based on the above WHO criteria was about 35%[26] while the same unacceptable high prevalence in Nigeria has remained a concern. The prevalence rate of 23.9% MS in this study further confirms the earlier reported high prevalence rate of 41.3%.[20] The prevalence rate of the individual components of MS observed in this study were, obesity (25.6%), hypercholesterolaemia (34.7%), hypertriglyceridemia (21%), Hypertension (31.4%), and Low HDL-C (60%). These prevalence rates are similar to the rates reported in an earlier study in the same centre[20]and comparable to the 22% observation reported by Akbar in Saudi Arabia.[27]

These revelations are beginning to generate a lot of interest amongst clinicians as various concerns such as the 'unholy alliance' and quadret morbidity of these components are now being vigorously screened for and routinely treated (dyslipidaemia being the latest.). Thus public health effort should be a major concern in the investigation of other (newer) components which are also controllable components of the syndrome which have been documented as independent CVD risk factors.[12,28-31]

The prevalence of a new component named hyperuricaemia among the NIDDM subjects studied was 10.7%. This finding further support earlier conclusion that hyperuricaemia as a finding in NIDDM.[12] A pervious study has observed an increasing evidence that NIDDM associated with hyperuricaemia is closely related to an increase oxidative stress response in NIDDM with its antecedent vascular complications.[32] Thus, the hyperuricaemia may be an indicator of an increased endogenous water-soluble antioxidant of the body.[33]

However, like the other components of MS, hyperuricaemia as an independent risk factor for cardiovascular disease is now well established[11]even though the mechanism(s) via which hyperuricaemia is associated with CVD remain unexplained. This may suggest that hyperuricaemia might be an 'innocent bystander,' a non specific marker of adverse pattern of risk factors.[11] The significant difference ($p<0.001$) in the average CHD risk ratio of 0.20 among male MS subjects and the high CHD risk ratio (0.18) in the females may suggest that hyperuricaemia could be an independent MS component especially in females.[13-16]

The relationship of uric acid with other components of MS was demonstrated in this study by a significant correlation ($r = 0.301$, $p<0.01$) between the BMI and total cholesterol, LDL-C and HDL-C/TC among the female subjects, while the male subjects showed significant correlation ($p<0.05$) between serum uric acid, BMI and the HDL-C is similar to earlier study.[12]

Even though many studies has suggested that insulin resistance may be a common aetiological factor for both the WHO components as well as the newer individual components of MS,[10,35-37,] interestingly, consensus concerning the components included in the definition rom of MS may not be over or far frombeen achieved. Recently, several other components of MS such as raised PAI-1, gamma glutamyl transpeptidase have been described[38]and are now becoming new markers included in the most frequently proposed metabolic abnormalities for MS. However, as earlier suggested[38]a clear description of the essential components of the syndrome is needed with more studies to correlate to the existing WHO components with emerging ones because the association between hyperuricaemia and other components of MS as demonstrated in this study may suggest a common etiological factor between the components Many studies have suggested insulin resistance as the common denominator. Thus a further investigation in this direction would be needed especially in this environment where there are very scanty existing literature and studies on the WHO criteria.

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