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Original Article

ASSESSMENT OF SERUM IL-6 LEVELS IN PATIENTS WITH DIABETIC NEPHROPATHY AND ITS CORRELATION WITH STAGE OF CHRONIC KIDNEY DISEASE

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ABSTRACT

Diabetic nephropathy is a state of inflammation where there is imbalance between proinflammatory and anti inflammatory cytokines. With uncontrolled elevation of proinflammatory cytokines , the inflammation would lead to renal fibrosis, of which few cytokines like IL-6,TNF@ were well studied (1-3) . Other inflammatory markers such as sialic acid and CRP-6 were also studied (4,5).IL-6 is a proinflammatory cytokine, thought to have major role in progression of various inflammatory diseases. It is well known that IL-6 levels are associated with progression of diabetic nephropathy. Chronic kidney disease being an inflammatory state is associated with high levels of serum IL-6.Though there are various biomarkers available to identify the progression of diabetic nephropathy, serum IL-6 as a biomarker for Diabetic nephropathy –CKD was not well studied. As both diabetes and CKD are inflammatory stages, it is understood that progressive elevation of serum IL-6 may be associated with progression of DN-CKD Hence we undertook this study to assess the serum levels of IL-6 in fifty sequential patients of different stages of CKD due to diabetic nephropathy.
AIM : To assess the serum levels of IL-6 in patients of Chronic kidney disease due to diabetic nephropathy.

Patients and Methods :

This observation study was done at our hospital, a tertiary care referral centre over a period of 6 months. Fifty sequential patients of diabetic nephropathy admitted to our hospital were included in the study. Diabetic nephropathy was diagnosed based on presence of proteinuria of more than 300 mg/day, diabetic retinopathy with or without renal insufficiency.

Inclusion criteria ;

Those patients with Chronic kidney disease due to diabetes

Exclusion criteria

Those patients of type 2 Diabetes presenting with acute kidney injury, Pregnancy, Rheumatoid arthritis, Carcinoma

Those who have given consent to participate in the study were assessed further. Demographic data, lab parameters were noted. Blood samples were collected in plain bottle for clotting and centrifugation was done for 15min at 1000 Gy.Serum was removed immediately and stored at -20C. Serum IL- 6 levels were assessed using Sandwich ELISA.

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Results:

Of 50 patients studied, mean age of the group was 50.2+9.8 years. Half (50%) of the study group was between 51-60 years of age. 18 patients were in 5th decade , 4 patients were aged between 61-70 years and 3 patients were more than 70 years of age.

Those patients with CKD stage V were 18 (36%) ,with CKD stage IV were 19 (38%).Number of patients in stage IIIa were 4 (8%),IIIb were 2 (4%) and in stage II CKD were 7(14%).Number of patients with retinopathy were 27 (54%) and those without retinopathy were 23(46%).

Table 1 : Baseline characteristics of the study group

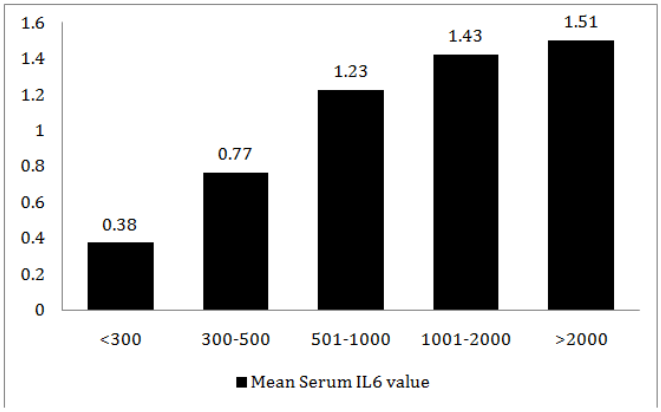
Characteristic		No (%)
Mearage (years)		50.2+9.8
	41-50	18 (36%)
	51-60	25(50%)
	61-70	4 (8%)
	>70	3 (6%)
Men : womer		35:15
CKD stage	II	7 (14%)
	IIIa	4(8%)
	IIIb	2(4%)
	IV	19(38%)
	V	18(36%)
Microalbuminuria		6 (12%)
Macroalbuminuria		44 (88%)
Mean duration of DM		7.68+4.32
Mean duration of HTN		3.42 +1.5
Means.creatinine		3.78+2.46
Retinopathy		28(56%)
Mean proteinuria		946+745
Mean serum IL-6		1.07+0.87

On comparison of patients with microalbuminuria and macroalbuminuria, mean levels of IL- 6 were high in those with macroalbuminuria (Table 2). Further it was served that (Fig 1) with increasing degree of proteinuria, the serum levels of IL-6 increased.

Table 2 : Serum IL-6 levels between microalbuminuria and macroalbuminuria

		MA	Macroalbuminuria	
Demographic Data				
	No. of Patients	6	44	
	Mean Age	53.3± 6.5	54.1±7.6	
	Males	3	32	
	Females	3	12	
				P Value
	Duration of DM	5.1±0.75	8.0±4.4	0.33
	Duration of HTN	1.33±0.5	3.7±3.6	0.12
	Retinopathy	33%	61%	**0.02**
	Mean IL6 Level	0.38	1.17	**0.03**

Fig 1 : Correlation of serum IL-6 with increasing degree of proteinuria

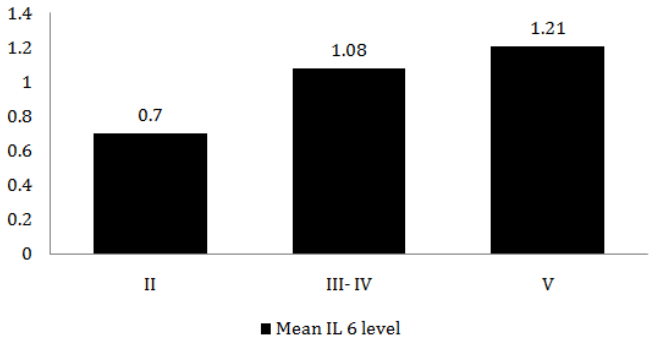


Baseline characteristics of all the stages of CKD were compared (Table 3).Serum IL-6 levels was analysed with stage of kidney disease. It was observed that with increasing stage of CKD, a variable increase in IL-6 levels was observed.(Table 3) (Fig2).

Table 3 : Baseline characteristics and IL-6 levels between CKD II-III/IV/V stages

Variable	II/III	IV	V	p
MeanAge	54.57	54.94	52.31	0.56
Duration of DM	7.07_4.1	7.05+4.31	8.77+4.2	0.39
Duration of HTN	2.7+3.3	3.8+4.5	3.3+2.3	0.68
Proteinuria	653+532	1237+879	851+700	0.08
IL-6	0.78+0.58	1.15+0.88	1.21+1.02	0.36

Fig 2 : Serum IL-6 with stage of CKD



In our study, factors correlating with IL-6 were assessed. Serum creatinine and degree of proteinuria showed a weak positive correlation though none of the factors had strong correlation with IL-6 levels.

Variable	r
Age	0.125
Duration of DM	0.013
Duration of HTN	0.095
S.creatinine	0.216
Proteinuria	0.297

DISCUSSION

Inflammatory cytokines play a significant role in diabetic nephropathy.Role of pro inflammatory cytokines and anti inflammatory cytokines causing damage to kidney has been assessed in few studies.Of the markers well studied, TNF-@,IL-6 and IL-18 were few of them.Serum IL-6 levels were found to be higher in those with diabetic nephropathy compared to those without nephropathy (6,7).Few studies detected presence of IL-6 mRNA coding in cells infiltartinng mesangium ,interstitium and tubules.IL-6 was also correlated with thickening of basement membrane and thus the progression of diabetic nephropathy (8,9). A direct correlation of urinary albumin excretion and serum IL-6 was demonstrated in few studies (10). Certain genetic studies have also shown an association between IL-6 and diabetic nephropathy (11).

In our study, relation between IL-6 and different stage of CKD due to DN was assessed. Fifty sequential patients of DN were included in the study , of which six patients had microalbuminuria and remaining 44 patients had macroalbuminuria.

This was cross sectional observational study of assessment of IL-6 levels with progression in CKD and also with proteinuria

Several studies tried to assess the relation between urine albumin excretion and the inflammatory markers. But a definitive understanding is yet to be achieved.

In our study, majority of the patients were in sixth decade. Mean degree of proteinuria in this group was 943 +763 mg.Based on GFR by MDRD , patients were categorized into different stages of CKD. Majority of the patients were in CKD –V and CKD-IV. The base characteristics of three groups of CKD patients were compared.

Patients with microalbuminuria and macroalbuminuria were compared. Serum IL-6 levels were high in those with macroalbuminuria compared to microalbuminuria. This observation is in concordance with that of previous studies.In a study by Chowdhary and Ahlawat etal, it was observed that serum IL-6 levels were higher in those with macroproteinuria.

In our study group, we found that there is positive association with increasing proteinuria. The serum levels of IL-6 were high in those with macro proteinuria.

Serum IL-6 levels were assessed with different stages of CKD.Though the baseline characteristics did not differ much between the three groups, IL-6 showed a variable increase amongst the groups. In patients with CKD-IV levels were slightly higher than in those with CKD-V ($p<0.05$).It was observed that in those with retinopathy serum IL-6 levels were high ($p=0.03$).

None of the factors studied showed a positive correlation with IL-6 levels though a weak positive trend was observed with proteinuria and creatinine.

In conclusion, our study showed an increase in serum IL-6 levels with progressing proteinuria. A high level of serum IL-6 was observed in those with retinopathy compared to those without retinopathy.

Serum IL-6 may be used as a biomarker for progressing proteinuria rather than the progressing kidney disease. This needs further evaluation in large population studies.

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