PART XV

GUEST LECTURE ON DIABETIC NEPHROPATHY

Chairmen: L Migone
           S Giovannetti
DIABETIC NEPHROPATHY: A PREVENTABLE COMPLICATION?

C G Viberti, M J Wiseman, J J Bending

Guy’s Hospital Medical School, London, United Kingdom

Renal failure is a complication of diabetes mellitus that occurs in approximately 45 per cent of insulin-dependent patients [1]. Its onset is heralded by the development of dipstick positive proteinuria (i.e. total urinary protein excretion >0.5g/24 hours) in a patient with usually 10 years or more of diabetes who has concomitant retinopathy and rising arterial pressure, but is free of other renal disease, urinary tract infection and cardiac failure. The incidence of diabetic nephropathy peaks at about 16 years after the onset of the disease and once manifest the condition progresses relentlessly to end-stage renal failure. If left untreated 50 per cent of the patients die within seven years [1]. With the appearance of persistent proteinuria glomerular filtration declines linearly with time at an average rate of 1.2ml/min/month, ranging widely between different individuals from 0.5 to 2.4ml/min/month [2]. The reasons for the different rates of decline are largely unknown but different degrees of blood pressure rise may play a role. Indeed arterial pressure starts to climb at a very early stage of renal involvement well before it was previously thought [3]. With the fall in glomerular filtration rate the proteinuria becomes heavier and the clearances of albumin and IgG increase [4]. There is a passage from a proteinuria highly selective for albumin in the early stages when the glomerular filtration rate is still normal or only moderately reduced to a low selectivity proteinuria with proportionally more IgG being cleared when the filtration rate is markedly reduced (Figure 1). One possible interpretation of this phenomenon is that size selectivity defects of the glomerular membrane develop in late nephropathy accounting for the proportionately increased transit of IgG [5], the early selective albuminuria being more likely explained by a change in the charge selectivity properties of the glomerular membrane [6]. A compensatory intraglomerular pressure increase in the surviving glomeruli would almost certainly accompany these membrane injuries and perhaps perpetuate them [7].

Management of established diabetic nephropathy

Therapeutic attempts of different kinds have been made in order to arrest progression of the disease. An obvious possibility was that improvement of
glycaemic control would affect the course of this condition. Results with strict diabetic control have been by and large disappointing and controlled studies have failed to show a significant effect of correction of hyperglycaemia [8]. More promising were the findings of Parving et al [9] showing that hypotensive treatment, started early in the course of diabetic renal failure, is capable of slowing deterioration of renal function. The effect of low protein diet has been little explored in diabetic renal failure, but is known to retard progression in other renal disease [10]. Figure 2 shows two patients with early and moderate diabetic renal failure followed for approximately five years. The blood pressure in these patients was kept stable throughout. Correction of hyperglycaemia with insulin pump treatment had little impact on the progressive linear deterioration of their renal function while on a normal protein intake of 80g of protein per day. Changing to low protein diet (40g/day) over the last year had a dramatic effect on their renal function which appears to have stabilised. This was so both in the patient who continued pump therapy (WP) and in the one who stopped it (RW). A longer follow-up is clearly needed to substantiate these findings, which nevertheless look promising. Except for the treatment of systemic arterial hypertension no pharmacological intervention has thus far been tried in order to remove some of the severe haemodynamic and chemical-physical disturbances that occur in the surviving glomeruli and contribute to renal disease, and perhaps future research should concentrate more on these aspects. The overall conclusion is that therapeutic manoeuvres in overt diabetic nephropathy can at best slow progression, but no arrest of reversal of the disease is possible at present.

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Figure 2. Glomerular filtration rate (GFR) changes over time in diabetic patients with clinical nephropathy. Institution of continuous subcutaneous insulin infusion (pump=1) with marked amelioration of glycaemic control did not affect significantly the rate of fall of GFR. Reduction of protein intake to 40g/day (open symbols; broken line) for up to one year appears to have stopped the decline in GFR.

Early diabetic renal disturbances: a new story

The state of affairs in established nephropathy has prompted a number of investigations aimed at characterising the early disturbances of renal function in diabetes before clinical proteinuria develops. A number of abnormalities have been demonstrated. It was found that both in newly diagnosed and in patients of some years standing the glomerular filtration rate is often elevated [11,12]. This seems to occur in approximately 20–30 per cent of the patients (Figure 3) and to be induced by moderate degrees of hyperglycaemia [12] as well as elevation of glucoregulatory hormones [13,14]. The determinants of this glomerular hyperfunction have been explored with micropuncture techniques in diabetic rats and have been shown to consist mainly of profound renal vaso-dilatation, more marked in afferent than efferent glomerular arterioles and so resulting in both increased glomerular plasma flow rate, and mean transglomerular hydraulic pressure gradient [15]. The high glomerular filtration rate in humans has been shown to be strongly associated with a large kidney volume [16,17]: so much so that although a large kidney volume can be associated with a normal glomerular filtration rate, a high glomerular filtration rate cannot occur in a normal size kidney (Figure 4). Large kidneys reflect primarily an increase in the tubular mass but large glomeruli are also present. The latter would increase the surface area available to filtration and a strong correlation has been described between glomerular filtration rate and glomerular filtering area in diabetic patients [18]. It is therefore possible that in man the elevation of glomerular filtration rate is a combination of increases not only in flow and pressure but also in the surface area available for filtration.
Figure 3. Glomerular filtration rate (GFR) in 118 non-proteinuric insulin-dependent diabetic patients divided by duration of diabetes. Supranormal GFR is present in approximately 20 per cent of the patients, the higher proportion in the younger group with diabetes duration between 1–10 years.

Figure 4. Relationship between 69 paired measurements of glomerular filtration rate (GFR) and kidney volume (KV) in 35 non-proteinuric insulin-dependent diabetics. Broken lines indicate the upper limit of normal for GFR and KV respectively. A large kidney can be associated with high or normal GFR, but a high GFR occurs only in large kidneys.
Another abnormality that can be encountered in the kidney in early diabetes is that of an increased urinary excretion of albumin [19]. This is below the limit of detection of conventional urine tests for albumin (e.g. Albustix test) but above the normal values that in our laboratory range between 2.0 and 25mg/24hr. Albumin excretion rates above 25mg/24h but usually below 250mg/24h have been defined as microalbuminuria. With excretion rates in excess of 250mg/24hr the Albustix test becomes positive and a different phase of macroalbuminuria and clinical proteinuria is entered (Table I). The microalbuminuria of diabetes is accompanied by increases in the urinary excretion

TABLE I. Definition of different levels of albumin excretion rate in healthy controls and in diabetic patients

<table>
<thead>
<tr>
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<th>Albumin excretion rate (mg/24hr)</th>
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<tbody>
<tr>
<td>Normal subjects (also ca 60% of insulin dependent diabetics)</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Microalbuminuric diabetics (ca 40% of insulin dependent diabetics)</td>
<td>25–250</td>
</tr>
<tr>
<td>Macroalbuminuric diabetics (up to 45% of insulin dependent diabetics eventually)</td>
<td>&gt;250</td>
</tr>
</tbody>
</table>

of IgG but not by changes in that of β2-microglobulin [6]. These findings, together with other theoretical and in vitro experimental data [20,21] suggest that the microalbuminuria of diabetes is glomerular in origin. Interestingly, the progressive increase of albumin excretion rates within the microalbuminuric range is not followed by a progressive proportional increase in the IgG excretion [6]. This leads to a fall in the selectivity index and to the appearance of a high selectivity proteinuria (for albumin), a condition encountered in early clinical nephropathy (Table II). Different studies have now shown that microalbuminuria

TABLE II. Urinary excretion of albumin and IgG and selectivity index (SI) in diabetic patients with normo- and microalbuminuria

<table>
<thead>
<tr>
<th></th>
<th>Normoalbuminuria</th>
<th>Microalbuminuria</th>
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<tbody>
<tr>
<td>Albumin (mg/24hr)</td>
<td>3.5</td>
<td>45</td>
</tr>
<tr>
<td>IgG (mg/24hr)</td>
<td>0.7</td>
<td>9</td>
</tr>
<tr>
<td>SI</td>
<td>0.56</td>
<td>0.56</td>
</tr>
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is associated with poorer glycaemic control and independently with higher blood pressure [22]. The arterial pressure need not be in the hypertensive range, but is found to be significantly higher than that of a matched normoalbuminuric group, although within the so-called normal range. These early
physiological changes are also accompanied by histological renal changes which have been better characterised in the diabetic animal model [23]. However, these are not meant to be part of this presentation and will not be discussed further.

Markers of diabetic nephropathy

The significance of these early diabetic renal abnormalities has remained obscure for several years. Only recently, long-term prospective studies [24–26] have indicated that certain levels of albumin excretion rate in the microalbuminuric range are strongly predictive of late diabetic nephropathy. Although no clear agreement has been reached on the discriminating level of albumin excretion rate that identifies an at risk patient, probably because of different study protocols, it would appear that values in excess of 45–50mg/24hr carry a risk of late nephropathy which is 20 times higher than that of patients with lower albumin excretion rates. Moreover, recent evidence suggests that diabetic patients with extreme hyperfiltration (i.e. glomerular filtration rate >150ml/min/1.73²) and microalbuminuria may lose glomerular function at a greater rate than normofiltering diabetics [26]. Although these data are preliminary and need confirmation they would support the hypothesis, generated by animal evidence, that glomerular hyperfunction and hypertension is, in the long-run, detrimental to the kidney, leading to glomerular destruction [7]. The glomerular hyperfiltration has also been claimed to be associated with marginal increases in arterial pressure by some workers [26] but this seems to be mediated only through an increase of albumin excretion rate [25,26]. Thus at least two early markers of diabetic renal disease have been identified: microalbuminuria (of a certain degree) and hyperfiltration (of a certain level).

Management of the early renal anomalies and potential for prevention of diabetic nephropathy

In sharp contrast to the relative insensitivity to treatment of established diabetic nephropathy the early phase abnormalities respond to therapeutic intervention. Both the microalbuminuria and the hyperfiltration are significantly reduced and often normalised by intensified insulin treatment and strict glycaemic control [27,28]. Moreover pharmacological intervention with a thromboxane synthetase inhibitor has been shown to reduce microalbuminuria independently of blood glucose changes [29].

Preliminary evidence in the diabetic rat would suggest that at similar levels of hyperglycaemia a low protein diet protects the kidney from hyperfiltration, albuminuria and the consequent histological lesions [30]. Interestingly recent observations in humans with different protein intakes indicate that vegans, who eat less protein, and all of vegetable origin, have significantly lower glomerular filtration rates than omnivores who eat more protein, largely of animal origin (Table III).

Thus the early abnormalities of the diabetic kidney are reversible, at least in part, by a variety of therapeutic manoeuvres. Correcting an early marker of
TABLE III. Mean (± SD) glomerular filtration rate (GFR) and daily protein intake (PI) in omnivore and vegan subjects

<table>
<thead>
<tr>
<th></th>
<th>GFR (ml/min/1.73m²)</th>
<th>PI (g/24hr)</th>
<th>Animal protein (g/24hr)</th>
<th>Vegetable protein (g/24hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnivores (n=17)</td>
<td>115±16</td>
<td>74±18</td>
<td>52±16</td>
<td>22±6</td>
</tr>
<tr>
<td>Vegans (n=14)</td>
<td>100±13**</td>
<td>59±22*</td>
<td>0</td>
<td>59±22</td>
</tr>
</tbody>
</table>

**=p<0.02; *=p<0.05

disease does not necessarily imply that the disease will be abolished; however, the possibility now exists to test, in controlled clinical trials of diabetic patients at risk of nephropathy, whether prevention of diabetic kidney failure is attainable.

Acknowledgments

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References

6. Viberti GC, Keen H. Diabetes 1984; 33: 686
Open Discussion

CHAIRMAN Thank you very much Dr Viberti. I want to congratulate you on your lecture.

SOBH (Egypt) The prostaglandin synthetase inhibitor indomethacin decreases glomerular filtration rate and proteinuria. Do you think it has a role in decreasing the rate of deterioration in kidney function in diabetic patients?

VIBERTI At what stage?

SOBH In the early stages to prevent the mesangial expansion by decreasing the glomerular filtration rate and protein filtration.

VIBERTI There have been a few studies done to test this hypothesis. They have not been published because the results have been negative. People have been giving indomethacin to patients with hyperfiltration over different periods of time – three days, one week – and they did not see any change.

SOBH In spite of a reduction in the glomerular filtration rate?

VIBERTI The glomerular filtration rate was not reduced. I think the results of this study will eventually be published but it is always more complex than we think.

HAAPANEN (Helsinki) I just wonder if it would be possible to influence the prognosis by treating the hypertension by a low sodium diet?

VIBERTI That is a good suggestion. There are a number of studies that are directed at correcting this marginal increase of blood pressure by different manoeuvres such as sodium restriction. People are using drugs and those who are using drugs find it very difficult to perform the study because of compliance. Certainly it is a good suggestion.

ANDREUCCI (Naples) Congratulations for your excellent presentation. Since we have so early in diabetic nephropathy, microalbuminuria, microhypertension and micro increase in renal perfusion, we should try to microconstrict the afferent arterioles to reduce the hyperfiltration. This will decrease the perfusion and the capillary hypertension and the transcapillary pressure gradient.

VIBERTI That is something that is obviously worth thinking about. What we have to do is to modify the balance between afferent and efferent arterioles,
which are both vasodilated in diabetes. The afferent is more vasodilated than the efferent so we will have to find a drug that refines the balance to reduce the glomerular hypertension. Maybe this will delay progression. However, in man there are other components, in addition to $\Delta P$ and $QA$, and I am convinced that the filtration surface area plays a role in the hyperfiltration. Whether that is of any importance in the progression of the condition I do not know.