Elevated Serum C-Reactive Protein Level and Microalbuminuria in Patients With Type 2 Diabetes Mellitus

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Introduction. Microalbuminuria is a marker of vascular endothelial damage. In addition, it is reported that high serum levels of C-reactive protein (CRP) is a novel cardiovascular risk factor that impairs endothelial function. The aim of this study was to evaluate the relationship between microalbuminuria and elevated serum level of high-sensitivity CRP (HS-CRP) in type 2 diabetic patients.
Materials and Methods. We measured serum levels of HS-CRP in 87 patients with type 2 diabetes mellitus. They were divided into a microalbuminuric group (n = 45) and those with a 24-hour urine albumin less than 30 mg/d (n = 42). The relationship of serum HS-CRP level with albuminuria and other characteristics of the patients was assessed.
Results. Patients with microalbuminuria were significantly older and affected by diabetes mellitus longer than those without microalbuminuria. Also, their mean HS-CRP was significantly higher (4.98 ± 1.45 mg/L versus 2.82 ± 2.10 mg/L; $P < .001$). The Pearson correlation test showed a significant correlation between HS-CRP level and urine albumin level (r = 0.43; $P < .001$). The specificity and sensitivity of HS-CRP for detection of microalbuminuria in were 78.5% and 68.8%, respectively, and the positive and negative predictive values were 77.5% and 70.2%, respectively.
Conclusions. In type 2 diabetic patients, microalbuminuria is accompanied by elevated HS-CRP, suggesting activation of inflammatory pathways in progression of renal and cardiovascular atherosclerotic disease. As an easier and cheaper test for assessment of diabetic nephropathy, we recommend further studies on HS-CRP in diabetic patients.

INTRODUCTION

Since kidney failure in this group of patients leads to mortality 20 to 40 times likelier than in those without DM,[1] prevention and early diagnosis of kidney dysfunction is very important.[2,3] Several epidemiological and clinical studies have demonstrated that the presence of microalbuminuria is an independent and strong predictor of cardiovascular mortality and morbidity in patients with diabetes mellitus (DM).[4-6] It has been shown that microalbuminuria is a marker of vascular damage and atherosclerosis.[3,7] On the other hand, high serum levels of C-reactive protein (CRP) is associated with complications of atherosclerosis such as myocardial infarction and stroke.[7-9] Hence, serum CRP might be potentially a marker that

is associated with a higher risk of mortality in atherosclerotic patients.[10]

In one study, it was reported that elevated serum CRP level increased diabetic risk up to 2.7 times.[11] Microalbuminuria is also associated with endothelial damage.[12-13] Therefore, it can be anticipated that albuminuria level can be associated with higher levels of serum CRP,[14] and activation of inflammatory pathways in progression of renal and cardiovascular atherosclerotic diseases can reflect in the CRP level. Accordingly, we carried out a study on patients with type 2 DM to investigate the relationship of serum CRP level and microalbuminuria as markers of kidney damage.

MATERIALS AND METHODS
Study Population

This cross-sectional study was conducted on patients with type 2 DM presented to the endocrinology and nephrology clinics of Ghaem and Imam Reza hospitals in Mashhad, Iran, from April 2005 to October 2005. The exclusion criteria were rheumatologic diseases, infectious diseases, cardiovascular diseases (recent myocardial infarction or cerebrovascular accident), pregnancy, cigarette smoking, body mass index greater than 30 kg/m^2, severe hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg), kidney failure (serum creatinine > 1.5 mg/dL), leukocytosis, hematuria, overt proteinuria (urine albumin > 300 mg/d), administration of statins, and thyroid disease. Cardiologic consultation, echocardiography, and electrocardiography were done for exclusion of patients with severe cardiovascular disease.

Outcome Measures

Microalbuminuria was defined as urine albumin excretion between 30 mg/d and 300 mg/d, and it was tested in 24-hour urine collection samples. The patients were divided into microalbuminuric and normoalbuminuric groups. Microalbuminuria was detected by the enzyme-linked immunosorbent assay (Immuno-Biological Laboratories, Minneapolis, USA), whose interassay and intra-assay coefficient of variations were 8% and 7%, respectively. Serum level of CRP was also measured in all of the participants. High-sensitivity CRP (HS-CRP) CRP levels were measured by photometry method (Dade Behring, Deerfield, USA). The minimum

detectable concentration of CRP by this assay system was 0.5 mg/L.

Lipid profile, blood glucose, and serum creatinine were also assessed and blood pressure was measured in a standard condition (sitting position, after 5 minutes of resting, and ceasing smoking, drinking tea or coffee, and eating food for at least half an hour). The total serum cholesterol was assessed by an enzymatic assay with the interassay and intra-assay coefficient of variations of 2.5% and 2.3%, respectively, and serum triglyceride by an enzymatic assay with the interassay and intra-assay coefficient of variations of 2% and 3.5%. The low-density lipoprotein level was calculated by the Friedwall equation.

Statistical Analyses

All statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA). The chi-square test and the Fisher exact test were used to evaluate the differences in proportions between the two groups. For comparison of quantitative variables, the independent t test and the Mann-Whitney test were utilized. The Pearson correlation coefficient test was used for assessment of correlation between urine albumin and HS-CRP as quantitative factors. Quantitative variables were demonstrated as mean ± standard deviation. A P value less than .05 was considered significant.

RESULTS

A total of 100 patients were enrolled in the study and 87 completed the study and were included in the analyses. The exclusion reasons in 13 eligible patients were the missing laboratory data due to incomplete 24-hour urine collection. Based on the albuminuria evaluation, 45 of the patients had microalbuminuria (mean urine albumin, 83.60 ± 51.68 mg/d), and 42 patients did not have this condition (mean urine albumin, 9.61 ± 5.25 mg/d). There was no significant difference in the kidney function, measured by serum creatinine levels, between these two groups (P = .69; Table 1).

Microalbuminuric patients were significantly older (P = .002) and were affected by DM for a longer duration (P = .01) when compared with diabetic patients without microalbuminuria. Also, their serum levels of triglyceride (P = .006), HDL (P < .001), and HS-CRP (P < .001) were significantly higher (Table 1).

Table 1. Characteristics of Diabetic Patients With and Without Microalbominuria*

	Microalbuminuria		
Parameters	Positive (n = 45)	Negative (n = 42)	P
Age, y	55.17 ± 10.58 (39 to 82)	48.71 ± 8.21 (35 to 70)	.002
Diabetes duration, y	7.60 ± 6.62 (1 to 22)	3.95 ± 2.97 (1 to 10)	.01
BMI, kg/m²	25.44 ± 2.20 (22 to 30)	26.02 ± 2.70 (21 to 30)	.27
Systolic BP, mmHg	121.11 ± 16.19 (90 to 145)	119.76 ± 15.73 (90 to 160)	.69
Diastolic BP, mmHg	75.11 ± 13.46 (50 to 100)	75.95 ± 11.54 (50 to 100)	.76
Serum parameters			
Cholesterol, mg/dL	216.60 ± 44.77 (124 to 284)	211.95 ± 30.83 (165 to) 278	.58
HDL, mg/dL	42.93 ± 8.23 (28 to 60)	48.80 ± 11.22 (35 to 82)	.006
LDL, mg/dL	124.77 ± 36.44 (60 to 196)	130.80 ± 27.63 (78 to 190)	.40
Triglyceride, mg/dL	266.71 ± 76.98 (90 to 380)	167.57 ± 54.30 (95 to 325)	< .001
Glucose, mg/dL	135.04 ± 19.47 (95 to 164)	140.95 ± 18.51 (115 to 170)	.15
Creatinine, mg/dL	1.04 ± 0.25 (0.7 to 1.6)	1.02 ± 0.24 (0.7 to 1.4)	.69
HS-CRP, mg/L†	4.98 ± 1.45 (0.6 to 7.3)	2.82 ± 2.10 (0 to 7.0)	< .001

*BMI indicates body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and HS-CRP, high-sensitivity C-reactive protein.
†Serum HS-CRP was measured for 83 patients.

Based on the manufacturer's instructions, serum HS-CRP levels higher than 5 mg/L were considered positive, and accordingly, the patients were classified as HS-CRP positives and HS-CRP negatives. The mean age, serum triglyceride, and duration of DM were significantly different in patients with a positive HS-CRP (Table 2). Further, urine albumin level was significantgly higher in HS-CRP positives than HS-CRP-negative diabetic patients (P < .001; Table 2).

The Pearson correlation test showed a significant correlation between HS-CRP level and urine albumin level (r = 0.43; P < .001). Of 45 patients with microalbuminuria, 14 (31.1%) had a negative HS-CRP, while 31 (68.9%) were HS-CRP positive. In contrast, of 42 patients without microalbuminuria, 33 (78.6%) were HS-CRP negative (P < .001). The specificity and sensitivity of HS-CRP for detection of microalbuminuria in were 78.5% and 68.8%, respectively, and the positive and negative predictive values were 77.5% and 70.2%, respectively.

DISCUSSION

In several studies, it has been reported that there is a correlation between serum CRP levels and microalbumiuia in diabetic patients and even in the general population.[7] These observations suggest that low-grade inflammation, reflected by high serum HS-CRP levels, may play a role in the induction

Table 2. Characteristics of Diabetic Patients With Positive and Negative C-Reactive Protein Tests*

	HS-CRP		
Parameters	Positive (n = 37)	Negative (n = 46)	P
Age, y	56.8 ± 10.7 (40 to 82)	48.6 ± 8.0 (35 to 68)	< .001
Diabetes duration, y	7.3 ± 6.2 (1 to 22)	4.6 ± 4.6 (1 to 20)	.03
BMI, kg/m²	25.8 ± 2.1 (22 to 30)	25.9 ± 2.6 (21 to 30)	.89
Systolic BP, mmHg	118.8 ± 15.5 (90 to 145)	12.5 ± 16.3 (90 to 160)	.62
Diastolic BP, mmHg	73.2 ± 13.3 (50 to 100)	76.1 ± 11.2 (50 to 100)	.29
Serum parameters			
Cholesterol, mg/dL	221.0 ± 42.5 (124 to 284)	207.4 ± 35.3 (140 to 278)	.11
HDL, mg/dL	45.0 ± 10.0 (31 to 54)	44.8 ± 6.8 (28 to 64)	.93
LDL, mg/dL	130.9 ± 37.9 (60 to 196)	124.5 ± 28.7 (75 to 190)	.38
Triglyceride, mg/dL	224.4 ± 77.7 (90 to 380)	177.9 ± 64.2 (95 to 325)	.004
Glucose, mg/dL	140.1 ± 20.9 (95 to 164)	136.1 ± 17.5 (111 to 170)	.35
Creatinine, mg/dL	1.04 ± 0.27 (0.7 to 1.6)	1.01 ± 0.23 (0.7 to 1.4)	.65
Urine albumin, mg/d	77.9 ± 59.6 (3 to 216)	26.2 ± 33.7 (3 to 135)	< .001

* HS-CRP indicates high-sensitivity C-reactive protein; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

of microalbuminuria, which can be considered as a risk factor of cardiovascular diseases.[15] On the other hand, drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers lessen the risk of cardiovascular mortality through reduction of microalbuminuria.[16,17]

Persistent microalbuminuria is a strong predictor of development of clinical diabetic nephropathy, which is reversible, but may lead to kidney failure if neglected. Therefore, early diagnosis may help to prevent of progression of kidney disease.[9,16] Accordingly, annual screening of microalbuminuria is recommended by experts in DM.[2,18]

It is reported that prevalence of microalbuminuria is about 12.6% to 25.3% in patients with type 2 DM.[19,20] There is limited data on type 2 DM nephropathy in Asia and also in Iran.[20] In order to find an easier method for detection of diabetic nephropathy as a screening method of diabetic nephropathy (before 24-hour urine collection), we tried to find a relation between HS-CRP as a marker of diabetic nephropathy and microalbuminuria. In some studies, it has been shown that there exist a relationship between microalbuminuria and age.[21-24] We found this result too. We also found an association between triglyceride level and microalbuminuria, which has not been reported before. In our study, it was shown that triglyceride and age correlated with HS-CRP, as well.

We did not find any association of microalbuminuria or HS-CRP with body mass index, blood pressure, blood glucose, serum creatinine, and serum cholesterol. Although other studies reported there was significant an association of body mass index and blood pressure with microalbuminuria,[3,25,26] likewise our study, they did not find a significant relation between hypercholesterolemia and microalbuminuria. They also reported there were no differences between men and women in terms of these parameters,[3] that is similar to our findings. A limitation of our study was that since many factors can affect CRP level, we had to limit our inclusion criteria to avoid confounding factors, such as administration of statins and angiotensin-converting enzyme inhibitor, which is used by many diabetic patients.

CONCLUSIONS

In our patients with type 2 DM, microalbuminuria was accompanied by elevated HS-CRP suggesting activation of inflammatory pathways in progression of kidney and cardiovascular atherosclerotic disease. Based on this study, we recommend measurement of serum HS-CRP as a screening method be considered in the future studies, in order to help us diagnosing early stages of diabetic nephropathy sooner and easier.

CONFLICT OF INTEREST

None declared.

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