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Diabetic Nephropathy and its Relation with Inflammatory Markers – IL6 and C - reactive protein: A Cross Sectional Study.

Swati Soni[1], Radhika Mathur[1], Shivam Shukla[2]

[1]Final Year MBBS Student, Teerthankar Mahaveer Medical College, TMU, Moradabad.

[2]Assistant Professor, Department of Medicine, Teerthankar Mahaveer Medical College, TMU, Moradabad.

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ABSTRACT

Background: Diabetic nephropathy is one of the commonest causes of chronic kidney failure throughout the world. Interleukin 6 (IL 6) acts as a pro-inflammatory as well as anti-inflammatory cytokines. C-reactive proteins (CRP) and IL 6 are considered as important markers of inflammation. Type 2 DM has been associated with risk of developing low grade inflammation. Therefore the present study was designed to investigate if there is any relation of inflammatory markers in the development and progression of albuminuia in diabetic nephropathy patients. **Methods:** This was a cress sectional type of study carried out in medicine department of TMMC & RC, Moradabad. A total of one hundred fifty (150) patients suffering with diabetes mellitus were selected for the study. All the DM patients were divided into three groups of 50 patients as per normal albuminuria (urinary albumin excretion (UAE) = <30 mg/d), microalbuminuria (UAE 30 mg/d to 300 mg/d), and macroalbuminuria (persistent UAE >300 mg/d). **Result:** HS-CRP was significantly high in microalbuminuria compare to normoalbumiuria. Whereas, HS-CRP was significantly high in macroalbuminuria compare to microalbumiuria diabetic nephropathy patients. IL 6 was significantly high in microalbuminuria diabetic nephropathy patients compare to normoalbumiuria. Whereas, IL 6 was significantly high in macroalbuminuria diabetic nephropathy patients compare to microalbumiuria diabetic nephropathy patients. **Conclusion:** Findings of the present study suggest that higher level of inflammatory markers like CRP and IL 6 may be an additional factor in the pathogenesis of development of diabetic nephropathy along with traditional metabolic factors. However, a hypothetical role of inflammatory markers CRP and IL 6 in the damage of kidney cannot be denied in type 2 DM. Nevertheless, more studies on larger population are required to establish an exact relation between inflammatory markers and renal damage in DM patients.

Keywords: Diabetic nephropathy, renal disease, IL 6, HS-CRP.

INTRODUCTION

Diabetic nephropathy is one of the commonest causes of chronic kidney failure throughout the world.[1] It is one of the commonest complications of diabetes mellitus (DM); which silently follow the DM patients for years and induce the morbidity and mortality in DM patients.[2] Various hemodynamic and metabolic factors may be involved in the developments of renal disorders among DM patients.[3] Increased blood sugar level is considered as a well-recognized causal factor for the onset of diabetic microvascular anomalieslike nephropathy.[4-6]

Interleukin 6 (IL 6) acts as a pro-inflammatory as well as anti-inflammatory cytokines.[7] C-reactive proteins (CRP) and IL 6 are considered as important markers of inflammation. Inflammatory and immune response of the body is induced by a group of non enzymatic protein cytokines.[8]

Type 2 DM has been associated with risk of developing low grade inflammation. 2 Various inflammatory markers like CRP, IL 6, IL 3, fibrinogen etc have been found associated with type 2 DM and diabetic nephropathy.[7–10] Inflammation plays an important role in onset as well as progression of renal disorder in DM patients.[11] Therefore the present study was designed to investigate if there is any relation of inflammatory markers in the development and progression of albuminuia in diabetic nephropathy patients.

Name & Address of Corresponding Author
Dr. Shivam Shukla
Assistant Professor, Department of Medicine,
Teerthankar Mahaveer Medical College,
TMU,
Moradabad.

MATERIALS AND METHODS

This was a cress sectional type of study carried out in medicine department of TMMC & RC, Moradabad. A total of one hundred fifty (150) patients suffering with diabetes mellitus were selected for the study. All the DM patients were divided into three groups of 50 patients as per

normal albuminuria (urinary albumin excretion (UAE) = <30 mg/d), microalbuminuria (UAE 30 mg/d to 300 mg/d), and macroalbuminuria (persistent UAE >300 mg/d). Fifty (50) healthy subjects of same age and sex matched were included in the study as a control group.

DM patients suffering from any type of chronic disease, smokers and alcoholic were excluded from the study. DM patients having history of acute illness in last one month were excluded from the study. The study was started from March 2017 and the study was completed in March 2018. The study was approved from ethical committee of TMMC & RC, Moradabad. Informed written consent was taken from each every participant before the study started. All the blood sample were collected early in the between 8am to 10am after overnight fasting. Fasting blood glucose level was measured by an automated enzymatic method. The glycosylated hemoglobin (HbA1c) concentration was estimated by ion exchange chromatography. All the participants were asked to give 24 hours urine collection for analysis UAE. Colorimetric method was used for estimation of albuminuria. Inflammatory markers high-sensitivity CRP (HS-CRP) and IL6 were measured enzyme linked immunosorbent assay and the Kits of Ray Biotech® Inc. and Diaclone, Stamford, USA were used respectively.

Statistical analysis

The results of the present study were expressed as mean ± SD. One way ANOVA was used to evaluate the results within the groups. Unpaired student t test was used for intergroup comparison. A p-value < 0.05 was considered statistically significant. IBM SPSS Statistics 21 manufactured by IBM USA was used for entire calculations.

RESULTS

[Table 1] shows that there was an insignificant difference between diabetic nephropathy patients regarding age, BMI, WHR. But FBG (p<0.01), serum creatinine (p<0.01), urinary albumin excretion (UAE) (p<0.01), HS-CRP (p<0.01) and IL 6 (p<0.01) were significantly high in DM group compare to control group.

Table 1: Comparison of basic characteristics in control and DM group.

	Control (n=50)	DM group (n=150)
Age	54.36 ± 7.52	54.26 ± 8.11
Duration of DM (Years)	----	12.26 ± 4.16
WHR	0.87 ± 0.17	0.84 ± 0.13
BMI (Kg/m2)	22.87 ± 3.38	22.74 ± 3.21
FBG (mg/dl)	87 ± 15	166 ± 33
Serum creatinine mg/dl()	0.89 ± 0.15	0.96 ± 0.13
UAE (mg/d)	4.3 ± 0.89	149 ± 18.28
HS-CRP (mg/L)	1.34 ± 0.14	2.46 ± 0.28
IL-6 (pg/ml)	0.95 ± 0.09	1.83 ± 0.08

It is evident from [Table 2] that there was no significant difference between age, BMI, WHR and duration of DM in all sub groups of diabetic nephropathy patients. Further, there was a significant difference between FBG, serum creatinine and UAE level of all three subgroups of diabetic nephropathy patients.

Table 2: Comparison of Characteristics in DM patients groups in relation to albuminuria status.

Characteristics	Normoalbuminuria (n=50)	Microalbuminuria (n=50)	Macroalbuminuria (n=50)
Age	54.16 ± 8.18	54.46 ± 7.81	54.22 ± 8.26
Duration of DM (Years)	11.86 ± 3.92	12.18 ± 4.28	12.38 ± 4.12
WHR	0.85 ± 0.16	0.84 ± 0.11	0.83 ± 0.14
BMI (Kg/m2)	22.92 ± 3.72	22.84 ± 3.32	22.54 ± 3.18
FBG (mg/dl)	124.4 ± 28.65	148.26 ± 37.28	388.38 ± 41.58
Serum creatinine (mg/dl)	0.86 ± 0.08	1.09 ± 0.23	1.26 ± 0.19
UAE (mg/d)	26 ± 6.22	145 ± 16.62	152 ± 19.98

HS-CRP was significantly high in microalbuminuria diabetic nephropathy patients compare to normoalbumiuria diabetic nephropathy patients. Whereas, HS-CRP was significantly high in macroalbuminuria diabetic nephropathy patients compare to microalbumiuria diabetic nephropathy patients. [Figure 1]

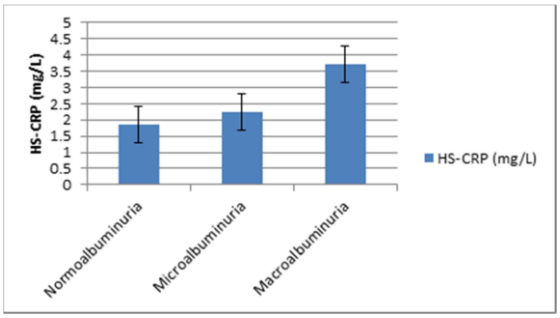

Figure 1: Comparison of HS-CRP in sub groups of diabetic nephropathy patients.

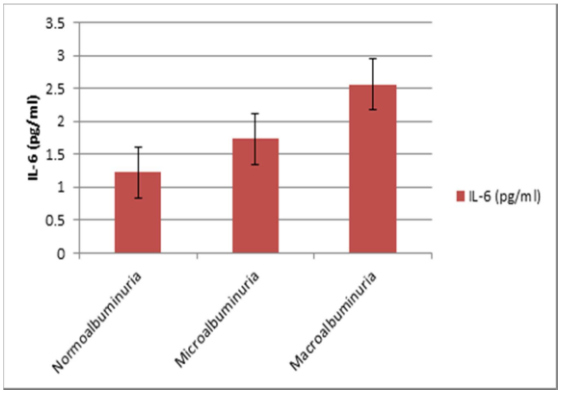

Figure 2: Comparison of IL 6 in sub groups of diabetic nephropathy patients.

It is evident from [Figure 2] that IL 6 was significantly high in microalbuminuria diabetic nephropathy patients compare to normoalbumiuria diabetic nephropathy patients. Whereas, IL 6 was significantly high in macroalbuminuria diabetic nephropathy patients compare to microalbumiuria diabetic nephropathy patients. [Figure 2]

[Figure 3] shows there was a positive correlation between CRP and UAE diabetic nephropathy patients. The p value was significant (<0.01) and r2 = 0.4.

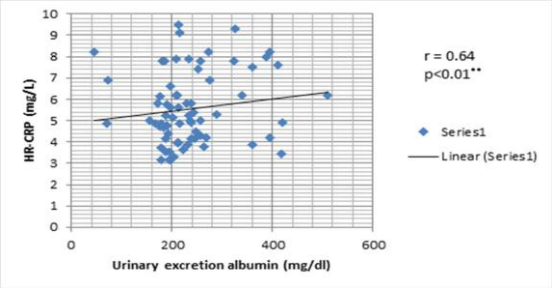

Figure 3: Correlation between HR-CRP and UAE.

It is evident from figure 4 that there was a positive correlation between IL 6 and UAE in type diabetes mellitus patients suffering with nephropathy. The p value was <0.01 and r2 = 0.51.

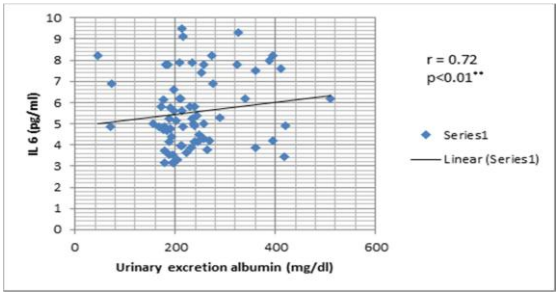

Figure 4: Correlation between IL 6 and UAE.

DISCUSSION

Various recent studies have suggested that DM leads to diverse types of inflammatory conditions like retinopathy, nephropathy etc. Moreover, urinary albumin excretion have been reported to have a relation with inflammation in DM patients.[7-11]

Findings of the current study have shown that serum level of inflammatory marker HS-CRP and IL 6 were significantly high in DM patients in compare of control subjects. Moreover, HS-CRP and IL 6 were significantly higher in microalbuminuria DM patients compare to normoalbuminuria DM patients. Further, HS-CRP and IL 6 were significantly higher in macroalbuminuria DM patients compare to microalbuminuria DM patients.

IL 6 belongs to cytokinase family including other inflammatory factors like leukemia inhibitor factor, cardiotrophin -1, oncostatin M, IL 11 etc. Previous study has demonstrated that IL 6 mRNA resides in glomerular cell of DM patients suffering with diabetic nephropathy.[12] These findings are consistent with the previous study of Moriwaki et al,[13] as they recorded a significantly high level of IL 6 in 151 DM patients compare to 80 healthy adults subjects.

This increase of IL 6 diabetic nephropathy may be due to increased infiltration of macrophages from glomeruli or interstitium of renal tissue of DM patients suffering from nephropathy. This higher infilatration rate of macrophages in the kidney may be accountable for the increased level of IL 6 in diabetic nephropathy patients.

Different studies recorded evidences of chronic inflammation in patients suffering from chronic renal failure, diabetic nephropathy etc.[14,15] Obesity may also leads to increase level of IL 6 as adipose tissue has been found associated with synthesis of considerable amount of IL 6.[16]

Findings of the current study do not show any significant difference between BMI of DM group and control group. However, BMI of diabetic patients was little bit lower in this study compare to control; although this difference is statically in significant. Hence it seems that increase level of IL 6 might be due to diabetic nephropathy instead of obesity.

There are few other possibilities which may explain the increase of IL 6 and HS – CRP in diabetic nephropathy patients compare to control subjects. Increase level of protein loss via proteinuria in diabetic nephropathy patients has been found.[14] Further, this higher level of inflammatory markers may be due to pre-existing inflammatory disorders like atherosclerosis present in the nephropathy patients.[15] Moreover, albumiuria may be induced by higher level of IL6 as it alters the functions of glomerular cells.[16]

Microalbuminuria can be a predictive marker for the development of diabetic nephropathy in the unrestrained diabetic patient. Nevertheless, progression of the DM and blood pressure have been found associated with increased albuminuria (UAE> 300 mg/day); which in turn leads to decrease of glomerular filtration rate.[17-19]

Various disorders have been found associated with UAE like inflammatory disorders, trauma, surgery etc. Furthermore, a strong relation of glomerular functions and IL 6 has been suggested.[12] Experimental data suggest that IL 6 causes increase infiltration of macrophages; moreover, it interferes with metabolism of glycosaminoglycans an important component of glomerular basement as well as vascular endothelium. 7 This may leads to various types of micro and macro vascular diseases.[9]

CONCLUSION

Findings of the present study suggest that higher level of inflammatory markers like CRP and IL 6 may be an additional factor in the pathogenesis of

development of diabetic nephropathy along with traditional metabolic factors. However, a hypothetical role of inflammatory markers CRP and IL 6 in the damage of kidney cannot be denied in type 2 DM. Nevertheless, more studies on larger population are required to establish an exact relation between inflammatory markers and renal damage in DM patients.

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