Original Article

Correlation of urinary adipokine retinol-binding protein-4 with renal function in Type 2 Diabetics

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Objective: To find the correlation between urinary Retinol-Binding Protein 4 (RBP-4) and renal function in Type 2 Diabetics.

Methodology: Study included 60 type 2 diabetics. 20 normal subjects were taken as control. Level of blood glucose, glycosylated hemoglobin, serum creatinine, and RBP-4 were estimated in both patients and control subjects.

Results: Mean age in patients and controls was in a range of 45 – 47 years with a mild increase in BMI. Levels of HbA1c and of RBP-4 were significantly high in patients compared to controls. Levels of serum creatinine were non-significantly increased in patients as compared to controls. A significant negative correlation of RBP-4 with serum creatinine was also observed. Positive correlation was observed between age and HbA1c with RBP-4.

Conclusion: Urinary RBP-4 may be an early marker of diabetic nephropathy in diabetic subjects and may be used as a tool for monitoring the disease.

Keywords: Retinol binding protein 4, serum creatinine, diabetic nephropathy.

INTRODUCTION

Diabetic nephropathy (DN) is one of the gravest microvascular complications of diabetes. It is due to poor glycemic control, duration of diabetes longer than 5 year, obesity and hypertension.[1] It is categorized by microalbuminuria and reduced renal function resulting in end-stage renal disease.[2] In some of the diabetic patients, there is no change in the level of albumin. It is therefore said that albuminuria is not an early marker of DN.[3]

The injuries to glomeruli and tubular part of kidney have a role in the pathogenesis of diabetic nephropathy. Known marker of kidney function or renal filtration is the level of serum creatinine as its level is increased with reduced function of kidney.[4] It is proposed that still there is a need of biomarkers for timely detection of impairment of renal function.[5]

Retinol-binding protein 4 (RBP4) is an adipokine belongs to the family of lipocalin produced in the liver and adipocytes.[6] Its exact role in the development of insulin resistance is not known. However, it is proposed that it has a role to increase the level of enzymes of gluconeogenesis in liver cells and alter the signaling pathway of insulin.[7] Some studies have demonstrated that upregulation of RBP4 is related with increased BMI and insulin resistant.[8,9] However, other researchers observed low level of RBP4 in diabetic patients and reported no relationship of RBP-4 with insulin resistance.[10,11] Some studies proposed that increased excretion of RBP4 indicate the initial stage of DN and may have a key role in developing DN.[12,13] Recently, studies have been carried out to find the highly specific, sensitive and predicting biomarkers which may help to know risk of developing kidney disease. A cross sectional study was, therefore, carried out to find the risk of DN in type 2 diabetic patients by measuring RBP-4 levels in urine, as early indicator of disease.

METHODOLOGY

After informed consent, 60 subjects with diabetes type 2 and 20 age and gender matched controls with no history of any disease were recruited from diabetic clinic of Sheikh Zayed Hospital, Lahore during June to Dec 2015. Patients suffering from Type II diabetes mellitus for less than 5 years and with age range 25 – 60 years were included in the study. Exclusion criteria were patients with diabetes for more than 5 years, acute/ chronic kidney, renal transplant and any other systemic disease or malignancy.

History of the subjects, and biochemical findings were recorded. Blood sample was drawn for estimation of HbA_1c, and serum creatinine.Urinary samples were collected randomly in aseptic containers. Urine was centrifuged to obtain clear supernatant for estimation of RBP-4.

Statistical Analysis: Spearman's correlation analysis

Table 1: Comparison of age, BMI and biochemical parameters of patients with controls.

Subjects	Mean Age (Years)	BMI (Kg/m^2)	HbA1c (%)	Serum Creatinine (mg/dl)	Retinol Binding Protein-4 (ng/ml)
Patients (60)	47.80 ± 7.70	26.50 ± 4.19	7.76 ± 1.50*	0.94 ± 0.23	82.90 ± 33.07**
Controls (20)	45.80 ± 4.31	24.84 ± 2.80	6.3 ± 0.34	0.85 ± 0.18	49.4535 ± 35.34

*P < 0.001 = significant **P<0.001 = highly significant

was performed to test the association between urinary RBP-4 and other parameters.

RESULTS

Mean age in patients and controls was in a range of 45 – 47 years. Mean BMI was high as compared to the BMI of control subjects. Levels of HbA1c, RBP-4 and serum creatinine are shown in Table 1.

Table 2: Correlations between RBP-4 and Age, BMI, HbA1c and serum creatinine.

Variable	RBP-4 (ng/ml)	
	Correlation Coefficient (r)	*p* value
Age (years)	0.176	0.180
BMI (kg/m^2)	-0.385	0.002
HbA1c (%)	0.092	0.454
Serum creatinine (mg/dl)	-0.755	0.001

Spearman's correlation analysis showed a negative correlation between RBP-4 and BMI. Positive correlation was observed between age and HbA1c with RBP4. A significant negative correlation of RBP4 with serum creatinine was also observed (Table 2).

DISCUSSION

DN is an increasing issue in the under developed countries in type 2 diabetes mellitus and is reported to be the most predominant complication in diabetic patients in Saudi Arabia.[14] Mean age of our patients and controls was in a range of 45 – 47 years. It is similar to a study which observed that duration of diabetes is 5 – 6 years in age of 45 – 47 years with a slight high BMI than control subjects.[15]

Our study observed significantly higher level of HbA1c in diabetic patients compared to their controls. HbA1c has high affinity for oxygen that results in anoxia of tissue and this help in developing the problem of microangiopathy. Besides, impaired glycemic control also has role in the development of DN.[16,17] Recently it is found that RBP-4 may be related to impaired metabolism of glucose.[18]

The present study observed a significantly increased level of serum RBP-4 level in diabetic patients. A group of workers also noted that increased level of RBP-4 in diabetic patients with microalbuminuria and may present primary stage of DN.[19] A study demonstrated that salvaging of retinol binding protein is done by kidneys and alteration in the metabolism of RBP-4 indicates altered function of kidney. Increased oxidative stress is common in diabetic patient which may increase by raised RBP-4 and results in altered function of endothelium.[20,21] It is therefore proposed that serum RBP4 may be a marker/indicator of kidney dysfunction diabetic patients.[15]

On the other hand, the level of serum creatinine was decreased in patients as compared to controls. An increased level of serum creatinine is seen in kidney dysfunction.[22] However, a study reported that serum creatinine is decreased in glomerulonephritis, tubular necrosis and polycystic kidney disease.[23] In our study, there was a mild increase in value of BMI in diabetic patients but the correlation of BMI with RBP-4 was negative. However, according to some studies there is no significant correlation between BMI and RBP-4.[23] It is thought that decreased level of serum creatinine is related with an increased risk of diabetes, with reduced volume of skeletal muscle i.e. a few site of action for insulin which may enhance insulin resistance and results in diabetes. However, a study found positive correlation between RBP-4 and serum creatinine.[24]

There have been a number of studies worldwide to assess the relationship of urinary RBP4 in Type 2 diabetics but there is little or no data of any such research done in Pakistan. Type 2 diabetes has been the subject of many genetic researches over the past few years and it has revealed the association of its pathogenesis with quite a few susceptibility loci. Mutations as well as polymorphisms in the candidate genes can affect insulin production, action and

resistance. Since the genetic polymorphism of diabetes is different in Pakistan and some genes differ from the rest of the world so this study was designed for our local ethnicity.

Limitation of study are that the study was limited to T2DM and not to T1DM. The number of patients was also small. Further studies are required on large number of patients with both type 1 and 2 to validate our results.

CONCLUSION

RBP-4 is most sensitive biomarker of proximal convoluted tubule and increased level of RBP-4 in urine and is a good indicator of renal dysfunction.

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