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Relationship of serum C-reactive protein and uric acid concentration with proportion of albuminuria in patients with type 2 diabetes mellitus

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ABSTRACT

Introduction: Prevalence of diabetes and its complications will be considerably increased in the future. This study focused on the correlation of some laboratory parameters with prevalence and severity of diabetic nephropathy which is the main cause of chronic renal failure (CRF) in our country.

Objectives: Regarding the importance of diabetic nephropathy and lack of studies on the effect of serum C-reactive protein (CRP) and uric acid on albuminuria and its severity, the current study was designed.

Methods: Through an analytic cross-sectional design, 200 type 2 diabetes mellitus (T2DM) cases were recruited between 2014 and 2015. Blood samples were drawn after 12 hours of starving to measure parameters including serum levels of CRP, triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C), cholesterol, Low-density lipoprotein (LDL-C), fasting blood sugar (FBS), and Hb-A1C. Albuminuria was assessed by collecting participants' 24 hours urine.

Results: Macro-albuminuria correlated with high serum uric acid (SUA) (odds ratio [OR]= 1.3) and high serum CRP (OR = 1.2) among diabetic patients. Both markers represented significant correlation with albuminuria. Logistic regression test confirmed the mentioned correlation when confounding factors were eliminated.

Conclusion: It seems that uric acid and CRP levels in serum are the most reliable parameters studied by the current study to predict life-threatening diabetic consequences like cardiovascular and chronic kidney disease in patients with type II diabetes mellitus.

Original

Implication for health policy/practice/research/medical education:
Prevalence of diabetes and its complications will be considerably increased in the future. This study focused on the correlation of some laboratory parameters with prevalence and severity of diabetic nephropathy which is the main cause of chronic renal failure in our country.

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Introduction

Diabetic nephropathy is the most common cause of chronic renal failure (CRF) in the Western world (1) and in charge for 45% of renal transplantation cases while being one of the main causes of cardiovascular diseases (2). A pronounced increase in cases of diabetic nephropathy shows epidemic rise of obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM) in recent decades. Hence, recognition of relevant risk factors and early diagnosis is vital in manage and follow up the subjects (3).

Hyperglycemia, hypertension and dyslipidemia are the most known pathophysiologic factors of diabetic nephropathy which all have inflammatory basis (4). Numerous studies revealed that subclinical chronic inflammation is also associated with insulin resistance syndrome to play a predominant role in the pathogenesis of diabetic nephropathy (5). C-reactive protein (CRP), made and released by liver macrophages as well as adipocytes, is an acute phase protein as a sensitive marker of inflammation in the early phase (6). It is possible that

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serum CRP correlates with diabetic nephropathy and neuropathy in type 1 and 2 of DM (7). Furthermore, uric acid as the final metabolite of purines, is an independent risk factor of renal dysfunction among patients with DM (8). Pieces of evidence showed that serum levels of uric acid could directly induct increased cytokines in blood flow like CRP, INF and IL-6 to cause renal dysfunction and augmentation of albumin excretion in urine (9). This means that high serum levels of uric acid may be a predictor for hypertension (10), Obesity (11), T2DM (12), metabolic syndrome (13) and cardiovascular diseases as well as reduced glomerular filtration rate (GFR) (14). CRP is usually released after uric acid enters vascular smooth muscles to activate an inflammatory cycle and endothelial dysfunction which, in turn, increases the risk of albuminuria in DM cases (15). Bonakdara et al evaluated 1275 cases of T2DM in 2011 to determine that high serum level of uric acid correlated with high albuminuria in that group of patients (16). Yan et al assessed separate effects of serum CRP and uric acid on albuminuria in DM patients (17). In addition, some authors believe that Tumor necrosis factor alpha (TNF-α) is also an inflammatory marker which its higher serum levels in addition to increased serum CRP is associated with higher risk of albuminuria (18).

Objectives

Regarding the importance of diabetic nephropathy and lack of studies on their effect of serum CRP and uric acid on albuminuria and its severity in our country, the current study intended to assess this effect among patients with T2DM in order to prevent it or achieve a good way to manage.

Patients and Methods

Study population

Through an analytic cross-sectional design, 200 T2DM cases were recruited by the current study. They referred to Firoozgar hospital in Tehran between 2014 and 2015. Patients with other types of diabetes, kidney disease or transplantation, subjects with kidney vascular problems and dialysis in addition to people who had obstructive uropathy, urinary tract infections, fever, acute medical conditions, congestive heart failure and malignancies as well as pregnant patients were excluded. Taking uric acid lowering medications were also considered as exclusion criteria as well. Demographics, vital signs and other clinical findings were gathered by a questionnaire. Blood samples were drawn after 12 hours of starving to measure parameters including serum levels of CRP, triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C), cholesterol, Low-density lipoprotein (LDL-C), fasting blood sugar (FBS), and Hb-A1C. Among which, for the first parameter we used an immunoturbidimetric method and the rest were assessed through enzymatic methods. Twenty-hour urine albumin level was measured with immunoturbidimetric method too. Past medical history, current treatments, duration of illness and smoking history were obtained as well.

Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained and 3) the research was approved by the ethical committee of Iran University of Medical Sciences (#94-01-30-25796).

Data analysis

Regarding the Cochrane's sample size formulation and considering study power of 0.8, CI of 95%, α type 1 error of 0.05 and the following formula the sample size was calculated (N = 200).

$$n = \frac{(N \times t2 \times p \times q)}{(N \times d2 + t2 \times p \times q}; d = 0.2, t = 1.6$$

Data entered statistical software to analyze with chi-square and *t* test in addition to logistic regression and analysis of variance (ANOVA). Quantitative data were reported using central tendencies and qualitative were claimed by percentages. Chart spots were provided using logistic regressions.

Results

A total of 200 patients with T2DM enrolled the current study including 108 (54%) males and 92(46%) females between 38 and 78 years of age. The mean age was 54.42 ± 9.28 years. The majority of the participants were in their 50's (38%) followed by patients younger than 50 years of age (36.5%) and older than 60 (25.5%). The least body mass index (BMI) was 19.52 kg/m^2 and its most value was 37.06 kg/m^2 with the mean of 26.58 ± 3.52 kg/m^2. On average, the total time of involvement with T2DM was 8.15 ± 5.62 years. Our patients had the disease from 1 to 30 years and 80.5% of them had the disease for less than 10 years. Of the participants, 46 (23%) were cigarette smokers. Table 1 summarizes the mentioned demographics and background information. The most used medical regimen to control DM was a combination of insulin and oral medications in 99 (49.5%) of patients while oral medications were administered alone in 35.5%. Insulin was the only medication in 15% of the cases. Systolic blood pressure ranged 80-190 mm Hg and diastolic pressure 40-110 mm Hg. The means of systolic and diastolic blood pressures were 125.2 ± 16.63 mm Hg and 76.82 ± 8.58 mm Hg, respectively. Table 2 shows the laboratory parameters of patients.

Serum uric acid (SUA) ranged 2.1-9.1 mg/dL with a mean of 5.11 ± 1.42 mg/dL while CRP had a mean of 2.72±2.81 mg/L and ranged 0.03-15.3 mg/L. Total 24 hours urine albumin ranged 1.3-485 mg/d with 66.35 ± 99.07 mg/d as mean ± SD. More than a half of participants had albumin <30 mg/d (albuminuria) in 24-hour urine while 79 (39.5%) had micro-albuminuria (30-300 mg/d) and 8 (4%) presented macro-albuminuria (>300 mg/d) as can be seen in Table 1. Table 3 represents that SUA and serum CRP level were directly correlated with the total level of albumin in 24 hours urine ($P = 0.007$). Linear regression

Table 1. Demographics and basic information of participants

Variable		No. (%)
Sex	Male	108 (54)
	Female	92 (46)
Age (y)	<50	73 (36.5)
	51-60	76 (38)
	>60	51 (25.5)
	Mean± SD	54.42±9.28
Duration of T2DM (y)	<10	161 (80.5)
	10-20	29 (14.5)
	>20	10 (5)
	Mean± SD	8.15±5.62
Smoking habit	No	154 (77)
	Yes	46 (23)
BMI (kg/m^2)	< 9	0 (0)
	19-25	74 (37)
	25-30	92 (46)
	>30	34 (17)
	Mean± SD	26.5±3.52
DM medications	Oral	71 (35.5)
	Insulin	30 (15)
	Oral/Insulin combination	99 (49.5)
	Total	200 (100)
Albuminuria (mg)	<30	113 (56.5)
	30-300	79 (39.5)
	> 300	8 (4)

Table 2. Overall measurements of selected lab data to study with their maximum and minimum in participants

Parameter	(Mean± SD)	Min	Max
FBS (mg/dL)	139.84±38.4	75	280
HBA$_1$C (%)	7.41±1.41	4	14.7
TG (mmol/L)	153.39±62.88	36	470
Cholesterol (mmol/L)	168.73±64.04	87	320
LDL (mmol/L)	98.44±34.89	43	247
HDL (mmol/L)	39.9±10.6	21	81
Uric acid (mg/dL)	5.11±1.42	2.1	9.1
CRP (mg/L)	2.72±2.81	0.03	15.3
24-urine albumin(mg)	66.35±99.07	1.3	485

test showed a diagram in this regard which is shown in Figure 1. The correlation was statistically more observable between SUA level and 24-hour urine albumin and the related diagram shows it in a good way ($P<0.001$).

Spearman's test also showed a significant direct correlation between serum CRP and SUA ($P=0.005$), which its regression diagram is observable in Figure 1. Using *t* test, the findings show no statistical relationship between age and BMI with the level of albuminuria ($P=0.78$ and P=0.49 respectively). There was also no correlation between the chronicity of DM and albuminuria when compared by Mann-Whitney U test ($P=0.321$). The same results were obtained for systolic and diastolic blood pressure in terms of correlation with albuminuria and its severity ($P=0.102$ and $P=0.76$ respectively). Table 4 shows the related information perfectly. Gender, cigarette smoking and medications were the next parameters to be assessed if had any correlation with albuminuria. Chi-square test presented no correlation in this matter ($P=0.36$, $P=0.3$ and $P=0.15$ respectively). Kruskal-Wallis test was used to find any relationship among lipid profile, FBS and HBA1C with albuminuria but failed to find it in all groups and the findings are seen in Table 5. Interestingly, there was a correlation between serum TG level and albuminuria in three groups which we studied as reported by Table 5 ($P=0.025$). SUA and serum CRP were compared in three levels of albuminuria using Kruskal-Wallis test to report strong correlations ($P=0.0001$ for both).

Table 3. Significance and coefficients of the direct correlation between SUA and CRP and the albumin concentration of 24-hour accumulated urine

	Parameter	Pearson's correlation	*P* value
Albumin in 24-h urine	Serum uric acid	0.242	0.001
	Serum CRP	0.199	0.005

As showed in Figure 2, macro-albuminuria closely correlated with high SUA and high serum CRP among diabetic patients. Both markers represented significant correlation with albuminuria level ($P=0.006$ and $P=0.003$ respectively). Logistic regression test confirmed the mentioned correlation when confounding factors were eliminated.

Additionally we found every unit of increased SUA could raise the risk of albuminuria up to 1.3 times which was feed by the odds ratio (OR) of 1.3 in the mentioned relationship while the OR for the role of CRP in the risk of albuminuria was 1.2.

Discussion

The current study tried to disclose any correlation between two key laboratory parameters in a group of patients with DM who had no other comorbidities with effects on SUA and CRP levels. There were wide ranges of SUA and CRP among our patients and there were odds ratios 1.3 and 1.2 for uric acid and CRP, respectively in terms of correlation with the risk of albuminuria in diabetic cases that was near to the findings by Fraser et al, in 2014 (19). SUA and CRP were also in a direct strong relationship when studied in our participants.

Diabetic patients are basically at risk of many consequences from organ failures to disabilities and even early death. Uric acid, as an end product of purine metabolism in human, may lead to a wide spectrum of medical conditions which the most familiar one is gouty arthritis (20). Hyperuricemia has been also recently focused as a risk factor of cardiovascular diseases as well as metabolic syndrome (21). Furthermore, some count on hyperuricemia and metabolic syndrome as independent predictors of chronic kidney disease (CKD) in T2DM (22).

The current study did not compare SUA levels in different control levels of T2DM like HbA1C. Hence, we could not find any changes in uric acid to link to the levels of

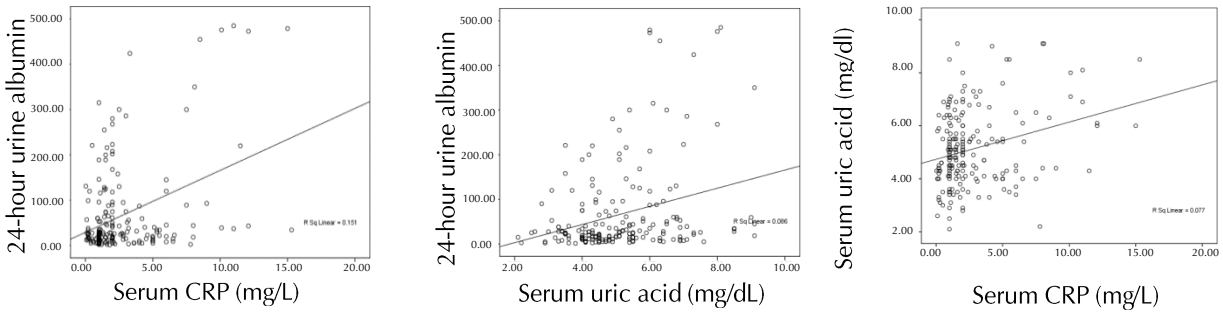

Figure 1. Linear diagram of separate correlation of serum CRP and serum uric acid with 24-hour urine albumin concentration (two left-side diagrams). The right dots plot shows the relationship between serum CRP and uric acid concentration.

HbA_1C. However, a study in 2011 showed a negative correlation between SUA and HbA_1C or fasting blood sugar (20). Hyperuricemia has been also recently focused as a risk factor of cardiovascular diseases as well as metabolic syndrome (21). Furthermore, some count on hyperuricemia and metabolic syndrome as independent predictors of CKD in T2DM (22). In another study published in 2016 by Solbu et al, SUA was unexpectedly associated with albuminuria in a positive manner (23). Since approximately 70% of SUA is eliminated by kidney and reabsorbed up to 90% in kidney, it can be actually involved in chronic kidney disease (CKD) as Dousdampanis et al, pointed out in 2014 (24). Hyperuricemia is due to impaired renal excretion of uric acid in 90% of cases (25). Diabetes is one of the main causes of CKD and microvascular complications of DM are associated with hyperuricemia in terms of pathogenesis (26). Hyperuricemia (HUA) is, in turn, a predisposing factor for hypertension and consequently cardiovascular mortality as animal studies believe (27,28). Diabetic nephropathy could be considered as one of the causal factors for end-stage renal disease as well. Likely, hyperuricemia can direct insulin resistance to develop hyperinsulinemia (29). On the contrary, Zhang et al, believed that HUA could disturb the glucose metabolism via an increased oxidative stress as well as inhibition of pancreatic β cells (30). In obese diabetic cases, hyperuricemia is not unusual since obesity predispose T2DM in some individuals among whom an increased hepatic production of uric acid is expected. It suggests a link between obesity, diabetes and uric acid changes (31) and also CKD independently of other metabolic syndrome components, (32) although we found no relationship between BMI and SUA in the current study. The correlation between uric acid and albuminuria is a

Table 4. Correlation of several demographic and clinical parameters with the level of albuminuria in our participants

	Albuminuria	N	Mean±SD	Test value	*P* value
Age	Macroalbuminuria	8	54.94±9.12	t=0.69	0.49
	Microalbuminuria	79	54.76±8.11		
	Normal	113	54.2±9.5		
BMI	Macroalbuminuria	8	26.61±3.46	T=0.26	0.78
	Microalbuminuria	79	26.54±3.12		
	Normal	113	26.52±3.45		
Duration of DM	Macroalbuminuria	8	8.11±5.12	Z=0.3	0.76
	Microalbuminuria	79	8.45±5.76		
	Normal	113	8.23±5.98		
SBP (mm Hg)	Macroalbuminuria	8	126.79±16.64	Z=1.63	0.102
	Microalbuminuria	79	126.89±16.49		
	Normal	113	123.89±16.95		
DBP (mm Hg)	Macroalbuminuria	8	77.14±8.13	Z=0.99	0.321
	Microalbuminuria	79	77.34±8.97		
	Normal	113	76.19±8.13		
Male	Macroalbuminuria	5	-	-	0.15
	Microalbuminuria	47	-	-	
	Normal	56	-	-	
Female	Macroalbuminuria	3	-	-	
	Microalbuminuria	32	-	-	
	Normal	57	-	-	
Smoker	Macroalbuminuria	6	-	-	0.3
	Microalbuminuria	64	-	-	
	Normal	84	-	-	

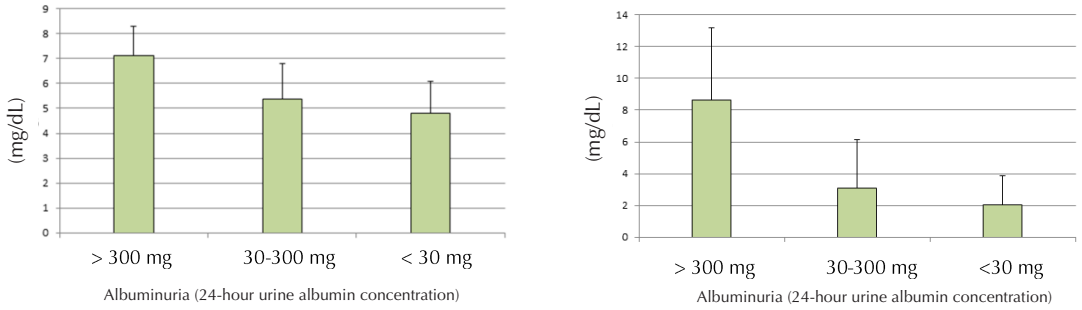

Figure 2. Distribution of albuminuria including micro and macro-albuminuria in patients with T2DM participating in the current study. The left chart belongs to the concentration of uric acid and the right one shows serum levels of CRP.

very important issue to rise in diabetic cases and evidence support the role of baseline SUA levels in the prediction of persistent macro-albuminuria in type1DM (33,34). Ficociello et al computed that 1 mg/dL rise in SUA level could increase the risk of micro- or macro- albuminuria by 80% which could be led by GFR loss in type 1 DM patients (35). BO et al showed a correlation between HUA and early onset of diabetic nephropathy in patients with T2DM (36,37).

Several studies highlighted the effect of lowering SUA on the progression of diabetic nephropathy; one of whom was a research team led by Momeni et al, who administered allopurinol in 40 patients with T2DM in 2010 in Iran. They determined a decrease in proteinuria only in 4 months of treatment (38).

Uric acid has another interesting role which is mostly predominant in vascular smooth muscle cells where promotes inflammation when activates NF-Kβ and enhances CRP expression (15). Studies show that CRP and uric acid may make an interact in the development of albuminuria and contribute to the progression towards CKD in patients with T2DM (39-41). Hence, it was not too strange to report increased CRP in serum along with HUA through the current study. In 2005, Kang et al focused on the primitive effect of uric acid on CRP expression via endothelial dysfunction and pathologic vascular remodeling (15). There is evidence of a systemic inflammatory response in individuals with hypertension or cardiovascular disease which is marked mainly by elevated serum CRP. CRP is a well-known marker for myocardial infarction, stroke and vascular death and CKD (42,43). CRP is not only a marker, but also facilitates apoptosis in endothelial cells in addition to being an active factor in plaque formation and cardiovascular

Table 5. Correlation of some important laboratory parameters with the level of albuminuria with the test values and significance. Beside SUA and CRP, serum triglyceride was the only factor to associate with the severity of albuminuria in our participants in term of general laboratory measures

Lab parameters	Albuminuria	n	Mean±SD	Test value	*P* value
FBS (mg/dL)	Macroalbuminuria	8	137.37±40.63	Z=3.74	0.154
	Microalbuminuria	79	134.56±36.1		
	Normal	113	143.69±39.8		
HBA_1C	Macroalbuminuria	8	7.23±0.36	Z=0.86	0.649
	Microalbuminuria	79	7.45±1.29		
	Normal	113	7.39±1.54		
TG (mmol/L)	Macroalbuminuria	8	141.37±56.32	Z=7.37	0.025
	Microalbuminuria	79	139.81±55.99		
	Normal	113	163.73±66.3		
Chol(mmol/L)	Macroalbuminuria	8	170.62±48.62	Z=2.97	0.22
	Microalbuminuria	79	162.91±46.84		
	Normal	113	172.67±45.28		
LDL (mmol/L)	Macroalbuminuria	8	95.0±21.66	Z=3.93	0.14
	Microalbuminuria	79	93.22±32.17		
	Normal	113	102.32±37.12		
HDL (mmol/L)	Macroalbuminuria	8	37.87±9.77	Z=0.902	0.63
	Microalbuminuria	79	38.53±8.53		
	Normal	113	41.0±11.84		
SUA (mg/dL)	Macroalbuminuria	8	7.11±1.18	Z=20.5	<0.001
	Microalbuminuria	79	5.37±1.42		
	Normal	113	4.79±1.29		
CRP (mg/L)	Macroalbuminuria	8	8.63±4.58	Z=20.47	<0.001
	Microalbuminuria	79	3.08±3.04		
	Normal	113	2.05±1.81		

morbidity (44). Despite the antioxidant role which some authors consider for uric acid (45) many authors believe in high levels of uric acid as a promoter for systemic inflammation, CRP expression, endothelial dysfunction, hypertension and cardiovascular diseases (46). Kang et al investigated the role of uric acid in CRP synthesis to suggest a pathologic linkage between uric acid and CRP in diabetes and cardiovascular diseases as well as CKD (39). Finally, CRP is considered more than a biomarker of inflammation since evidence shows that CRP has also a direct effect to promote atherosclerotic process and endothelial cell dysfunction (15).

However, albuminuria and its correlation with two main parameters including SUA and CRP were important factors to assess in the current study. We found a strong linear correlation in this regard although there were not big ORs to discuss.

There was no correlation between albuminuria and lipid profile, FBS, HbA_1C, blood pressure and medications throughout our study.

Conclusion

It seems that uric acid and CRP levels in serum are the most reliable parameters studied by the current study to predict life-threatening diabetic consequences like cardiovascular disease (CVD) and CKD in patients with T2DM.

Limitations of the study

This study conducted with a small sample size and the results should be validated by multi-centric studies with larger sample size.

Authors' contribution

FS; study design, preparation of the manuscript, and final revision. HR; study design, data gathering, manuscript preparation.

Conflicts of interest

The authors declared no competing interests.

Ethical Considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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