Dear Sir,

The kidney undergoes structural and functional alterations throughout the course of diabetes, microalbuminuria being the first manifestation of nephropathy [1]. Albumin excretion depends mainly on glomerular hyperfiltration and changes in charge selectivity and pore size in the glomerular basement membrane (GBM) [2]. Although the structural basis of diabetic nephropathy is unknown, it is related with expansion of the mesangium and thickening of the GBM. This membrane, which represents a selective barrier to glomerular filtration, is formed of a dense network of collagen filaments, polypeptides of different chain structures, and glycosaminoglycans (GAG), heparan sulfate proteoglycan being the major type. The GAG play an important role as a selective filter in the GBM, ensuring that a negative charge is maintained. In diabetes mellitus, the negative charge on the GBM is reduced because of a decrease in heparan sulfate proteoglycan [3]. As a result, albuminuria and pore size are both increased.

The early phase of nephropathy is characterized by an increase in the activity of the enzymes responsible for glycoprotein (N-acetylglucosaminidase) and mucopolysaccharide metabolism (β-glucuronidase). These enzymes break down complex intracellular macromolecules and degrade glycoconjuncti-gates on the endothelial membrane [4], leading to structural alterations in the GBM, and the abnormal excretion of GAG [5].

We investigated the urinary excretion of GAG in 129 patients in different stages of nephropathy caused by insulin-dependent diabetes: 63 patients without hypertension or microalbuminuria (group B), 37 patients without hypertension but with microalbuminuria (group C), and 29 patients with both (group D). As a control group we studied 52 healthy control subjects (group A).
Glycosaminoglycan excretion was quantified in a sample of urine collected between 9.00 and 18.00 h. We excluded all samples from patients with urinary tract infection, or receiving treatment with nonsteroidal anti-inflammatory agents or heparin. The colorimetric method of Pennock [6] was used, and the results were expressed as U/g creatinine. Normality of the results was checked with the Kolgomorov-Smirnoff test. The differences between mean values for the different groups were tested with Student’s t test. Alternatively, we used one-way analysis of variance and the Kruskall-Wallis nonparametric test for variables whose distribution was not normal. The differences were considered significant when \( p < 0.05 \).

Urinary excretion of GAG differed in diabetic patients with different degrees of nephropathy (table 1); this biochemical parameter may thus be a useful indicator of the stage of progression of insulin-dependent diabetes.

Glycosaminoglycan excretion was significantly lower in healthy controls than in patients with no clinical or biochemical signs of kidney disease (group B, \( p < 0.001 \)), and versus patients with microalbuminuria (group C, \( p < 0.05 \)). We suspect that in the initial stages of kidney disease, alterations in the GAG of the GBM leads to a selective charge; this change may nonetheless go unnoticed because the pores of the membrane are too small to filter albumin. Evidence in support of this hypothesis has been found in rats [7]. The decreased synthesis of GAG in general, and heparan sulfate in particular [8], results in increased urinary excretion of these proteins [9].

In patients with advanced nephropathy (group D), GAG excretion was increased as a result of changes in the GBM and mesangium [10]. Incipient nephropathy should be suspected in patients with insulin-dependent diabetes mellitus in whom the urinary excretion of GAG is elevated, in the absence of microalbuminuria.

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References


GAG Excretion in Diabetic Nephropathy
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