SIGNIFICANCE OF PROTEINURIA IN DIABETES

RAMACHANDRAN, A.* MOHAN VISWANATHAN,* SNEHALATHA, C.**, KRISHNAPRIYA, P. K.*** and VISWANATHAN, M.†

INTRODUCTION:

Proteinuria is considered to be an early sign of diabetic nephropathy. It has been reported that lesions in the kidney, detectable only by electron microscope can occur in early stages of diabetes and mild proteinuria may accompany such changes (Sabour, McDonald and Robson, 1962; Malins, 1968). These findings may be taken as early indications of diabetic microangiopathy.

At the Diebetes Research Centre, Madras, during routine estimations of 24-hour proteinuria in diabetic patients, it was observed that the patients who had proteinuria at the time of admission showed definite reduction in protein excretion during the course of treatment. Hence a study was undertaken to evaluate the significance of proteinuria in diabetics. This paper deals with the preliminary results of the study.

MATERIALS AND METHODS:

224 patients admitted to our centre for the control of diabetes during the last one year, formed the study group. They were subjected to a detailed clinical examination. Severity of diabetes was judged initially by an oral G.T.T. The criteria used by us were as follows. (Table 1). (Viswanathan et al, 1978).

<table>
<thead>
<tr>
<th>Severity of diabetes</th>
<th>Blood sugar mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasting</td>
</tr>
<tr>
<td>Mild</td>
<td>&lt; 120</td>
</tr>
<tr>
<td>Moderate</td>
<td>121 – 180</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 180</td>
</tr>
</tbody>
</table>

The blood sugar estimations were done by the Ortho-toluidine method (Hyvarinen and Nikki, 1962).

Complete urine examination including urine culture was done in all cases. Patients with evidence of urinary tract infection were not included in the study. Kidney function tests including blood urea, creatinine and creatinine clearance were performed in all patients. A 24-hour protein excretion was determined in these patients, on admission and protein was estimated by the sulphosalicylic acid method (Varley, 1969). It was repeated after the control of diabetes which was usually after 3-4 days. Patients were

* Research Assistant,
** Head, Department of Biochemistry,
*** Biochemist,
† Director, Diabetes Research Centre.
Address : 5-7, Main Rd., Madras-600 013.
Received for publication on 9-11-1978.
allowed to carry out the usual routine and were not in bed rest. The nature of physical activity was similar during the initial and follow up investigations.

The upper normal limit of proteinuria was fixed at 150 mg/day, based on the results obtained in 20 normal volunteers. Patients were arbitrarily divided into three groups, based on the 24-hour protein excretion.

Group A — Patients with proteinuria below 150 mg/day.
Group B — Patients with proteinuria between 151-999 mg/day.
Group C — Those with proteinuria of 1 gm and above.

Group A was taken to be normal. Diabetics in Group B were considered to have mild proteinuria, whereas diabetics in Group C with proteinuria of 1 gm or more were having severe proteinuria.

RESULTS:

The distribution of patients in the three groups according to proteinuria is given in the Table 2.

### TABLE 2
DISTRIBUTION OF PATIENTS ACCORDING TO PROTEIN EXCRETION

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>71 (31.6)</td>
<td>130 (58.1)</td>
<td>23 (10.3)</td>
</tr>
<tr>
<td>(Percentage in brackets)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect of severity of diabetes: The incidence of proteinuria increased with increasing severity of diabetes (Table 3).

Thus the incidence of proteinuria showed a positive correlation with the severity of diabetes.

### TABLE 3
PROTEINURIA IN RELATION TO SEVERITY OF DIABETES

<table>
<thead>
<tr>
<th>Degree of severity</th>
<th>Total No. of patients</th>
<th>Group A per cent</th>
<th>Group B per cent</th>
<th>Group C per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>20</td>
<td>60</td>
<td>40</td>
<td>Nil</td>
</tr>
<tr>
<td>Moderate</td>
<td>62</td>
<td>30.6</td>
<td>58.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Severe</td>
<td>142</td>
<td>28.1</td>
<td>60.6</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Effect of duration of diabetes: The next table (Table 4) shows the effect of duration of diabetes on the incidence of proteinuria in diabetes.

The incidence of severe proteinuria showed correlation with the duration of diabetes. Maximum incidence was seen in diabetics with 10 years of duration. On the other hand, there was no correlation between the incidence of mild proteinuria and duration of diabetes.

All the 23 patients in Group C had evidence of associated retinopathy. Of the 130 patients with mild proteinuria, 40 had evidence of retinopathy. In Group A, 27 had evidence of retinopathy.

### TABLE 4
PROTEINURIA IN RELATION TO DURATION OF DIABETES

<table>
<thead>
<tr>
<th>Duration in years</th>
<th>5 years</th>
<th>5-10 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>93</td>
<td>51</td>
<td>80</td>
</tr>
<tr>
<td>Percentage with mild proteinuria</td>
<td>60.1 per cent</td>
<td>50.4 per cent</td>
<td>62.5 per cent</td>
</tr>
<tr>
<td>Percentage with severe proteinuria</td>
<td>3.7 per cent</td>
<td>13.4 per cent</td>
<td>16.3 per cent</td>
</tr>
</tbody>
</table>
FOLLOW-UP:

Follow-up studies were possible in 39 patients with mild proteinuria (Group B) and in 7 patients with proteinuria of 1 gm or more (Group C). Table 5 shows the follow-up data in Group B.

| TABLE 5 |
| PROTEINURIA BEFORE AND AFTER TREATMENT IN GROUP B |
| Parameters | Initial | Follow-up |
| Post-prandial blood sugar | 368.9±112.7 | 180.3±58.7 |
| 24-hour proteinuria | 374.5±140 | 250.3±148.6 |

When the post-prandial blood sugar fell from a mean of 368.9 mg per cent to 180.3 mg per cent, there was a corresponding fall in proteinuria from a mean of 374.5 mg/day to 250.3 mg, which was statistically very significant.

32 patients out of these 39 patients showed very marked reduction in the proteinuria and in 10 of them it had reached even normal levels. It was noticed that even in a patient with 800 mgs of protein excretion it came to normal level. Only in 7 patients, the levels had not been very much influenced within this short period.

In Group C, even though there was a reduction, it was only from an initial level of 2.46±2.2 gm/day to 1.7±1.3 gm/day, and it remained still at very high levels. On the other hand, in patients in Group B, there was a marked reduction in protein excretion.

DISCUSSION:

This study shows that a large number of diabetics have mild proteinuria which may be undetected unless measurement of the 24-hour protein excretion is made. It is necessary to employ sensitive methods for detection of proteinuria. Using the specific and sensitive immunological techniques, it is possible to determine small amounts of proteins both qualitatively and quantitatively. However, these tests cannot be employed for routine clinical use. The sulphosalicylic acid method has proved to be a satisfactory tool for such purposes.

The leakage of small amounts of proteins is likely to be due to changes in the permeability properties of the vasculature. The morphological alterations responsible for these have been detected even in very early stages of diabetes (Sabour et al, 1962; Ditzel and Junker, 1972). The haemodynamic properties governing the penetrations of the basement membrane by the macromolecules are also altered in diabetics (McMillan, 1975). Parving (1976) has demonstrated an increased microvascular protein passage even at the onset of diabetes and suggests that this is an initial and perhaps decisive event in the morphogenesis of diabetic microangiopathy.

Out of a total of 224 patients studied, 153 patients, i.e., more than 68 per cent had abnormal amounts of protein in the urine. But only 10.3 per cent had levels of more than 1 gm of proteinuria. The rest had only mild proteinuria.

Out of 39 patients with mild proteinuria, in whom follow-up study was possible, there was definite quantitative reduction in the protein excretion with the metabolic control of diabetes. In 10 of them, the protein excretion reversed even to normal levels.

This study reveals that proteinuria may be present in many diabetics even in the
early stages and even at the time of onset of the disease. The significance of this can be evaluated only by having a quantitative estimation, followed by periodical reassessment.

The observation made in this study as well as by some earlier workers like Mogens- sen (1976) and Parving (1976) showed that early mild proteinuria in diabetics is reversible with good metabolic control. This is of great importance in view of the present controversy regarding the use of oral antidiabetic agents. It is generally agreed that in the presence of renal complications, oral drugs are not to be used. It is our contention that mild proteinuria especially if it is reversible may not be a contraindication for the use of oral hypoglycaemic agents.

**SUMMARY**

Proteinuria in a diabetic patient is taken as an ominous sign since it usually indicates renal involvement. We observed that very often proteinuria which was detected at the time of admission by semi-quantitative tests like salicylic acid test or heat test cleared after the control of diabetes. This prompted us to study the significance of proteinuria in diabetes.

224 maturity onset diabetic patients admitted at our centre were taken up for the study. The 24-hour protein excretion was estimated immediately on admission and after the control of blood sugar was achieved. Apart from routine clinical examination, renal function tests like urine, creatinine and creatinine clearance were also carried out. 20 normal subjects were also studied for control.

Based on the 24-hour protein excretion patients were divided into 3 groups:

- **Group A** — Proteinuria of 150 mg and below.
- **Group B** — Proteinuria between 151 — 999 mg.
- **Group C** — Proteinuria of 1 gm and above.

Group A was taken as normal. Group B was considered to have mild proteinuria and Group C, severe proteinuria respectively.

During the follow-up studies in Group B, the proteinuria came down after the control of blood sugar. Thus it seems that proteinuria in uncontrolled diabetes is very often reversible.

**ACKNOWLEDGEMENT**

This paper is based on a symposium on 'Diabetic Nephropathy' held at the Diabetes Research Centre. We are grateful to Prof. M. S. Amarean, Professor of Nephrology, Madras Medical College, for his valuable guidance, in this study.

**REFERENCES**


