RADIONUCLEAR DETERMINATION OF GLOMERULAR
FILTRATION RATE AND RENAL PLASMA FLOW TO
DETECT EARLY DECREASE OF RENAL FUNCTION
IN INSULIN DEPENDENT DIABETES

C Cascone, G Beltramello, N Borsato, F Cavallin, P Calzavara,
M De Luca, F Susanna, D Madia, P Zanco, B Saitta,
M Camerani, G Ferlin

General Hospital, Castelfranco Veneto, Italy

Summary
To evaluate the role of renal haemodynamic factors in the pathophysiology of diabetic nephropathy, we determined by radionuclear techniques glomerular filtration rate (GFR) and renal plasma flow (RPF) in 18 patients affected by insulin dependent diabetes mellitus (IDDM) in good metabolic control, with normal blood pressure and plasma creatinine. GFR and RPF measured in the same patients after ten months correlated with proteinuria and duration of diabetes.

Our finding of a significant correlation between the decline of RPF and duration of diabetes may support the haemodynamic hypothesis of progression of diabetic nephropathy.

Introduction
In spite of the noteworthy contributions given by Danish authors [1–4] and Viberti [5–7] in the study of the pathophysiology of diabetic nephropathy, we cannot explain the reasons why more than 50 per cent of insulin-dependent diabetics are protected against the development of clinical nephropathy. Viberti [5] has emphasised the role played by microproteinuria, Hostetter [8], on the basis of his studies on diabetic rats, pointed out the hypothetical role of glomerular hyperfiltration in the initiation and progression of diabetic nephropathy.

The aim of the present study was to verify this haemodynamic hypothesis in patients affected by IDDM.

Patients and methods
Eighteen patients, ten males and eight females, 13–58 years old (mean 38), affected by IDDM from 2–34 years (mean 12) were studied.

All patients had a normal plasma creatinine (less than 1.2mg/100ml in our laboratory) and blood pressure and good metabolic control in the preceding
year. We evaluated twice (the second time after 10 months) the following parameters:

1. GFR by a single injection (5mCi) of Tc$^{99m}$-DTPA according to a previously described technique [9].

2. RPF by a single injection (800μCi) of I$^{123}$-Orthoiodo-hippurate (OIH) and calculation made as previously described.

3. Daily proteinuria by biuret method and radial immunodiffusion (LC-Partigen Behringwerke AG, Marburg, WG).

4. Urinary excretion of lysozyme (Quantiplate. Lysozyme Test Kit. Kallestad, Chaska, Mn, USA) in the first study, of Beta 2-Microglobulin (Phadezym Beta 2-micro Test. Pharmacia Diagnostics, Uppsala, Sweden) in the second, in order to exclude tubular dysfunction responsible for proteinuria.

The correlation between these parameters and the duration of the disease were determined by linear regression analysis, statistical significance by Student’s ‘t’ test and Fisher’s test.

Results

Results are summarised in Table I.

<table>
<thead>
<tr>
<th></th>
<th>1st Study</th>
<th>2nd Study</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR, ml/min</td>
<td>67–154 (Mean 103±23 SD)</td>
<td>54–154 (Mean 107±29 SD)</td>
<td>NS</td>
</tr>
<tr>
<td>RPF, ml/min</td>
<td>450–770 (Mean 611±95 SD)</td>
<td>390–894 (Mean 621±149SD)</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria, mg/day</td>
<td>60–1295 (Mean 334±321SD)</td>
<td>30–1030 (Mean 231±284SD)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Lysozyme (1st study): small traces in the urine of two patients.

Beta 2-microglobulin: urinary excretion in the normal range in all patients.

GFR was below the normal limit in three patients and increased in one (Figure 1). RPF was at the upper normal limit in four patients and decreased in five (Figure 2). A poor statistical correlation was found between proteinuria and duration of diabetes (Figure 3).

A significant negative correlation was observed (Figure 2) between the duration of diabetes and RPF, while duration of the disease does not correlate with GFR (Figure 1). The values of the second study are not significantly different from the first findings, but the evaluation of the single cases gives a
Figure 1. Poor statistical correlation between duration of diabetes (abscissa) and GFR. Only three patients with normal plasma creatinine are just below the lower normal limit (dotted line).
Figure 2. Correlation between duration of diabetes (abscissa) and RPF. The comparison with GFR (Figure 1) supports the hypothesis that other factors (transcapillary hydraulic pressure differences and glomerular capillary ultrafiltration coefficient) may determine variation of GFR in diabetics without clinical nephropathy.
Figure 3. Poor statistical correlation between duration of diabetes (abscissa) and proteinuria. Dotted line indicates the upper normal limit of proteinuria (150mg/day)
partial confirmation about the predictive value of heavy proteinuria. In fact two of the four patients with daily proteinuria greater than 0.5g showed significant decline of their GFR and RPF after the short period of 10 months. Such a decline was not found in patients with microproteinuria.

Discussion

A general agreement exists among the investigators about two features of diabetic nephropathy; the increase of GFR and RPF in early diabetes and the progressive decline in renal function in diabetics with constant gross proteinuria. Some conflicting opinions have been expressed about the importance of microproteinuria in the initiation and progression of clinical nephropathy. An obvious question arises — is proteinuria only a ‘marker’ of a functional and reversible derangement or does it indicate an irreversible structural damage?

The hypothesis of Hostetter et al [8] is fascinating, since it postulates that haemodynamic factors may be responsible for the glomerular structural damage and consequently for proteinuria. This hypothesis needs confirmation from clinical studies, because of the great number of variables which are difficult to quantify such as physical activity and metabolic control. Although we were conscious of these difficulties, we thought it interesting to evaluate renal haemodynamic factors before the initiation of overt clinical nephropathy and to subsequently restudy the same patients to detect some derangements responsible for clinical manifestations. Our data, documenting a slight but statistically significant decline in RPF in the course of IDDM, without a parallel change of GFR, may indicate that other factors, other than RPF, contribute to determine GFR. Indeed we do not know the role played by the transcapillary hydraulic pressure gradient and the glomerular capillary ultrafiltration coefficient.

However our finding of a parallel decline in GFR and RPF in patients with constant gross proteinuria may indicate that in the evolutive phase of diabetic nephropathy RPF is the main determinant of GFR.

Finally, if the role of microproteinuria postulated by Viberti is confirmed, the question posed by Deckert and Poulsen [5] could be reviewed with new dramatic significance since strict metabolic control capable of reversing microproteinuria could be obtained only by an artificial pancreas.

References

2 Mogensen CE, Osterby R, Gundersen HJG. Diabetologia 1979; 17: 71
3 Sandahl Christiansen J, Frandsen M, Parving HH. Diabetologia 1981; 21: 368
4 Deckert T, Poulsen JE. Diabetologia 1981; 21: 178
5 Viberti GC, Jarrett RJ, Mahmud U et al. Lancet 1982; ii: 1430
7 Viberti GC, Wiseman MJ. Diabetic Nephropathy 1983; 2: 22

647
Open Discussion

SCHARER (Heidelberg) I wonder if you corrected your figures of proteinuria, GFR and plasma flow for the body surface area because you included children in your study?

CASCONE All the data was corrected to surface area of 1.73m², but we had only one child of 13 years and all the other patients were more than 20 years of age.

MIGONE (Chairman) Did you perform renal biopsy to look for other parameters in your patients?

CASCONE No, we followed the general concept that biopsy is useful in diabetic patients only if we can determine some new element for prognosis and therapy.