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DIABETIC NEPHROPATHY AND ITS RELATION TO INFLAMMATION

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ABSTRACT

Diabetic nephropathy occurs in 20- 40% patients with diabetes. It is the leading cause of end stage renal disease. Despite improvement in the knowledge of diverse aspects related to diabetes mellitus, the pathogenesis and initial molecular events leading to diabetic nephropathy are still elusive. Recent studies have shown that chronic subclinical inflammation is a part of type 2 DM based on increased plasma concentrations of inflammatory parameters such as hs – CRP, fibrinogen, IL-1, IL-6 and TNF ∝. Inflammation can emerge as a potential mechanism in the pathogenesis of early renal injury in type 2 DM. The aim of the present study was to explore the relationship between low grade inflammatory markers (hs-CRP and IL-6) and renal microangiopathy in patients with type 2 DM. We test the hypothesis that inflammatory parameters are independently associated with UAE in patients with type 2DM with early stages of renal involvement (proteinuria <3G/d and normal renal function). The present study was conducted on outpatients and inpatients of Sri Ramachandra Medical College and Research Institute, Chennai between October 2006 and September 2008. Age and Gender matched controls were taken. Diabetic patients were further divided into normoalbuminurics, microalbuminurics and macroalbuminurics based on 24 hours urinary albumin excretion. Patients with these criteria are included: Patients of type 2 diabetes;Proteinuria <3G/day ;Serum creatinine <1.3 mg/dl. And patients with these criteria's are excluded: Current acute illness including infectious diseases within past 1 week; Cigarettee smoking; Active immunological diseases; Confounding factors for proteinuria like severe uncontrolled hypertension (>160/100mg) and Malignancy. A detailed history was taken and information on age, gender, duration of diabetes, treatment and hypertension was recorded. Then patients were subjected to physical examination with special emphasis on height, weight, BMI and blood pressure. The initial investigations included urine routine/microscopy, fasting plasma glucose, renal function test. Urinary albumin excretion (UAE) by 24-hours urine collection was done. Highly sensitive – CRP and Interlukin – 6 (EASIA) were measured. The mean age of controls was 56.2 ± 4.85 years, and the mean age of diabetic patients were 56.1 ± 5.16, 55.8 ± 5.15 and 55.9 ± 4.69 years in normoalbuminuric, microalbuminuric and macroalbuminuric group respectively. There were 10 males and 10 females in each of the four groups. There was no difference in body mass index (BMI) in the four groups. The mean BMI were 22.2 ± 2.26, 23.32 ± 2.22 23.32 ± 2.69 and 23.17 ± 2.59 kg/m^2 in controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Mean years since detection of diabetes were 6.7 ±2.002, 6.8 ±2.52 and 7.55±2.74 years in normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Mean fasting plasma glucose (FPG) was 88.15 ± 11.14, 132.4 ± 19.8,127.7 ± 22.02 and 129.5 ± 16.83 mg/dl in controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. UAE was 10.05 ± 6.18, 16.35 ± 6.92, 160.6 ±62.63 and 643.15 ± 214.32 mg/d in controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Mean levels – CRP were 1.08 ± 0.32, 2.31 ± 0.49, 5.16 ± 1.84 and 6.31±2.54 mg/L in controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Mean levels of interleukin-6 were 18.1 ± 10.97, 126.41 ± 34.38, 268.39 ± 125.88 and 574.44±186.22 pg/ml in controls, normoalbuminuric microalbuminuric and macroalbuminuric patients respectively. Using Pearson correlation for association a correlation coefficient of 0.582 was found between UAE and hs- CRP levels and 0.782 between UAE and IL – 6. Correlation coefficient was 0.514 between hs – CRP and IL-6.

KEY WORDS

Diabetes; Albuminuria; Nephropathy

INTRODUCTION

Diabetic nephropathy occurs in 20-40% patients with diabetes. It is the leading cause of End Stage Renal Disease, with renal disease as a major cause of morbidity and mortality in the diabetic population. An interaction of metabolic and hemodynamic factors has been considered a traditional aspect in the development of renal lesions in patients with Type 2 DM. Despite improvement in the knowledge of diverse aspects related to diabetes mellitus, the pathogenesis and initial molecular events leading to diabetic nephropathy are still elusive.

Recent studies have shown that chronic subclinical inflammation is a part of type 2 DM based on increased plasma concentrations of inflammatory parameters such as hs-CRP, fibrinogen, IL-1, IL-6 and TNF ά. However data about the potential relation between inflammation and early nephropathy in Type 2 DM are scarce. Inflammation can emerge as a potential mechanism in the pathogenesis of early renal injury in type 2 DM. The present study is devised to find out the correlation between inflammatory markers and diabetic nephropathy.

AIMS AND OBJECTIVES

1. To study the role of subclinical inflammation in Type 2 diabetic patients having nephropathy
2. To study the correlation between various inflammatory markers and albuminuria in these patients.

MATERIALS AND METHODS

The study was done on patients with type 2 diabetes attending the Outpatient Department and inpatients admitted in Sri Ramachandra Medical College & Research Institute, Chennai between October 2006 to September 2008. Informed consent was taken from each patient before enrolling into the study.

Inclusion criteria:

1. Patients of type 2 diabetes
2. Proteinuria < 3 G/day.
3. Serum creatinine < 1.3 mg/dL

Exclusion criteria:

1. Current acute illness including infectious diseases within past 1 week
2. Cigarette smoking.
3. Active immunological diseases.
4. Confounding factors for proteinuria like severe uncontrolled hypertension (> 160/100)
5. Malignancy.

Methods of Study:

A total of 60 patients who were age and gender matched, meeting the above mentioned criteria were included in the study after obtaining a written informed consent. In addition, 20 age and gender matched controls from the normal population were taken. Type 2 diabetes was defined as diabetes treated by diet alone or by diet combined with oral hypoglycemic agents, or patients on insulin plus diabetes onset after the age of 40 years.

A detailed history was taken and the following details recorded: age, gender, duration of diabetes, treatment, family history of diabetes and hypertension.

The patients were thereafter subjected to a detailed physical examination with special emphasis on blood pressure, retinopathy, height, weight and BMI.

The initial investigations included:

- Urine routine/microscopy
- Plasma glucose- fasting
- Renal function tests RFT

Plasma glucose level was assayed by means of an automated enzymatic method.

Two 24 hour urine samples were collected from subjects. Urinary albumin excretion (UAE) was confirmed in the 2 samples, and the mean value was computed. Urinary albumin was quantified by using colorimetric method. Normoalbuminuria was defined as UAE rate of <30 mg/24 hr, microalbuminuria as UAE of 30 to 300 mg/24 hr and macroalbuminuria as UAE> 300 mg/24 hr. Highly sensitive CRP (hs-CRP) was measured by means of an ultra sensitive solid phase enzyme linked immunosorbent assay (Calbiotech Inc., CA, USA). The procedure had a sensitivity of 0.2 mg/L. Expected values were classified as: low risk (<1 mg/L), normal (1-3 mg/L) and high risk (>3mg/L). Enzyme amplified sensitivity immunoassay, EASIA (Biosources Europe S.A) was used for detection of interleukin 6. The intra assay coefficient of variation was 4.2% and the inter assay coefficient of variation was 5.4%.

OBSERVATIONS AND RESULTS

The study includes 20 controls and 60 diabetics from the outpatient department and inpatients of Sri Ramachandra Medical College and Research Institute. These patients belonged to the age group 40-70 years and were age and gender matched. Details were recorded in a pre-structured proforma using questionnaire method and a detailed history was taken followed by clinical examination and investigations were also recorded in the proforma. The patients were then divided into 4 groups: controls and diabetic patients having normoalbuminuria, microalbuminuria and macroalbuminuria, each group comprising of 20 subjects. Data was analyzed by appropriate statistical methods.

Age and gender distribution:

Of the 20 subjects in each of the 4 groups, 10 were males (50%) and 10 females (50%). The mean age of controls was 56.2$\pm$ 4.85 years and the mean age of diabetic population were 56.1$\pm$ 5.16, 55.8$\pm$ 5.15 and 55.9 $\pm$ 4.69 years in normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Analysis of age difference between the groups did not show any statistical significance (P= 0.994).

Table 1: Number, Gender and Age distribution of subjects

Group	Total patients	Sex M/F	Min	Max	Range	Mean	Standard Deviation
Controls	20	10/10	49	68	19	56.2	4.85
normoalbuminuric	20	10/10	48	67	19	56.1	5.159
microalbuminuric	20	10/10	48	69	21	55.8	5.156
macroalbuminuric	20	10/10	49	66	17	55.9	4.689

Body mass index (BMI) :

The mean BMI of controls was 22.21 $\pm$ 2.26 kg/m^2 and the mean BMI of diabetics were 23.32 $\pm$ 2.22, 23.32 $\pm$ 2.69, and 23.17 $\pm$ 2.59 kg/m^2 in normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Analysis of BMI between the groups did not show any statistical significance (p=0.419).

Table 2: BMI of subjects

Group	Min	Max	Range	Mean	Standard Deviation
Controls	17.9	25.9	8.0	22.21	2.26
Normoalbuminuric	18.4	26.7	8.3	23.32	2.22
Microalbuminuric	18.4	27.8	9.4	23.32	2.69
Macroalbuminuric	18.5	27.4	8.9	23.17	2.59

DURATION OF DIABETES:

Mean years since detection of diabetes were 6.7 ± 2.002, 6.8 ± 2.52 and 7.55 ± 2.74 years in normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively with no statistical difference between normoalbuminuric and microalbuminuric (p=0.882), normoalbuminuric and macroalbuminuric (p=0.208) and microalbuminuric and macroalbuminuric (p=0.266) patients respectively.

BLOOD PRESSURE:

Both systolic and diastolic blood pressure were comparable between the 4 groups.

Mean systolic blood pressure (SBP) was 122.1 ± 8.71 mmHg in controls and was 123.6 ± 8.47, 123.4 ± 8.73 and 122.5 ± 10.6 mmHg in normoalbuminuric, microalbuminuric and macroalbuminuric patients with no statistically significant difference (p=0.947). Similarly, mean diastolic blood pressure (DBP) was 78.2 ± 5.06 mmHg in controls and was 79 ± 5.25, 79.5 ± 4.93 and 78 ± 5.42 mmHg in normoalbuminuric, microalbuminuric and macroalbuminuric patients with no statistically significant difference (p=0.778).

PLASMA GLUCOSE (FASTING)

The mean fasting plasma glucose was 88.15 ± 11.14, 132 ± 19.8, 127.7 ± 22 .02 and 129.5 ± 16.83 mg/dl in controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Analysis gave a significant p value of <0.001 between controls and diabetic patients. There was no statistical significant difference between normoalbuminuric and microalbuminuric (p=0.470), normoalbuminuric and macroalbuminuric (p=0.670) and microalbuminuric and macroalbuminuric (p=0.752) patients respectively.

URINARY ALBUMIN EXCRETION

The urinary albumin excretion (UAE) was 10.05 ± 6.18, 16.35 ± 6.92, 160.6 ± 62.32 and 643.15 ± 214.32 mg/d in controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively with statistically significant difference (p<0.001).

Table 3: Urinary Albumin Excretion (UAE) of subjects

	Controls	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Minimum	0	0	62	394
Maximum	22	28	284	1098
Range	22	28	222	704
Mean	10.05	16.35	160.6	643.15
SD	6.18	6.92	62.32	214.32

INFLAMMATORY MARKERS (HS – CRP AND IL – 6)

Highly sensitive - C-reactive protein

The mean values of hs-CRP were 1.08 ± 0.322, 2.31 ± 0.49, 5.16 ± 1.84 and 6.31± 2.54 mg/L controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively showing an increase in the levels as the albuminuria increases.

There was statistically significant difference in hs-CRP levels between controls and normoalbuminuric (p=0.17), microalbuminuric (p<0.001) and macroalbuminuric (p< 0.001) patients respectively. Similarly, there was statistically significant difference between normoalbuminuric patients and microalbuminuric (p<0.001) and macroalbuminuric patients (p< 0.001). Similarly, there was statistically significant difference between microalbuminuric and macroalbuminuric patients (p= 0.025).

Table 4. Highly sensitive –CRP levels in subjects

	Control	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Minimum	0.6	1.4	1.9	2.3
Maximum	1.8	3.3	8.3	10.7
Range	1.2	1.9	6.4	8.4
Mean	1.08	2.31	5.16	6.31
SD	0.322	0.49	1.84	2.54

INTERLEUKIN 6:

The mean values of interleukin -6 were 18.1 ± 10.97, 126.41 ± 34.38, 268.39 ± 125.88 and 574.8 ± 186.22 pg/ml in controls, normoalbuminuric, microalbuminuric and macroalbuminuric patients respectively. There was statistically significant difference in IL – 6 level between controls and normoalbuminuric (p= 0.04), microalbuminuric (p<0.001) and macroalbuminuric (p< 0.001) patients respectively. Similarly, there was statistically significant difference between normoalbuminuric patients and microalbuminuric (p<0.001) and macroalbuminuric (p<0.001) patients respectively. Similarly, there was statistically significant difference between microalbuminuric and macroalbuminuric patients (p< 0.001).

Table 5: Interleukin - 6 levels in subjects

IL-6	Control	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Minimum	5.7	55.7	135.6	279.3
Maximum	43.5	191.5	562	1181.6
Range	37.8	135.8	426.4	902.3
Mean	18.1	126.41	268.39	574.4
SD	10.97	34.38	125.88	186.22

Correlation between Protenuria and Inflammation

Pearson's correlation test was used to find the correlation between inflammatory markers and level of albuminuria in the diabetic patients. In diabetic significant positive correlation was found between UAE and hs-CRP and between UAE and IL – 6. Similarly positive correlation was

also found between hs- CRP and IL – 6. The controls did not show any correlation between levels of protenuria and inflammatory markers.

Table 6: Correlation between UAE and inflammatory markers (hs- CRP and IL-6) in patients with diabetes

Correlations[a]

		UAE	HSCRP	IL 6
UAE	Pearson Correlation	1	.582**	.782**
	Sig. (2-tailed)		.000	.000
	N	60	60	60
HSCRP	Pearson Correlation	.582**	1	.514**
	Sig. (2-tailed)	.000		.000
	N	60	60	60
IL 6	Pearson Correlation	.782**	.514**	1
	Sig. (2-tailed)	.000	.000	
	N	60	60	60

**. Correlation is significant at the 0.01 level (2-tailed).

a. Group = DM

Table 7: Characteristics of healthy controls and diabetic patients

Characteristics	Controls	Diabetics
Age (years)	56.2 ± 4.85	55.9 ± 4.92
Number of patients	20	60
Duration of DM (years)	_	7.01 ± 2.43
BMI (kg/m^2)	22.2 ± 2.226	23.27 ± 2.47
Systolic BP mmHg	122.1 ± 8.71	123.1 ± 9.17
Diabetic BP mmHg	78.2 ± 5.06	78.83 ± 5.15
FPG mg/dl	88.15 ± 11.15	129.86 ± 19.43
Serum creatinine mg/dl	0.7 ± 0.18	0.9 ± 0.17
UAE mg/d	10.05 ± 6.18	273.36 ± 298.52
hs-CRP mg/L	1.08 ± 0.32	4.59 ± 2.47
IL – 6 pg/ml	18.1 ± 10.97	323.08 ± 228.46

Values are expressed as mean ± standard deviation , DM, diabetes mellitus, BMI, body mass index, BP, blood pressure, FPG, fasting plasma glucose UAE , urinary albumin excretion hs – CRP high sensitivity C- reactive protein and IL – 6 interleukin - 6.

Table 8: Characteristics of diabetic patients.

Characteristics	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Number of patients	20	20	20
Age (years)	56.1 ± 5.15	55.8 ± 5.15	55.9 ± 4.68
Duration of DM (years)	6.7 ± 2.00	6.08 ± 2.52	7.55 ± 2.74
BMI (kg/m^2)	23.32 ± 2.22	23.32 ± 2.69	23.17 ± 2.59
Systolic BP mmHg	123.6 ± 8.47	123.4 ± 8.73	122.5 ± 10.6
Diabetic BP mmHg	79.0 ± 5.25	79.5 ± 4.93	78.0 ± 5.42
FPG mg/dl	132.4 ± 19.8	127.7 ± 22.02	129.5 ± 16.83
Serum creatinine mg/dl	0.85 ± 0.16	0.91 ± 0.18	0.92 ± 0.16
UAE mg/d	16.35 ± 6.92	160.6 ± 62.32	643.15 ± 214.32.17
hs-CRP mg/L	2.31 ± 0.49	5.16 ± 1..84	6.31 ± 2..54
IL – 6 pg/ml	126.41 ± 34.38	2.68.39 ± 125.88	574.44 ± 86.22

Values are expressed as mean ± standard deviation , DM, diabetes mellitus, BMI, body mass index, BP, blood pressure, FPG, fasting plasma glucose UAE , urinary albumin excretion, hs – CRP high sensitivity C- reactive protein and IL – 6 interleukin - 6.

DISCUSSION

Type 2 diabetes is frequently associated with an acute phase reaction, suggestive of a low grade inflammatory status. In fact, markers of acute phase response, including serum amyloid A (SAA), C-reactive protein (CRP) and Interleukin-6 (IL-6), the main mediators of the response, have been shown to be elevated in patients with type 2 diabetes and with the metabolic syndrome. It is well known that in the general population, as well as in diabetics, these acute-phase markers are associated with increased cardiovascular risk, because chronic inflammation is one of the pathogenetic mechanisms of atherosclerosis. In contrast, the relationship between low grade inflammation and diabetic microangiopathy are still unclear. As far as nephropathy is concerned, several studies have examined the relationship with inflammation, leading to conflicting results. However most studies have reported an increase in acute-phase markers in patients with nephropathy and also in patients with microalbumiuria.

The aim of the present study was to explore the relationship between low grade inflammation and renal microangiopathy in patients with Type 2 DM. We test the hypothesis that inflammatory parameters are independently associated with UAE in patients with type 2 DM with early stages of renal involvement (proteinuria < 3 G/d and normal renal function).

The present study was conducted on diabetic patients at Sri Ramachandra Medical College and Research Institute, Chennai. Age and gender matched controls were taken. Diabetic patients were grouped as normoalbuminurics, microalbuminurics and macroalbuminurics based on 24-hour urinary albumin excretion.

20 patients were included in each group, comprising of 10 males and 10 females. Age and gender matching was done to remove any bias arising out of differences between the

demographic profiles of the subjects. Both controls and diabetic subjects had a similar BMI, thus excluding differences in further analysis of nephropathy and inflammation arising due to dissimilar physical profiles of the subjects.

Correlation between Proteinuria and Inflammation

Highly sensitive – CRP has become an exquisite marker of chronic subclinical inflammation. In normal population, value of hs – CRP is <3mg / L. In the present study, hs – CRP levels in controls was 1.08 ± 0.32 mg/L. hs- CRP levels in normoalbuminurics, microalbuminurics and macroalbuminurics were 2.31± 0.49, 5.16± 1.84 and 6.31± 2.54 mg/L respectively showing significant rise with urinary albumin excretion. In patients with microalbuminuria and macroalbuminuria, hs – CRP levels were significantly higher than in normoalbuminuric patients with diabetes.

These findings are in agreement with some previous studies. Data by the Insulin Resistant Atherosclerosis Study[1] showed a significant and independent association of CRP level with UAE in the microalbuminuric range in patients with types 2 diabetes. 1481 subjects were studied and levels of CRP and fibrinogen compared with UAE. Both were related to urinary albumin to creatinine ratio (r=.17 for CRP and 14 for fibrinogen, both P=.0001). The study proposed chronic inflammation as a possible mediator between microalbuminuria and macrovascular disease and raised question regarding the beneficial effect of anti-inflammatory treatment on urinary albumin excretion and macrovascular disease.

Nikhil choudary et al[2] in a study including 60 patients with type 2DM found that increased UAE and chronic inflammation were interrelated processes. Hs – CRP levels were 1.31 ± 0.42, 2.73 ± 0.695, 5.06 ± 2.18 and 5.9 ± 2.16 mg/ L in controls, normalbuminuric, microalbuminuric and macroalbuminuric patients respectively.

Stehouwer et al[3] in prospective study including 328 patients with type 2 diabetes followed up for 9 years, found that increased UAE, endothelial dysfunction and chronic inflammation were interrelated processes and the longitudinal development of UAE was significantly and independently determined by such inflammatory markers as hs- CRP and fibrinogen. They proposed that both endothelial dysfunction and inflammation are involved in the pathogenesis of albuminuria but this phenomenon cannot explain the latter's association with risk of death.

Jager et al[4] investigated the role of low grade inflammation in the development of elevated UAE rates. These investigators performed a prospective study in a population based cohort. After a mean follow up period of 6.1 years, 316 subjects were reexamined. They found that the development of an elevated UAE rate was significantly associated with elevated hs – CRP level, with no differences after adjustment for hypertension, BMI or creatinine clearance.

Navarro JF et al[5] studied 65 patients with diabetes having microalbuminuria or mild proteinuria and 22 non – diabetic subjects. They concluded that albuminuria was related to CRP and TNF – alpha and hypothesized on the participation of inflammation in diabetic nephropathy.

Gomes et al[6] in a study on acute phase reactants and microalbuminuria among patients with type 2 diabetes concluded that acute phase reactants were associated with microalbuminuria independently of clinical cardiovascular risk. They analysed 64 non – smoking patients with type 2 diabetes and found a correlation coefficient of 0.41 between UAE and CRP.

The association between low grade inflammatory markers and diabetic nephropathy

has also been confirmed in the type 1 diabetic population in a study by Saraheimo et al.[7]

Conversely, Otto et al[8] did not find an association between UAE and hs – CRP & IL 6 levels in patients with type 2 diabetes, although they observed a significant association between UAE and fibrinogen level, another marker of inflammation. Furthermore, the main objective was not to analyze the relationship between inflammation and UAE, but to elucidate the mechanism of elevated fibrinogen levels observed in patients with diabetes. However, the number of patients included in the study was too small (n = 32), to give conclusive results.

A similar non association in the values of the new coronary risk factors and diabetic nephropathy is reported by Yeo et al,[9] they analysed 108 diabetic patients and did not find any correlation between levels of CRP or fibrinogen and UAE. However they cited the limited number of patients and laboratory limitations in the method of CRP estimation as lacunae in their study.

Finally Tan et al[10] investigated the effect of losartan (50 mg/day) on endothelial dysfunction in patients with type 2 diabetes with microalbuminuria, and second, they analyzed the evolution of plasma hs–CRP levels. At baseline, patients with diabetes had significantly greater plasma hs-CRP levels than non – diabetic control subjects. Treatment of patients with diabetes with losartan reduced microalbuminuria but no difference was found in plasma hs – CRP levels between losartan and placebo treated groups. Therefore, investigators concluded that decreasing UAE by means of an angiotension receptor antagonist is not associated with a significant anti- inflammatory effect.

However, there are 2 important points to be considered. First, data by Tan et al[10] do not discard the fact that modulation of inflammation may be a factor contributing to reduction in UAE. Second, an important limitation in the study by Tan et al may be the dosage of losartan (50 mg/day). A study by Anderson et al[11] evaluated the losartan dose for renoprotection in diabetic nephropathy and concluded that the optimal dose is 100 mg/ day.

IL – 6 levels when measured by EASIA were 18.1± 10.97 126.41 ± 34.38, 268.39± 125.88 and 574.44 ± 186.22 pg/ml in controls, normalbuminuric, microalbuminuric and macroalbuminuric patients respectively. Normal values of IL- 6 are generally <50pg/ml. In the present study, we found that plasma concentrations of the proinflammatory cytokine IL-6 were significantly higher in patients with overt albuminuria than in those with normalbuminuria or microalbuminuria. Several studies confirm that patients with renal insufficiency or uremia manifest evidence of chronic inflammation. Considerable IL-6 is synthesized by adipose tissues which necessitates caution in attributing differences in IL-6 to differing severity of diabetic nephropathy in the present study. Since BMI did not differ between subgroups defined by such severity, our study supported a relationship between diabetic nephropathy and low grade inflammation in patients with type 2 diabetes.

In addition to promoting inflammation, IL – 6 acts as the principal procoagulant cytokine by stimulating fibrinogen production in the liver. In a previous study, it has been demonstrated that increased plasma IL – 6 was associated not only with significantly increased plasma fibrinogen but also with increased plasma D dimer, a marker of cross – linked fibrin turnover, in patients with poorly controlled type 2 diabetes. Thus, elevated plasma IL – 6 may foster a procoagulant as well as a proinflammatory state in patients with type 2 diabetes.[12]

Association of IL-6 levels and urinary albumin excretion has also been reported in a study by

Moriwaki et al.[13] They compared levels of interleukin (IL)-18, tumor necrosis factor – alpha (TNF-α), and IL-6 in serum and studied 151 type 2 diabetes mellitus patients with various degrees of nephropathy, as well as 80 healthy volunteers. Although the level of IL – 6 did not differ between cases and controls, IL – 6 showed a linear correlation with urinary albumin excretion.

CONCLUSIONS

To conclude, our findings suggest there may be an additional potential aspect related to the development of renal damage in diabetes apart from traditional metabolic and hemodynamic factors. The significant association between inflammatory parameters and UAE indicates that inflammation may be a pathogenetic mechanism of diabetic nephropathy. It is possible to hypothesize on the participation of locally released cytokines such as IL – 6 in the development of renal damage in type 2 DM. Further analysis are necessary to confirm the intrarenal production and implication of inflammation in the pathogenesis of diabetic nephropathy. Prevention of obesity, use of antioxidant and other anti-inflammatory treatments may be beneficial in addressing the early progressive inflammatory response associated with diabetes and microvascular disease and mandate further studies in the area.

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