GENESIS AND EVOLUTION OF PROTEINURIA IN DIABETES MELLITUS

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Diabetic nephropathy will affect up to 45% of insulin-dependent diabetics, and this complication is the major cause of death in these patients. Classically, the appearance of proteins in clinically detectable amounts (positive Albustix test) in the urine of a diabetic of 10 or more years duration, without other causes, is the first sign of this progressive condition. Indeed, once Albustix-positive proteinuria has developed, a relentless decline in glomerular filtration rate (GFR) follows, leading inexorably to end-stage renal failure. However, it has become clear through recent studies that well before this stage of overt diabetic renal disease there are detectable abnormalities of renal function which precede and, in some cases predict, the later changes. This review will follow the chronological course of diabetic proteinuria; parts of this history will necessarily be hypothetical, as the reader will realize.

Early changes

Almost as soon as sensitive radioimmunoassays allowed the detection in urine of albumin in small amounts, it became apparent that newly diagnosed diabetics, while negative to the Albustix test, could still excrete abnormally large amounts of albumin, and the term microalbuminuria was adopted. This microalbuminuria, i.e. elevated urinary albumin excretion rates (AER), but negative Albustix test, in newly diagnosed insulin-dependent diabetics, is promptly reversed by the institution of insulin treatment. Nevertheless, up to 45% of established insulin-dependent diabetic (IDD) patients still demonstrate microalbuminuria. Further, these patients also show increased urinary excretion of IgG, but the excretion of β2-microglobulin, a sensitive indicator of tubular function, is normal. Present evidence suggests that the increased

Key-words: Albumin excretion rate; Diabetic nephropathy; Glomerular filtration rate; IgG; Insulin-dependent diabetes mellitus; Proteinuria; Renal disease.

Accepted for publication on October 25, 1984.

excretion of albumin and IgG is of glomerular origin. Under average glycemic control, the physical exercise can increase AER in diabetics significantly more than in non-diabetic control subjects, even if resting AER is normal. β2-microglobulin excretion remains normal under these conditions, confirming the glomerular origin of microalbuminuria.

This is probably mediated by increased exercise-related intraglomerular pressure; values of filtration fraction during exercise appear to be considerably higher in diabetics than in controls. It is likely that increased intraglomerular pressure is also responsible, at least partly, for microalbuminuria and increased IgG excretion under resting conditions. The selectivity index (SI = IgG clearance/albumin clearance) in diabetics with AER up to 30 μg/min is not different from that of non-diabetic controls (AER < 12 μg/min). Albumin is a polyanion of 36 Å Stokes radius, and IgG a neutral molecule of 55 Å Stokes radius; the constancy of their co-excretion strongly suggests that charge and size selectivity of the glomerular membrane is intact at this level of microalbuminuria and that the elevated flux can only be due to a raised transglomerular pressure. Indeed, experimentally diabetic animals have been shown, using micropuncture techniques, to have an elevated transglomerular pressure gradient. As proteinuria nears dipstick positivity, IgG excretion remains essentially constant, while albumin is excreted in increasingly large amounts, resulting in a fall of SI. This is interpreted as a loss of the fixed negative charge on the glomerular membrane, which restricts albumin filtration, but has little effect on filtration of the neutral IgG, which is affected more by size selective properties (pore size and number) and transglomerular pressure.

**Microproteinuria: clinical associations**

**Glycemia** - The increased IgG and albumin excretion in diabetes mellitus, both at rest and during exercise, has been shown to be related to glycemic control. Cross-sectional studies have shown a significant correlation between HbA1 levels on the one hand and albumin and IgG excretion rates on the other. Furthermore, the correction of hyperglycemia returns the increased excretion of these proteins to normal values, not only in the short-term but, as more recent studies have shown, over a period of 8 months. Thus, at least at this stage, the abnormal albuminuria is reversible.

**Blood pressure** - It has been known for many years that severe kidney disease results almost invariably in a raised arterial pressure. Conversely, elevated

<table>
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<th>group</th>
<th>AER (μg/min)</th>
<th>urine collection (h)</th>
<th>follow-up (years)</th>
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<td>overnight</td>
<td>14</td>
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<tr>
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<tr>
<td>Aarhus University</td>
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<td>1-2</td>
<td>10</td>
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Tab. 1 - Levels of albumin excretion rate predictive of late nephropathy. Different techniques for urine collection and periods of follow-up at different centres result in different apparent discriminatory levels of albumin excretion. The differences may be more apparent than real (see the text).