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A Study of Correlation Between Levels of Acute Phase Reactants (Serum CRP, Serum Fibrinogen) and Severity of Albuminuria in Patients with Type II Diabetes Mellitus

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Abstract

Background: In this study, we wanted to evaluate the correlation between levels of acute phase reactants (serum CRP, serum fibrinogen) and severity of albuminuria in patients with type 2 diabetes mellitus. **Material and Methods:** This was a hospital based observational study conducted among 100 patients who presented with type 2 diabetes mellitus to the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, over a period of 6 months after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants. **Results:** HbA1c correlates with excretion of albumin with a p value of 0.001. Higher albumin excretion rates are associated with higher levels of Sr. Fibrinogen (p value = 0.001) Albuminuria grade correlates with serum creatinine values (p value = 0.001). Micro albuminuria and macro albuminuria are associated with higher levels of CRP when compared to the normoalbuminuric patients. Serum fibrinogen is elevated in overt and macro albuminuric groups than normoalbuminuric group. Micro and macro albuminuric groups are noted to have higher HbA1c levels than the normoalbuminuric group, implying that a tighter glycemic control can reduce the risk of nephropathy. **Conclusion:** Higher HbA1c and longer duration of diabetes can lead to more severe nephropathy. Thus, a poor glycemic control predicts greater degrees of nephropathy. Acute phase reactants namely serum CRP and serum fibrinogen are elevated in diabetic nephropathy, suggesting that it is an inflammatory state. Hence, serum CRP and fibrinogen may be used as predictors of nephropathy in diabetic patients.

Keywords: Correlation, Acute Phase Reactants, Albuminuria, Type 2 Diabetes Mellitus.

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Introduction

Diabetes is a major non communicable disease worldwide. Recent data indicate that around 390 million people across the globe have diabetes and this number is expected to rise up to 595 million over the next twenty years. In India there are about 65 million diabetics. Diabetes is associated with both micro vascular complications (retinopathy, neuropathy, nephropathy) as well as macro vascular complications like cerebro-vascular diseases, peripheral arterial

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diseases and cardiovascular diseases. The risk of chronic complications increases with the duration of diabetes. Several theories have been proposed for the pathogenesis of such chronic complications including –

- Advanced glycosylation end products
- Sorbitol pathway
- Protein Kinase C pathway
- Hexosamine pathway
- Oxidative stress

Recent studies have shown that the above mentioned advanced glycation end products elicit a chronic low grade inflammation which correlates with the degree of organ damage. Hence, our study is aimed at assessing the levels of two of the markers of inflammation (acute phase reactants) namely serum CRP and serum fibrinogen in patients with long standing type 2 diabetes and determining whether they correlate with the degree of albuminuria (an indicator of the degree of nephropathy).

Aims and Objectives

To study the correlation between levels of acute phase reactants (serum CRP, serum fibrinogen) and severity of albuminuria in patients admitted with type 2 diabetes mellitus. To assess the clinical and laboratory profile (BMI, WHR, BP, RFT, Fasting glucose) of diabetic patients with varying levels of albuminuria.

Methodology

This was a hospital based observational study conducted among 100 patients who presented with type 2 diabetes mellitus to the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, over a period of 6 months after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Inclusion Criteria

- Patients with type 2 diabetes mellitus (less than 10 years of duration) attending the OPD
- Age: Less than 50 years

Exclusion Criteria

- Patients with current or recent (< 1 week) infectious diseases (UTI, LRI, sepsis, AGE, viral fever etc)
- Patients with cancer
- Patients with uncontrolled hypertension (> 160/90)
- Smokers
- Known cases of immunological disorders
- Patients with clinical history of cardiovascular diseases
- Pregnancy
- Patients with known history of CVA, CAD
- Known cases of CKD

Statistical Methods

Data was entered in MS Excel and analysed using Statistical Package for Social Sciences (SPSS) software. Results were presented as tables.

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RESULTS

Table 1: ?

Crosstab				
Urine_ACR_Class		CRP_Class		Total
		Normal up to 10	Abnormal above 10	
< 30 Normal	count	22	8	30
	% within Urine_acr_class	73.3 %	26.7 %	100.0 %
30 - 300 Micro albuminuria	count	29	12	41
	% within Urine_acr_class	70.7 %	29.3 %	100.0 %
> 300 Macroalbuminuria	count	6	23	29
	% within Urine_acr_class	20.7 %	79.3 %	100.0 %
Total	count	57	43	100
	% within Urine_acr_class	57.0 %	43.0 %	100.0 %
Chi-square = 22.019* p < 0.001				
Urine_ACR_Class * Fibrinogen Cross Tabulation				
Urine_ACR_Class		Fibrinogen		Total
		Normal up to 350	Abnormal above 350	
< 30 Normal	count	29	1	30
	% within Urine_acr_class	96.7 %	3.3 %	100.0 %
30 - 300 Micro albuminuria	count	39	2	41
	% within Urine_acr_class	95.1 %	4.9 %	100.0 %
> 300 Macro albuminuria	count	7	22	29
	% within Urine_acr_class	24.1 %	75.9 %	100.0 %
Total	count	75	25	100
	% within Urine_acr_class	75.0 %	25.0 %	100.0 %

Micro albuminuria and macro albuminuria are associated with higher levels of CRP when compared to the normoalbuminuric patients.
Serum fibrinogen is elevated in overt and macro albuminuric groups than normoalbuminuric group.

Table 2: ?

Urine_ACR_Class		SERUM_CREATININE		Total
		NORMAL UP TO 1.2	ABNORMAL ABOVE 1.2	
Count < 30 Normal		28	2	30
% within urine_acr_class		93.3 %	6.7 %	100.0 %
30 - 300 micro count		29	12	41
ALBUMINURIA % within urine_acr_class		70.7 %	29.3 %	100.0 %
> 300 macro count		7	22	29
ALBUMINURIA % within urine_acr_class		24.1 %	75.9 %	100.0 %
Total	Count	64	36	100
	% within urine_acr_class	64.0 %	36.0 %	100.0 %
Chi-square = 32.010* p < 0.001				
Urine_ACR_Class		BLOOD_PRESSURE		Total

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		Upto 120/80	Above 120/80	
Count		13	17	30
< 30 Normal % within Urine_acr_class		43.3 %	56.7 %	100.0 %
Count 30 - 300 MICRO		22	19	41
% within ALBUMINURIA Urine_acr_class		53.7 %	46.3 %	100.0 %
Count > 300 MACRO		3	26	29
% within ALBUMINURIA Urine_acr_class		10.3 %	89.7 %	100.0 %
Total	Count	38	62	100
	% within Urine_acr_class	38.0 %	62.0 %	100.0 %

Table 3: ?

Urine_ACR_Class		Duration_dm			Total
		1 - 3 years	4 - 6 years	Above 7 years	
Count		24	5	1	30
< 30 Normal % within Urine_acr_class		80.0 %	16.7 %	3.3 %	100.0 %
Count 30 - 300 MICRO		34	7	0	41
% within ALBUMINURIA Urine_acr_class		82.9 %	17.1 %	0.0 %	100.0 %
Count > 300 MACRO		8	11	10	29
% within ALBUMINURIA Urine_acr_class		27.6 %	37.9 %	34.5 %	100.0 %
Total	Count	66	23	11	100
	% within Urine_acr_class	66.0 %	23.0 %	11.0 %	100.0 %
Chi-square = 33.766* p < 0.001					
Urine_acr_class		hba1c_class			Total
		< 6.5 Normal		> 6.5 Abnormal	
Count		25		5	30
< 30 Normal % within Urine_acr_class		83.3 %		16.7 %	100.0 %
Count 30 - 300 MICRO		30		11	41
% within ALBUMINURIA Urine_acr_class		73.2 %		26.8 %	100.0 %
Count > 300 MACRO		5		24	29
% within ALBUMINURIA Urine_acr_class		17.2 %		82.8 %	100.0 %
Total	Count	60		40	100
	% within Urine_acr_class	60.0 %		40.0 %	100.0 %
Chi-square=31.861* p < 0.001					

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Table 4: ?

	URINE ACR	N	Mean	Std. Deviation	Std. Error Mean	t value	P value
SYSTOLIC BP	>= 30.00 Abnormal	70	132.8857	22.41024	2.67854	1.709	0.092
	< 30.00 Normal	30	126.0000	16.49242	3.01109		
DIASTOLIC BP	>= 30.00 Abnormal	70	84.8857	12.32241	1.47281	3.321*	0.001
	< 30.00 Normal	30	78.0667	7.83420	1.43032		
BMI	>= 30.00 Abnormal	70	25.9457	4.52294	.54060	3.581*	0.001
	< 30.00 Normal	30	23.3567	2.62897	.47998		
FBS	>= 30.00 Abnormal	70	142.9429	39.52320	4.72393	1.946	0.06
	< 30.00 Normal	30	129.6667	26.95889	4.92200		
HBA1C	>= 30.00 Abnormal	70	7.0757	1.45138	.17347	4.248*	p<0.001
	< 30.00 Normal	30	6.2000	.61026	.11142		
CRP	>= 30.00 Abnormal	70	11.6429	6.89473	.82408	2.197*	0.031
	< 30.00 Normal	30	8.9333	5.02362	.91718		
FIBRINOGEN	>= 30.00 Abnormal	70	320.2714	111.97618	13.38371	4.42	p<0.001
	< 30.00 Normal	30	246.3667	54.90210	10.02371		
SR.CREATININE	>= 30.00 Abnormal	70	1.3571	.65199	.07793	5.125*	p<0.001
	< 30.00 Normal	30	.8500	.33399	.06098		

Higher levels of albumin excretion correspond to higher levels of serum creatinine. Thus, albumin excretion in the urine is a good indicator of the glomerular filtration.

Higher blood pressures in diabetics are associated with greater albuminuria. Thus, hypertension is an important contributor to the diabetic nephropathy. A direct comparison by means of Chi square indicated that diastolic BP correlates well with albuminuria, but systolic BP does not correlate to it.[Table 2]

The study included only people below 50 years of age, since age itself is a confounding factor for the two variables – CRP and fibrinogen. Despite this limitation, the study shows that greater duration of diabetes is associated with greater degrees of albuminuria.

The micro and macro albuminuric groups are noted to have higher HbA1c levels than the normoalbuminuric group, implying that a tighter glycemic control can reduce the risk of nephropathy. [Table 3]

Comparison of multiple parameters between normoalbuminuric group and micro/overt albuminuric group. The systolic BP did not correlate with degree of albuminuria (p value = 0.092), but the diastolic BP shows a good correlation with severity of albuminuria (p value = 0.001). A higher BMI was noted to be associated with a higher degree of albuminuria (p value = 0.001). Fasting blood sugar did not show a correlation with albuminuria (p value = 0.06). HbA1c correlates with excretion of albumin as shown by the p value of 0.001. Higher albumin excretion rates are associated with higher levels of CRP (p value = 0.031). Higher albumin excretion rates are associated with higher levels of Sr. Fibrinogen (p value = 0.001). Albuminuria grade correlates with serum creatinine values (p value = 0.001). [Table 4]

DISCUSSION

The study included 100 diabetic patients without other known co-morbids and aged less than 50 years. These patients were subjected to several laboratory investigations namely HbA1c, fasting blood sugar, serum creatinine, serum fibrinogen, serum CRP, urine albumin creatinine ratio and physical findings like BMI, blood pressure were recorded.[1] Several previous investigators have proposed that diabetes is in itself an inflammatory state and that the grade of diabetic nephropathy corresponds to the severity of the inflammation. Joydeep Gosh, Mrinal Pal et al. showed that serum sialic acid, an inflammatory marker is elevated in

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diabetics, especially so in diabetic nephropathy cases. The extent of elevation corresponds to the degree of proteinuria. This suggests that diabetes and diabetic nephropathy are inflammatory states.[2] Sumesh Raj, G.V.Rajan et al. showed a similar relationship between the degree of albuminuria and levels of serum ferritin. Similar studies were conducted with other major acute phase reactants. Vishakha V, Mahajan et al. conducted a study in three major acute phase reactants - serum CRP, serum ceruloplasmin and serum sialic acid. They demonstrated a positive correlation between the levels of these acute phase reactants and the complications of diabetes especially diabetic nephropathy. Tan K.C. et al. showed that in diabetes, there is production of advanced end glycation products by non-enzymatic reaction which is responsible for a pro-inflammatory state. The inflammation may have a role in the development of the proteinuria. Michele Dalla Vestra et al. showed a significant correlation between the elevated levels of serum fibrinogen, serum CRP, IL 6, SAA and grade of proteinuria. This study revealed that the elevated fibrinogen causes glomerular matrix thickening via inflammatory pathways. This GBM thickening leads to protenuria. This study concluded that low grade inflammation is causes nephropathy by causing basement membrane alterations.[3] The Casale Monferrato study showed that fibrinogen is a single independent marker to assess the progression diabetic nephropathy.[4] Chaudhary et al. study explained the 3 major mechanisms of progression of albuminuria and its correlation with acute phase reactant. They proposed that elevated levels of acute phase reactants directly injure the glomeruli and thereby alter their function.[5] In our study, there is a positive correlation between the levels of CRP- fibrinogen and the severity of albuminuria (measured by urine albumin excretion ratio). This suggests that diabetes itself is a chronic inflammatory state and this inflammatory damage may be responsible for some of the diabetic complications, especially diabetic nephropathy.[6-8] Other parameters were also correlated to the grade of albuminuria in the study. Results show that a higher diastolic BP correlates well with a higher degree of albuminuria, but systolic BP did not have a correlation with albuminuria. A study by Azeem Taj et al. came up with similar results. It showed that diabetics with a higher blood pressure were more likely to have nephropathy. Our study also showed that greater BMI levels are associated with higher urinary albumin excretion. Likewise, higher HbA1c levels and greater duration of diabetes were noted to correlate to higher grades of albuminuria. Similar results had been obtained by M.Afkhami et al. However, fasting sugar level did not have a significant association with albuminuria in our study.

CONCLUSION

Diabetics with higher blood pressure are more likely to develop nephropathy than the normotensive diabetic people. A higher body mass index is associated with higher grade of albuminuria. In other words, obese diabetic patients are more prone for developing nephropathy than others. Higher HbA1c and longer duration of diabetes can lead to more severe nephropathy. Thus a poor glycemic control predicts greater degrees of nephropathy. Acute phase reactants namely serum CRP and serum fibrinogen are elevated in diabetic nephropathy, suggesting that it is an inflammatory state. Hence, serum CRP and fibrinogen may be used as predictors of nephropathy in diabetic patients.

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