CLINICAL SIGNIFICANCE AND PROGNOSTIC VALUE OF LOW MOLECULAR WEIGHT ‘TUBULAR’ PROTEIN, APHA-1-ACID GLYCOPROTEIN IN DIABETES

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Background: Tubular damage as suggested by tubular proteinuria is a recognized feature of glomerulonephritis in diabetics. Study Design: Study endeavoured to find out the level of alpha-1-acid glycoprotein (AGP) in urine of diabetic patient and tired to correlate the functional outcome of AGP with the patterns of proteinuria. Material and Methods: Fifty registered Type II diabetic patients were studied. Patients were divided on the basis of age into group A (41–60 yrs) and group B (>60 yrs) admitted in medical and visited the out door department of Sir Ganga Ram Hospitals, Lahore were included in the study. Duration of study was period of one year (from Jan 2005 to Jan 2006). Twenty normal subjects with no history of diabetes were taken as controls. Main Outcome Measures: Blood and urine samples of patients were collected and estimated the pH, specific gravity and protein level by strip and chemical method. Level of urinary AGP was found by using the technique of SDS gel electrophoresis. Level of blood glucose was estimated by auto analyzer. Results: Comparison of biochemical and other parameters in different age group of diabetics with normal subjects was carried out. Mean age of group A was 50 yrs and of group B was 65.80 yrs. The pH of urine was low in both groups as compared to normal subjects. A slight change in the specific gravity of urine was observed in group B and normal subjects while specific gravity of urine of group A was similar to normal control. Although the level of urinary protein of group A and B was greater than normal subjects but this shows no significant difference. Average raw volume of AGP was markedly increased in both groups A and B as compared to normal subjects. Level of blood sugar was significantly increased in group B as compared to group A. Conclusion: The best predictive value for either CRF outcome or for response to therapy was provided by the level of AGP. By screening this marker protein we may able to prevent or delay the progression of the disease.

Keywords: Apha-1-acid glycoprotein, Diabetic nephropathy.

INTRODUCTION

Small amounts of urinary proteins observed at early stages of diabetic nephropathy may result from both glomerular and proximal tubular dysfunction. In most cases of glomerulonephritis long-term course lead to chronic renal failure. The progressive renal failure consists of focal and segmental glomerulosclerosis and tubulointerstitial nephritis. The tubulointerstitial changes focus almost all forms of progressive glomerular and vascular injury. Tubular ischaemia results from obliteration of peritubular capillaries, adaptation of tubular function with increased oxygen consumption and increased glomerular capillary permeability to macromolecules are reasons of chronic tubular damage.

Tubular damage as suggested by enzymuria and tubular proteinuria is a recognized feature of glomerulonephritis with clinical proteinuria and both incipient and overt diabetic nephropathy. Patients with massive proteinuria had diminished urine concentrating ability, impaired acidifying mechanism, but elevated maximum tubular secretory capacity compared with patients having minimal proteinuria.

Apha-1-acid glycoprotein (AGP) or orosomucoid is 41–43-kDa glycoprotein with a pI of 2.8–3.8. It is heavily glycosylated (45%) and negatively charged due to the presence of sialic acids. AGP is an acute phase protein in all mammals investigated to date. The peptide moiety of AGP is a single chain of 183 amino acids and structurally similar to serum retinol-binding protein (RBP), beta-lactoglobulin, alpha 2-globulin, and alpha 1-globulin. Like RBP and others, it has an ability to bind with lipophilic drugs and some steroids to show its biological action. Expression of the AGP gene is controlled by a combination of the major regulatory mediators, i.e., glucocorticoids and a cytokine network involving mainly interleukin-1 beta, tumour necrosis factor-alpha, interleukin-6 (IL-6) and IL-6 related cytokines.

The acute phase protein alpha-1-acid glycoprotein has been shown to be protective against experimental ischemia-reperfusion injury. The effects of AGP are thought to be mediated by fucose groups expressed on the AGP protein inhibiting neutrophil infiltration. AGP can be regarded as a potential new therapeutic intervention in the treatment of acute renal failure, as seen after transplantation of
ischemically injured kidneys. \(^{10}\) It is indicated that it is the carbohydrate chains on AGP that are important in modulating the immune system and not the AGP molecule itself. \(^{11}\)

It is experimented and confirmed that AGP prevents gram-negative infections and may be an essential component in non-specific resistance to infection. \(^{12}\)

Proteinuria was evaluated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and classified into four main patterns on the basis of molecular weight: physiological (70 kd), pure glomerular (150 kd), mixed with low molecular weight proteins as low as 23 kd (23 kd), and mixed with very low molecular weight proteins (20 to 10 kd; termed 10 kd). The relative frequencies were 70 kd, 0.7%; 150 kd, 1.4%; 23 kd, 61%; and 10 kd, 37%. \(^{12}\)

Present study endeavour to find out the level of ACP in urine of diabetic patient and tired to correlate the functional outcome of ACP with the patterns of proteinuria.

**MATERIAL AND METHODS**

Fifty registered Type II diabetic patients were studied. Patients were divided on the basis of age into group A (age range 41–60 yrs) and group B (>60 yrs) admitted in medical and visited the out door department of Sir Ganga Ram Hospitals, Lahore were included in the study. Duration of study was period of one year (from Jan 2005 to Jan 2006). Twenty normal subjects with no history of diabetes were taken as controls.

**Main outcome measures:**

Blood and urine samples of patients were collected and estimated the pH, specific gravity and protein level by strip and chemical method. Level of urinary AGP was found by using the technique of SDS gel electrophoresis. Level of blood glucose was estimated by auto analyser.

Twenty-four hour urine sample of all groups including of patients and normal subjects were collected. Level of urinary proteins and blood sugar were estimated. Urinary samples of these patients were analyzed by SDS-PAGE Gel Electrophoresis. \(^{14}\)

**Table-1: Comparison of biochemical and other parameters in different age groups of diabetics with normal subjects**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (41–60 yrs)</th>
<th>Group B (&gt;60 yrs)</th>
<th>Normal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>50.1±6.03</td>
<td>65.8±3.01</td>
<td>60.4±2.80</td>
</tr>
<tr>
<td>pH of urine</td>
<td>4.9±2.73</td>
<td>5.8±0.79</td>
<td>6.2±1.80</td>
</tr>
<tr>
<td>Sp. gravity of urine</td>
<td>1.008±3.17</td>
<td>1.01±0.0</td>
<td>1.008±3.42</td>
</tr>
<tr>
<td>Urinary Protein (mg/dl)</td>
<td>0.22±0.35</td>
<td>0.22±0.15</td>
<td>0.17±0.09</td>
</tr>
<tr>
<td>Blood sugar (mg/dl)</td>
<td>266.0±31.43</td>
<td>305.5±43.55</td>
<td>140.4±24.10</td>
</tr>
<tr>
<td>AGP (average raw volume)</td>
<td>5020.42</td>
<td>5979.68</td>
<td>162.65</td>
</tr>
</tbody>
</table>

**RESULTS**

Comparison of biochemical and other parameters in different age group of diabetics with normal subjects was tabulated. It is observed that mean age of group A was 50 yrs and of group B was 65.80 yrs. Mean age of normal subjects was 60.43 yrs which is in between the age ranges of group A and B. The pH of urine was low in both groups as compared to the pH of normal subjects. A slight change in the specific gravity of urine was observed in group B and normal subjects. While sp gravity of urine of group A was similar to normal control. Although the level of urinary protein of group A and B was greater than normal subjects but this shows no significant difference. Average raw volume of AGP was markedly increased in both groups A and B as compared to normal subjects. Level of blood sugar was significantly increased in group B as compared to group A.

**DISCUSSION**

Measurement of urinary excretion of low molecular weight proteins was valuable supplement in estimation of tubulointerstitial system malfunction. These proteins are readily filtered by normal glomeruli and virtually completely reabsorbed by normal proximal tubules. \(^{2}\)

Comparison of biochemical and other parameters in different age group of diabetics with normal subjects was carried out. It is observed that mean age of group A was 50.10 yrs and of group B was 65.80 yrs. A group of worker stated that in middle age the risk of diabetic nephropathy is only 2%. \(^{15}\) However a group of workers in the same year study the progression of kidney disease with the age and found that fast progressors of developing kidney disease are the middle age diabetics. \(^{16}\) Level of urinary pH, specific gravity is decreased in the group A (age range 41–60 years) as compared to group B and of pH of group of C. According to a study the low specific gravity (1.008) is due to increased amount of glucose. \(^{17}\)

Present study observed a minimal proteinuria. It is observed that although the level of urinary protein of group A and B was greater than normal subjects but this shows no significant difference. A group of workers also observed minimal proteinuria in diabetics. They stated that only a subset of type 2 diabetic patients have the typical diabetic glomerulopathy. \(^{19}\) Number of studies reported that proteinuria in diabetic patients especially with the degree of chronicity. According to a study the degree of proteinuria was the strongest determinants of faster GFR decline in diabetics and it is greater with increasing age. \(^{19}\) Another study
postulated that in NIDDM the quantification of urinary protein excretion rate-independent of the pattern of underlying glomerular involvement, discriminates the progressors from nonprogressors of developing kidney disease. It also shows the quantification of renal tissue injury that predicts the risk of end stage renal failure.\(^\text{20}\) The results of SDS-PAGE electrophoresis showed that the average raw volume of AGP was markedly increased in both groups A and B as compared to normal subjects. Present study also observed the electrophoretic band of AGP of 41–42 Kda. According to a study the increased level of AGP may be a predictor of development of chronic renal failure. Study observed that a total of 12.5% of 64 diabetic patients with mixed proteinuria (excretion of low molecular weight protein) developed CRF.\(^\text{13}\) Another study reported that serum concentration of AGP increases in response to systemic tissue injury, inflammation or infection, and these changes in serum protein concentrations have been correlated with increases in hepatic synthesis.\(^\text{6}\)

**CONCLUSION**

Therefore, the best predictive value for either CRF outcome or for response to therapy was provided by the level of AGP a low molecular weight protein marker associated with tubulointerstitial damage. By screening the marker protein we may able to prevent or delay the progression of the disease.

**REFERENCE**


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