Is hyperuricaemia one of the cardiovascular risk factors clustering in type 2 diabetic patients?

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Abstract: Background & Aim: The prevalence of hyperuricaemia (HU) in type 2 diabetic patients (T2DM) and its relation with diabetic micro- and macro-vascular complications has been conflicting. The aim of the present study was to investigate the relationship between HU and both micro and macroangiopathies (IHD and diabetic nephropathy and neuropathy) in patients with type 2 diabetes mellitus. **Methods:** The cohort of this cross-sectional study was sixty T2 diabetic patients (26 men and 34 women, aged 52.4±8.6 years). They have been recruited from the Outpatient Department of Menofia University Hospital between January and June, 2010. In addition to comprehensive clinical examination, they were subjected to laboratory check-up for serum uric acid, fasting blood glucose (FBG) and postprandial blood glucose (PPBG), glycated hemoglobin A1c (HbA1c), serum lipids, 24-hours urine collection for microalbuminuria (μA), stress ECG and coronary angiography as indicated. **Results:** HU was detected in 18 out of out 60 (30%) type 2 diabetic patients. The frequency of hypertension (HT), ischaemic heart disease (IHD), peripheral neuropathy (PN) and μA were significantly higher in diabetic patients with (78%, 67%, 78% and 78%, respectively) than in those without HU (48%, 5%, 38% and 33% respectively) (*P*=0.04, 0.0001, 0.01 and 0.001, respectively). We also observed a significantly higher FBG, PPBG and HbA1c in the diabetic patients with compared to those without HU (*P*=0.02, 0.01 and 0.01 respectively) have. Likewise, total cholesterol, triglyceride (TG) and creatinine levels in diabetic patients with HU were again significantly (*P*=0.02, 0.001 and 0.001, respectively) above their counterparts values in diabetics without HU. **Conclusion:** The cheap, basically available and modifiable serum uric acid level we observed to prevail in T2 diabetic patients would be a useful investigational tool to prompt a cost-effective search for other cardiovascular risk factors known to cluster in them.
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1. Introduction

Serum uric acid (SUA) is produced by xanthine oxidase from xanthine and hypoxanthine, which are in turn produced from purine (1). It has been shown at population-based epidemiological surveys to be associated with an increased risk of hypertension (HT), cardiovascular disease (CVD) and chronic kidney disease (CKD) (2, 3). Also, an elevated level of uric acid (hyperuricemia; HU) was remarkably associated with insulin resistance (4) as well as markers of metabolic syndrome (MS) such as dyslipidemia, glucose intolerance, high blood pressure, and central obesity, which are accepted as risk factors for developing CVDs. In fact, it's not only the development but also the progression of cardiovascular events and even kidney dysfunction on long-term scale (5, 6). Further, SUA was also elevated in the individuals with impaired glucose tolerance (7) and even has recently been reported to be associated with the onset of diabetes mellitus and metabolic syndrome (8, 9). Hyperuricemia is probably associated with glucose intolerance due to various mechanisms (8, 10) including among others reduced urinary excretion of uric acid due to activation of its proximal tubular transporter by hyperinsulinemia (11, 12).

Diabetes mellitus is a chronic disorder that is not only associated with cardiovascular complications of which the MS plays a prominent role (13) but also a well-known major risk factor for atherosclerotic disease and CKD (14).

Although several studies have reported a relationship between HU and both diabetic micro- and macro-angiopathies, such as coronary heart disease (CHD), and peripheral neuropathy, yet the conclusions have been fragmented and controversial (15, 16). Moreover, the influence of HUA on the renal functions has received little attention and has been insufficiently investigated in patients with T2DM.

The aim, therefore, of the present study was to investigate the relationship between HU and both micro and macroangiopathies (IHD and diabetic nephropathy and neuropathy) in patients with type 2 diabetes mellitus.

2. Patients and Methods:

A total of 60 patients with type 2 DM (26 men and 34 women) aged between 38 and 68 years were randomly selected as every other patient from those attending Outpatient Clinic of Internal Medicine Department, Menoufiya University Hospitals during the first half of 2010 and were asked to participate in

the present study. An informed consent was signed by all contributors and the study was approved by the local Medical Research and Ethics committee.

Inclusion criteria were type 2 DM diagnosed after the age of 30 years and absence of ketones at diagnosis. All patients with severe hypertension, end-stage renal disease receiving maintenance dialysis and patients with orthopaedic or neurological disabilities which may interfere with stress ECG testing were excluded from the study. Pregnancy was also an exclusion criterion.

All patients were interviewed and asked about the age of diabetes diagnosis, antihypertensive treatment, family history of IHD, smoking and their knowledge of the presence of any of the diabetic complications. They also underwent comprehensive physical examination including: measurements of height, weight to calculate their body mass index (BMI; weight (Kg) divided by the square root of height in meter), blood pressure measurement, cardiac examination and peripheral neuropathy (PN) examination. Diabetic PN was diagnosed by the presence of two or more components among clinical symptoms (bilateral spontaneous pain, hypoesthesia, or paraesthesia of the legs), the absence of ankle tendon reflexes and decreased vibration sensations using a C128 tuning fork according to the guidelines published by the Japan Diabetes Society (17).

Fasting venous blood was sampled from an antecubital vein for the measurement of FBG, total cholesterol (TC), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, serum triglycerides (TG), serum creatinine, serum uric acid and HbA1c. Another venous blood was withdrawn after 2 hours for PPBG estimation. Twenty four hours urine sample was collected for determination of urinary-albumin excretion (UAE) rate (18).

Patients were considered to have arterial hypertension if systolic blood pressure was ≥140 mmHg and diastolic blood pressure ≥90 mmHg or were currently receiving antihypertensive treatment. Hyperuricaemia (HU) was defined by the presence of SUA levels more than 7 mg/dl in males and more than 6 mg/dl in females (19) while µA was present when UAE ranged from 30 mg to 300 mg/24 hrs (20).

Resting ECG and stress ECG was done for all patients and coronary angiography was done for those who showed ischaemic changes in their stress ECG for detection of significant coronary artery disease.

Statistical Analysis:

Results are presented as mean ± standard deviation (SD) unless otherwise stated. Comparison between groups was performed using unpaired *t* test and non-parametric Mann-Whitney test. Fisher Exact analysis was also applied to compare proportions between groups. The correlation coefficient analysis was employed to detect the significance of relationships between two qualitative variables using Spearman's correlation. A p of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 10.

3. Results:

Hyperuricaemia (HU) was detected in 18 patients out of 60 patients with type 2 DM. The frequency of HUA was 30%. Table 1 shows a comparison between diabetic patients with and without HU. There was no significant difference between diabetic patients with and without HU with regard to age, gender, smoking, family history of IHD and LDL level. The frequency of HT, IHD, PN and µA were significantly higher in diabetic patients with HU (78%, 67%, 78% and 78% respectively) than in diabetic patients without HU (48%, 5%, 38% and 33%, respectively) (*P*=0.04, 0.0001, 0.01 and 0.001, respectively) (Figure 1).

Diabetic patients with HU have significantly higher FBG, PPBG and HbA1c% than diabetic patients without HU (*P*=0.02, 0.01 and 0.01, respectively). Total cholesterol, TG and creatinine levels are significantly higher (*P*=0.02, 0.001 and 0.001, respectively) while the level of HDL was significantly lower in diabetic patients with HU than in those without HU (*P*=0.001). Diabetic patients with HU were of significantly (*P* =0.001) higher BMI than diabetic patients without HU (BMI=26.8 and 25.1 kg/m^2, respectively) although both groups were below the defining figure for obesity. Again, DM duration was significantly longer in diabetic patients with than in those patients without HU (*P* =0.01).

Table II shows the comparison between T2DM patients with and without IHD. There was no significant difference between diabetic patients with and without IHD with regard to gender and smoking. The frequency of HT, PN, µA and positive family history for IHD were significantly (*P* =0.02, 0.001, 0.0001 and 0.02 respectively) higher in diabetic patients with IHD (86%, 86%, 100% and 57%, respectively) than in diabetic patients without IHD (48%, 39%, 30% and 22%, respectively). Diabetic patients with IHD have significantly higher FBG, PPBG and HbA1c% than diabetic patients without IHD (*P* =0.001, 0.0001 and 0.0001, respectively). Total cholesterol, TG, LDL and creatinine levels were significantly higher in diabetic patients with IHD than diabetic patients without IHD (*P* =0.0001, 0.0001, 0.001 and 0.0001 respectively). Duration of DM was significantly longer in diabetic patients with IHD than diabetic patients without IHD (*P* =0.0001). Diabetic patients with IHD are significantly more obese and

older than diabetic patients without IHD (*P* =0.001 for both). Level of HDL is significantly lower in diabetic patients with IHD than diabetic patients without IHD (*P* =0.001). Diabetic patients with IHD have significantly higher serum uric acid level than diabetic patients without IHD (*P* =0.0001) (Figure 2).

Table III shows a comparison between DM patients with and without µA. There was no significant difference between diabetic patients with and without µA with regard to gender, smoking and family history of IHD. The frequency of HT and PN are significantly higher in diabetic patients with µA (79% for both) than in diabetic patients without µA (38% and 25%, respectively) (*P* =0.001 and 0.0001, respectively). Diabetic patients with µA have significantly higher FBG, PPBG and HbA1c% than diabetic patients without µA (*P*=0.03, 0.0001 and 0.0001, respectively). Total cholesterol, TG and LDL levels are significantly higher in diabetic patients with µA than in diabetic patients without µA (*P* =0.02, 0.0001 and 0.0001, respectively). Duration of DM was significantly longer in diabetic patients with MA than diabetic patients without µA (*P* =0.01). Diabetic patients with µA are significantly more obese and older than diabetic patients without µA (*P* =0.001 for both). Level of HDL is significantly lower in diabetic patients with MA than diabetic patients without µA (*P* =0.02). Diabetic patients with µA have significantly higher SUA and creatinine levels than diabetic patients without µA (*P* =0.04 and 0.0001 respectively) (Figure 2).

Table IV shows a comparison between DM patients with and without PN. There was no significant difference between diabetic patients with and without PN with regard to gender, smoking, family history of IHD and total cholesterol and LDL levels. The frequency of HT is significantly higher in diabetic patients with PN (80%) than in those without PN (33% & *P* =0.0001). Diabetic patients with PN have significantly higher FBG, PPBG and HbA1c% than diabetic patients without PN (*P* =0.001, 0.0001 and 0.0001, respectively). Duration of DM was significantly longer in diabetic patients with PN than in diabetic patients without PN (*P* =0.0001). Diabetic patients with PN have significantly higher SUA and creatinine levels than diabetic patients without PN (*P* =0.04 and 0.0001, respectively) (Figure 2). Diabetic patients with PN are significantly older than diabetic patients without PN (*P* =0.0001). Diabetic patients with PN have significantly higher TG level and lower HDL level than diabetic patients without PN (*P* =0.001 and 0.0001, respectively). Diabetic patients with PN are comparable in terms of body weight to those without PN.

Interestingly, non-parametric correlation coefficient between the evaluated micro- and macro-angiopathic complications in our T2 diabetic patients with HU was significant. Precisely, the exact level of significance between PN and µA and PTCA were 0.015, and 0.048, respectively while the level of significance between µA and PTCA was 0.007 as seen in Table V of correlation matrix.

Table I. Comparison between DM patients with and without hyperuricemia:

VARIABLE	DM with Hyperuricaemia (n=18)	DM without Hyperuricaemia (n=42)	P-value
Age (years)	54.6 ± 9.3	51.3 ± 8.3	0.1
Gender (Male %)	39% (n = 7)	45% (n = 19)	0.9
Smoker %	22% (n = 4)	43% (n = 18)	0.2
DM duration (years)	11.1 ± 5.1	7.7 ± 5.6	0.01*
Arterial hypertension%	78% (n = 14)	48% (n = 16)	0.04*
BMI (kg/m2)	26.8 ± 2.2	25.1 ± 2.1	0.001*
Family history of IHD %	44%(n=8)	24%(n=10)	0.1
IHD %	67%(n=12)	5%(n=2)	0.0001*
Peripheral neuropathy %	78%(n=14)	38%(n=16)	0.01*
Microalbuminuria %	78%(n=14)	33%(n=14)	0.001*
FBG (mg/dl)	148.1 ± 32.4	131.9 ± 44.7	0.02*
PPBG (mg/dl)	252.3 ± 78.6	204 ± 55.5	0.01*
HbA1c (%)	7.5 ± 0.6	7.1 ± 0.5	0.01*
Total Cholesterol (mg/dl)	206.4 ± 44.4	176.2 ± 62.2	0.02*
HDL (mg/dl)	29.3 ± 7.3	37.2 ± 8.7	0.001*
LDL (mg/dl)	143.3 ± 38.5	135.8 ± 47.9	0.2
Triglycerides (mg/dl)	291.3 ± 108.3	221.9 ± 86.7	0.001*
Creatinine (mg/dl)	2 ± 1.3	1.1 ± 0.7	0.001*

DM= diabetes mellitus BMI=body mass index FBG=fasting blood glucose
PPBG=post-prandial blood glucose HDL=high-density lipoprotein L=low-density lipoprotein
IHD=ischaemic heart disease n=number *=significant.
Data are expressed as mean±SD, unless otherwise stated.

Table II: Comparison between DM patients with and without IHD:

VARIABLE	DM with IHD (n=14)	DM without IHD (n=46)	P-value
Age (years)	57.3 ± 9.9	50.4 ± 7.7	0.001*
Gender (Male %)	43% (n = 6)	43% (n = 20)	1
Smoker %	43% (n = 6)	35% (n = 16)	0.7
DM duration (years)	14.4 ± 6.7	6.8 ± 3.7	0.0001*
Arterial hypertension%	86% (n = 12)	48% (n = 22)	0.02*
BMI (kg/m2)	27.2 ± 2.1	25.1 ± 2	0.001*
Family history of IHD %	57%(n=8)	22%(n=10)	0.02*
Uric acid (mg/dl)	7.3 ± 0.9	5.1 ± 1.3	0.0001*
Peripheral neuropathy %	86%(n=12)	39%(n=18)	0.001*
Microalbuminuria %	100%(n=14)	30%(n=14)	0.0001*
FBG (mg/dl)	154.8 ± 30.4	132.5 ± 44.6	0.001*
PPBG (mg/dl)	271.6 ± 57.2	205.6 ± 67.6	0.0001*
HbA1c (%)	7.8 ± 0.5	7.1 ± 0.4	0.0001*
Total Cholesterol (mg/dl)	227.9 ± 50	172.2 ± 54.8	0.0001*
HDL (mg/dl)	28.3 ± 7.2	36.7 ± 8.8	0.001*
LDL (mg/dl)	159.2 ± 40.6	132.3 ± 45.1	0.001*
Triglycerides (mg/dl)	331.3 ± 87.5	217 ± 86.2	0.0001*
Creatinine (mg/dl)	2.4 ± 1.2	1 ± 0.6	0.0001*

DM= diabetes mellitus BMI=body mass index FBG=fasting blood glucose
PPBG=post-prandial blood glucose HDL=high-density lipoprotein
LDL=low-density lipoprotein, IHD=ischaemic heart disease n=number
*=significant. HbA1c= Glycated haemoglobin
Data were expressed as mean±SD

Table III. Comparison between DM patients with and without µA:

VARIABLE	DM with microalbuminuria (n=28)	DM without microalbuminuria (n=32)	P-value
Age (years)	55.4 ± 9.1	49.6 ± 7.3	0.001*
Gender (Male %)	50% (n = 14)	37% (n = 12)	0.4
Smoker %	43% (n = 12)	31% (n = 10)	0.4
DM duration (years)	11.3 ± 6.8	6.5 ± 3.2	0.01*
Arterial hypertension%	79% (n = 22)	38% (n = 12)	0.001*
BMI (kg/m2)	26.6 ± 2.1	24.8 ± 2	0.001*
Family history of IHD %	36%(n=10)	25%(n=8)	0.4
Uric acid (mg/dl)	6 ± 1.7	5.2 ± 1.2	0.04*
Peripheral neuropathy %	79%(n=22)	25%(n=8)	0.0001*
FBG (mg/dl)	144.1 ± 32.4	130.4 ± 48.1	0.03*
PPBG (mg/dl)	254.8 ± 65.5	186.8 ± 49.5	0.0001*
HbA1c (%)	7.6 ± 0.5	7 ± 0.3	0.0001*
Total Cholesterol (mg/dl)	204.5 ± 57.5	168.6 ± 55.5	0.02*
HDL (mg/dl)	32.3 ± 9.3	37.1 ± 8.3	0.02*
LDL (mg/dl)	160 ± 45.4	118.9 ± 35.5	0.0001*
Triglycerides (mg/dl)	298.9 ± 98.3	193.6 ± 67.5	0.0001*
Creatinine (mg/dl)	1.9 ± 1.2	0.9 ± 0.3	0.0001*

DM= diabetes mellitus BMI=body mass index FBG=fasting blood glucose PPBG=post-prandial blood glucose HDL=high-density lipoprotein LDL=low-density lipoprotein IHD=ischaemic heart disease n=number *=significant
HbA1c= Glycated haemoglobin µA=microalbuminuria
Data were expressed as mean±SD.

Table IV. Comparison between DM patients with and without PN:

VARIABLE	DM with peripheral neuropathy (n=30)	DM without peripheral neuropathy (n=30)	P-value
Age (years)	56.4 ± 7.3	48.2 ± 7.9	0.0001*
Gender (Male %)	47% (n = 14)	40% (n = 12)	0.8
Smoker %	47% (n = 14)	27% (n = 8)	0.2
DM duration (years)	11.9 ± 6.1	5.5 ± 2.6	0.0001*
Arterial hypertension%	80% (n = 24)	33% (n = 10)	0.0001*
BMI (kg/m2)	26.2 ± 2	25.1 ± 2.4	0.06
Family history of IHD %	27%(n=8)	33%(n=10)	0.8
Uric acid (mg/dl)	6 ± 1.6	5.2 ± 1.3	0.04*
FBG (mg/dl)	145.5 ± 32.1	128.1 ± 48.6	0.001*
PPBG (mg/dl)	252.9 ± 66.4	184.2 ± 46.3	0.0001*
HbA1c (%)	7.5 ± 0.5	7 ± 0.3	0.0001*
Total Cholesterol (mg/dl)	194.5 ± 59	176.2 ± 58.2	0.2
HDL (mg/dl)	31.1 ± 8	38.6 ± 8.5	0.0001*
LDL (mg/dl)	146.1 ± 46.5	130.1 ± 43	0.2
Triglycerides (mg/dl)	284.7 ± 100.7	200.7 ± 76.1	0.001*
Creatinine (mg/dl)	1.7 ± 1.1	1 ± 0.7	0.0001*

DM= diabetes mellitus BMI=body mass index FBG=fasting blood glucose
PPBG=post-prandial blood glucose HDL=high-density lipoprotein LDL=low-density lipoprotein,
IHD=ischaemic heart disease n=number *=significant.
PN=peripheral neuropathy HbA1c= Glycated haemoglobin
Data were expressed as mean±SD, unless otherwise stated.

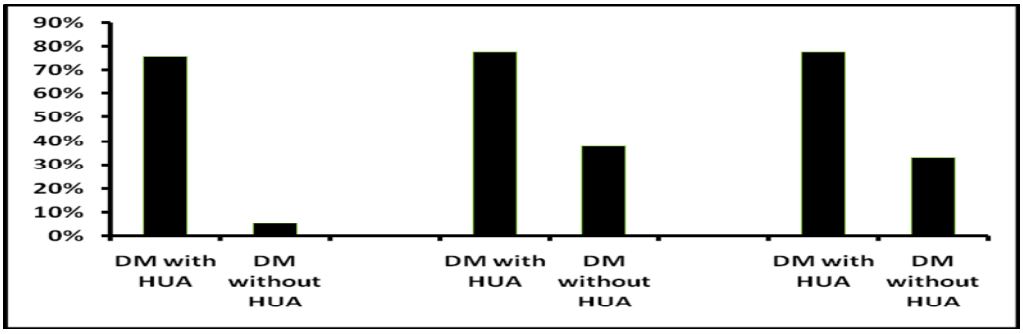

Figure 1: Frequency of ischaemic heart disease (IHD), microalbuminuria (µA) and peripheral neuropathy (PN) in diabetic patients with and without HU.

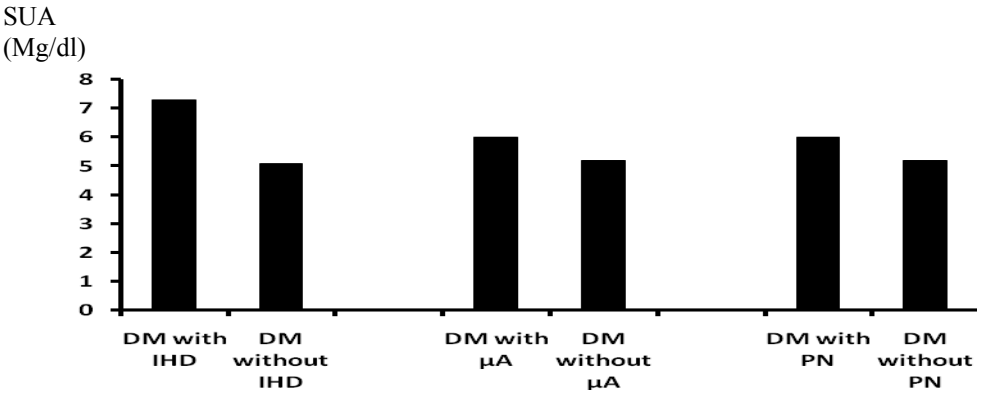

Figure 2: Level of uric acid in diabetic patients with and without the observed micro- and macro-angiopathies; ischaemic heart disease (IHD), microalbuminuria (µA) and peripheral neuropathy (PN).

Table V: Spearman's correlation matrix for micro- and macro- angiopathic Complications among hyperuricaemic T2 diabetic patients.

VARIABLES	Spearman's Correlation	PN	µA	STRESS ECG	PTCA
Peripheral Neuropathy	Correlation Coefficient	1.000	.564	.189	.472
	Sig. (2-tailed)	.	.015	.453	.048
	N	18	18	18	18
Microalbuminuria	Correlation Coefficient	.564	1.000	.614	.614
	Sig. (2-tailed)	.015	.	.007	.007
	N	18	18	18	18
STRESS ECG	Correlation Coefficient	.189	.614	1.000	.500
	Sig. (2-tailed)	.453	.007	.	.035
	N	18	18	18	18
PTCA	Correlation Coefficient	.472	.614	.500	1.000
	Sig. (2-tailed)	.048	.007	.035	.
	N	18	18	18	18

PTCA=Percutaneous transarterial coronary angiography N=number

4. Discussion

In the present study, we noticed an appreciable frequency of hyperuricaemia (HU) in our T2 diabetics and the same observation was reported by others (21, 22). Serum uric acid (SUA) may inhibit glucose-induced insulin secretion via binding to an essential arginine residue in pancreatic β-cells (23). By contrast, some studies reported that serum uric acid is inversely associated with diabetes mellitus (24, 25). Moreover, Wen and co-workers (2010) described a negative correlation between SUA and the blood glucose level in an approximately half a million population in Taiwan (26). A plausible mechanism for the reported conflicting results may either be related to the inhibition of uric acid reabsorption in the proximal tubule by high glucose levels in diabetic individuals (7) or the difference in the studied population.

Markers of poor glycemic control evaluated in this investigation such as FBG, PPBG and HbA1c were remarkably higher in patients with than in those without HU. This would be explained by the ability of high SUA to augment insulin resistance and to promote the impaired insulin secretion by its pro-oxidative capacity as recently reported (27).

Our results showed that hyperuricemic individuals had higher rates of coexistence of other cardiovascular risk factors such as hypertension, hypercholesterolemia, hypertriglyceridemia, and hypo-HDL cholesterolemia than those of non-hyperuricemic individuals. Our findings were not different from that noticed by Nagahamas and associates (2004) who reported that subjects with HU had increased rates of coexisting CV risk factors such as HT, hypertriglyceridemia, and dyslipidemia than did subjects without hyperuricemia (28). Insulin resistance may constitute a common pathophysiologic feature of obesity, hypertension, dyslipidemia, and hyperuricemia. We conjectured that insulin resistance might have affected the interaction between hyperuricemia and the cardiovascular risk factors and there is evidence that the association between SUA concentration and insulin resistance may be mediated by increased triglyceride (29).

Although the measurements of BMI have not reached the defining level of obesity in our study cohort, yet those with HU had significantly higher values than those without HU. Some previous studies that focused on general populations reported that the SUA levels were positively correlated with BMI correlated independently (30) in general as well as with both the visceral the subcutaneous fat areas; particularly, the serum uric acid levels were more closely correlated with the visceral fat (31, 32).

Our study investigated the association between diabetic macro-vascular complications and the existence of HU. Our data suggested that IHD was clearly more prevalent in the patients with compared with those without HU and that T2DM patients with IHD had significantly higher SUA than those without IHD. This is in concordance with the work done by Rathmann and colleagues (1993) as they reported significant association between HU coronary heart disease (CHD) in their 4,047 type 2 diabetic patients (33). The discrepancy between our findings and that observed by Ong and coworkers is merely apparent as they were interested in studying the CV and all-cause mortality in their 1,268 type 2 diabetic in Western Australia (16).

The frequency of hypertension (HT) was significantly higher in the patients with HU than in those with normal SUA in the current study. The correlation between hypertension and HU has been well established in clinical studies as several groups have reported that higher levels of SUA might be a marker of susceptibility or an intermediate step in the pathways leading to hypertension (34) and independently increase not only the risk for the development of hypertension (30) and but also strongly predicted BP progression (35). In a series of elegant experiments in rats, it was demonstrated that HU trigged HT and impaired nitric oxide (NO) generation in the macula densa and both HT and renal injury were reduced by the NO precursor l-arginine treatment (36). On the other hand, another study found that the proportion of hypertensive and non hypertensive patients with HU was comparable and there was no association between SUA and blood pressure readings (37). Such difference could be attributed to fact that they studied Chinese patients who are definitely different from our Egyptian population.

In the present study, the frequency of µA is significantly higher in the patients with HU compared with those without HU and T2diabetics patients with µA have significantly higher SUA level than diabetic patients without µA. Studies conducted in the past few years provided new evidence to support the observation that elevated SUA is a novel yet well-established risk factor for renal dysfunction (38). A more recent report confirmed the fact that HU is an independent risk factor for the progression of renal dysfunction (5).

Tseng and associates (2005) (39) and Fukui and colleagues (2008) (40) reported that the SUA level was elevated, along with increased UAE and reduced glometrular filtration rate (GFR) in their studied population with type 2 diabetes using a cross-sectional design. The relationship between renal function and uric acid has been known for a long time and the renal lesion consists of variable degrees of arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis, often with focal deposition of urate crystals in the outer medulla. It is, in fact, an interrelationship, as excess uric acid impairs renal function and insufficient kidneys filter uric acid out of the circulation to a lower degree. The significance of HU is further emphasized by studies showing that reducing its concentration with allopurinol results in a slower development of renal failure in a parallel reduction of CV risk (41).

Of significance was our observation in the present study that SUA levels were increased in the presence of peripheral neuropathy (PN) among patients with T2DM. The presence of HU and dyslipidemia in our T2diabetic patients with PN is in concordance with what has previously been shown that peripheral neuropathy is associated with increased TGs and TC, but not HDL-C, in type 2 DM (42). Despite some minor differences in the lipid fractions involved, these findings highlight the importance of dyslipidaemia in diabetic neuropathy. Our results are in agreement with experimental evidence that elevated TG is neurotoxic via oxidative stress, independently of hyperglycemia (43). Others have also implicated hyperlipidaemia in diabetic PN and identified elevated serum lipids as a potential additional therapeutic target in the management of this micro-vascular complication (44, 45).

Importantly, we observed a remarkable association between PN, µA and CHD which represent the three facets of cardiovascular complications detected among the studied T2 diabetics with HU. The mechanisms that could possibly link HU to the observed macro- and micro-vascular complications might include its deleterious effects on platelet adhesiveness and aggregation, on endothelial dysfunction which is thought to be an important early step in the development of atherosclerosis (46), oxidative stress through the xanthine oxidase pathways (47) as well as its capacity to increase in reactive oxygen species (ROS) by activation of the NADPH oxidase, and sustained inflammation (27) and recently, a close association between elevated SUA and numerous markers of inflammation such as white blood cells, TNF-α, CRP (48) or interleukin-6 (49).

Therefore, since HU is potentially a modifiable factor, measuring SUA that is cheap and logistically easily available, it might provide a cost-beneficial investigational tool allowing identification at risk T2 diabetic patients who may benefit from a full work up for the risk factors associated with micro- and macro-angiopathies. Conversely, comprehensive and meticulous clinical examination is mandatory to detect the vascular complications at bed-side level when HU is found in patients with type 2 diabetes mellitus. Collectively, these findings provide support for aggressive management of cardiometabolic risk factors including HT and dyslipidaemia along with lifestyle modifications in T2 diabetic patients with hyperuricemia. Although allopurinol administration to lower SUA concentrations has been shown to be beneficial in conditions such as post coronary artery bypass surgery where it reduced ischemic events and produced less ST

segment depression (50) As well as in improving endothelial dysfunction and reducing oxidative stress burden in patients T2 DM (51) yet it should not be prescribed except for those with clear-cut indications to avoid the serious allopurinol toxicity.

In conclusion, the cheap, usually available and modifiable serum uric acid elevations we observed to prevail in T2 diabetic patients would be a useful investigational tool to prompt a cost-effective search for other cardiovascular risk factors known to cluster in them as well as meticulous clinical examination for a possible presence of diabetic micro- and macroangiopathies such as ischaemic heart disease, renal dysfunction and peripheral neuropathy.

Limitations:

Of the limitations to be declared are the small sample size of this study and its performance in a single centre besides absence of control group. Further, exclusion of those with chronic disabilities as well as major psychiatric disorders for sure would limit the generalization of our finding to the wider Egyptian population.

References

1. Baillie JK, Bates MG, Thompson AA, Waring WS, Partridge RW and Schnopp MF., 2005. Endogenous urate production augments plasma antioxidant capacity in healthy lowland subjects exposed to high altitude". Chest; 131 (5): 1473-1478.
2. Shankar A, Klein R, B. Klein BEK, and Nieto FJ., 2006. The association between serum uric acid level and long-term incidence of hypertension: population-based cohort study. Journal of Human Hypertension; 20 (12): 937–945.
3. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF. ,2007. Relationship of uric acid with progression of kidney disease. American Journal of Kidney Diseases; 50 (2): 239–247.
4. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, Lee MH, Park JR, Kim H, Rhee EJ, Lee WY, Kim SW, Ryu SH, Keum DG. ,2005. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circulation Journal; 69 (8): 928–933.
5. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, *et al.,* 2009. Uric acid and long-term outcomes in CKD. Am J Kidney Dis.; 53: 796–803.
6. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA., 2010. Hyperuricemia and coronary heart disease: a systematic review and meta analysis. Arthritis Care Res.; 62: 170–180.
7. Tuomilehto J, Zimmet P, Wolf E, Taylor R, Ram P, *et al.,* 1988. Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. Am J Epidemiol; 127: 321-336.
8. 8. Dehghan A, VanHoek M, E. Sijbrands EJG, Hofman A, and Witteman JCM. ,2008. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care; 31 (2): 361–362.
9. Sui X, Church TS, Meriwether RA, Lobelo F and Blair SN., 2008. Uric acid and the development of metabolic syndrome in women and men. Metabolism; 57: 845–852.
10. Kramer CK, Von M¨uhlen D, Jassal SK, and Barrett-Connor E., 2009. Serum uric acid levels improve prediction of incident type 2 diabetes in individuals with impaired fasting glucose: the Rancho Bernardo Study. Diabetes Care; 32 (7): 1272–1273.
11. Facchini F, Chen YD, Hollenbeck CB, Reaven GM., 1991. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA; 266: 3008–3011.
12. Strazzullo P, Barbato A, Galletti F, Barba G, Siani A, Iacone R, D'Elia L, Russo O, Versiero M, Farinaro E, Cappuccio FP., 2006. Abnormalities of renal sodium handling in the metabolic syndrome: results of the Olivetti Heart Study. J Hypertens; 24(8):1633-39.
13. Deedwania PC and Gupta R., 2006. Management issues in the metabolic syndrome. J Assoc Physicians India; 54: 797-810.
14. Fang J and Alderman MH., 2000. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA; 283: 2404–2410.
15. Zoppini G, Targher G, Negri C, Stoico V, Perrone F, Muggeo M, Bonora E. ,2009. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care; 32: 1716–1720.

16. Ong G, Davis WA and Davis TM., 2010. Serum uric acid does not predict cardiovascular or all-cause mortality in type 2 diabetes: the Fremantle Diabetes Study. Diabetologia; 53: 1288–1294.
17. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. ,2010. Hyperuricemia and coronary heart disease: a systematic review and meta analysis. Arthritis Care Res.; 62: 170–180.
18. Gavin JB.,2004. Which albumin should we measure? Kidney Int; 66: S16-S17.
19. Sui X, Church TS, Meriwether RA, Lobelo F and Blair SN., 2008. Uric acid and the development of metabolic syndrome in women and men. Metabolism; 57: 845-852.
20. Jager A, Kostense PJ, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD ,1998. Microalbuminuria is strongly associated with non-insulin dependent diabetes mellitus and hypertension, but not with insulin resistance syndrome: The Hoorn Study. Diabetologia; 41(6): 694-700.
21. Kramer CK, Von M¨uhlen D, Jassal SK, and Barrett-Connor E., 2009. Serum uric acid levels improve prediction of incident type 2 diabetes in individuals with impaired fasting glucose. The Rancho Bernardo Study. Diabetes Care; 32 (7): 1272–1273.
22. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, Saito A, Sone H. ,2009. Association between serum uric acid and development of type 2 diabetes. Diabetes Care; 32 (9):1737–1742.
23. Roˇci´c B, Vuˇci´c-Lovrenˇci´c M, Poje N, Poje M and Bertuzzi F., 2005. Uric acid may inhibit glucose-induced insulin secretion via binding to an essential arginine residue in rat pancreatic β-cells. Bioorganic and Medicinal Chemistry Letters; 15 (4):1181–1184.
24. Oda E, R. Kawai R, Sukumaran V and Watanabe K., 2009. Uric acid is positively associated with metabolic syndrome but negatively associated with diabetes in Japanese men. Internal Medicine; 48 (20):1785–1791.
25. Nan H, Dong Y, Gao W, Tuomilehto J, and Qiao Q. ,2007. Diabetes associated with a low serum uric acid level in a general Chinese population. Diabetes Research and Clinical Practice; 76 (1): 68–74.
26. Wen CP, David Cheng TY, Chan HT, Tsai MK, Chung WS, Tsai SP, Wahlqvist ML, Yang YC, Wu SB, Chiang PH, Wen SF. ,2010. Is high serum uric acid a risk marker or a target for treatment? Examination of its independent effect in a large cohort with low cardiovascular risk. Am J Kidney Dis.; 56: 273–288.
27. So A and Thorens B., 2010. Uric acid transport and disease. Journal of Clinical Investigation; 120 (6): 1791–1799.
28. Nagahama K, Iseki K, Taku Inoue T, Touma T, Ikemiya Y, and Shuichi Takishita S. ,2004. Hyperuricemia and cardiovascular risk factor clustering in a screened cohort in okinawa, japan. Hypertens Res; 27: 227–233.
29. Giacomello A, Di Sciascio N and Quaratino CP., 1997. Relation between serum triglyceride level, serum urate concentration, and fractional urate excretion. Metabolism; 46 (9):1085-1089.
30. Nakanishi N, Tatara K, Nakamura K and Suzuki K., 1999. Risk factors for the incidence of hyperuricemia: a 6-year longitudinal study of middle-aged Japanese men. Int J Epidemiol.; 28: 888–893.
31. Tamba S, Nishizawa H, Funahashi T, Okauchi Y, Ogawa T, Noguchi M, Fujita K, Ryo M, Kihara S, Iwahashi H, Yamagata K, Nakamura T, Shimomura I and Matsuzawa Y. ,2008. Relationship between the serum uric acid level, visceral fat accumulation and serum adiponectin concentration in Japanese men. Intern Med. ; 47:1175-1180.
32. Hikita M, Ohno I, Mori Y, Ichida K, Yokose T and Hosoya T., 2007. Relationship between hyperuricemia and body fat distribution. Intern Med.; 46: 1353-1358.
33. Rathmann W, Hauner H, Dannehl K and Gries FA. ,1993. Association of elevated serum uric acid with coronary heart disease in diabetes mellitus. Diabet Metab.;19:159-66.
34. Selby JV, Friedman GD and Quesenberry CP., 1990. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol.; 131: 1017–1027.
35. Sundstrom J, Sullivan L, D'Agostino RB, Levy D, Kannel WB and Vasan RS. ,2005. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension; 45: 28–33.
36. Sanchez-Lozada LG, Tapia E, Santamaria J, Avila-Casado C, Soto V, Nepomuceno T, Rodriguez-Iturbe B, Johnson RJ and Herrera-Acosta J. ,2005. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int.; 67: 237–247.

37. Lu Z, Dong B, Wu H, Chen T, Zhang Y and Xiao H., 2008. Serum uric acid level in primary hypertension among Chinese Nonagenarians/Centenarians. J Hum Hypertens; 23 (2): 113-121.
38. Nakagawa T, Kang DH, Feig D, Sanchez-Lozada LG, Srinivas TR, Sautin Y, Ejaz AA, Segal M, Johnson RJ., 2006. Unearthing uric acid:An ancient factor with recently found significance in renal and cardiovascular disease. Kidney Int; 69: 1722—1725.
39. Tseng CH., 2005. Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. Kidney Int; 68: 796–801.
40. Fukui M, Tanaka M, Shiraishi E, Harusato I, Hosoda H, Asano M, Kadono M, Hasegawa G, Yoshikawa T, Nakamura N., 2008. Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. Metabolism; 57: 625–629.
41. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, Arroyo D, Luño J. ,2010. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol; 5: 1388–1393.
42. Papanas N, Katsiki N, Papatheodorou K, Demetriou M, Papazoglou D, Gioka T, Maltezos E. ,2011. Peripheral neuropathy is associated with increased serum levels of uric acid in type 2 diabetes mellitus. Angiology; 62 (4): 291–295.
43. Vincent AM, Hayes JM, McLean LL, Vivekanandan-Giri A, Pennathur S, and Feldman EL., 2009. Dyslipidemia-induced neuropathy in mice: the role of oxLDL/LOX-1. Diabetes; 58 (10): 2376–2385.
44. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AAF, and Feldman EL. ,2009. Elevated triglycerides correlate with progression of diabetic neuropathy. Diabetes; 58 (7): 1634–1640.
45. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, Witte DR, Fuller JH; 2005. EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. N Engl J Med; 352 (4): 341–350.
46. Landmesser U, Hornig B and Drexler H., 2004. Endothelial function: a critical determinant in atherosclerosis? Circulation; 109 (Suppl. 1): II27–II33.
47. George J and Struthers AD., 2009. Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. Vascular Health and Risk Management; 5: 265–272.
48. Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, Lauretani F, Bandinelli S, Senin U, Ferrucci L., 2006. Uric acid and inflammatory markers. Eur Heart J; 27: 1174–1181.
49. Herder C, Lankisch M, Ziegler D, Rathmann W, Koenig W, Illig T, Döring A, Thorand B, Holle R, Giani G, Martin S, Meisinger C., 2009. Subclinical inflammation and diabetic polyneuropathy: MONICA/KORA survey F3 (Augsburg, Germany). Diabetes Care; 32 (4): 680–682.
50. Sisto T, Paajanen H, Metsa-Ketela T, Harmoinen A, Nordback I and Tarkka M., 1995. Pretreatment with antioxidants and allopurinol diminishes cardiac onset events in coronary artery bypass grafting. Ann Thorac Surg.; 59 (6): 1519–1523.
51. Yiginer O, Ozcelik F, Inanc T, Aparci M, Ozmen N, Cingozbay BY, Kardesoglu E, Suleymanoglu S, Sener G, Cebeci BS., 2008. Allopurinol improves endothelial function and reduces oxidant-inflammatory enzyme of myeloperoxidase in metabolic syndrome. Clin Res Cardiol; 97 (5): 334–340.

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