Antiproteinuric Effect of Glycosaminoglycans?

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Dear Sir,

A 33-year-old man was hospitalized in February 1989 for nephrotic syndrome. Four weeks earlier he had noticed widespread edema, and a 10-kg increase in body weight. On admission, urinary protein loss ranged from 10 to 28 g/day. Total serum protein was 4.0 g/dl with 1.8 g/dl albumin, serum creatinine was 1.19 mg/dl, cholesterol 434 mg/dl, and triglycerides 291 mg/dl. Blood pressure was 150/110 mm Hg. The nephrotic syndrome was complicated by left renal vein thrombosis, and the patients developed pulmonary arterial embolism. A percutaneous renal biopsy demonstrated a membranous nephropathy. In light of the normal immunological and serological parameters, a diagnosis of idiopathic membranous glomerulopathy was made. The patient was initially treated with intravenous heparin for 10 days, followed by an oral anticoagulant, methylprednisolone (1 g boluses on each of 3 consecutive days) followed by oral prednisone (0.5 mg/kg daily as a single morning dose), and enalapril (20 mg daily) to control blood pressure. While 30 days later renal vein thrombosis had disappeared, the treatment was ineffective in inducing remission of the nephrotic syndrome, so a cytotoxic drug was added to the previous therapeutic regimen (pulse intravenous cyclophosphamide 0.5 g/m2, repeated 3 times in 6 months). This combined approach also had no beneficial effect on the disease, which at the end of February 1990 had worsened (total serum protein decreased to 3.7 g/dl). At that time, considering some preliminary findings of an ongoing study on streptozotocin-induced diabetic rats demonstrating that the onset of proteinuria could be prevented by glycosaminoglycan (GAG) administration [1], the patient’s informed consent was obtained the previous treatment was stopped, and a mammalian mucosa extractive mixture of a heparin-like fraction (80%) and dermatan sulfate (20%);

Fig. 1. Temporal profiles of serum proteins and albumin and 24-hour urinary proteins in the first patient. The arrow signals the beginning of the oral treatment with GAGs.
oral anticoagulant and no antihypertensive agents, and serological and urinary parameters are stable.

Encouraged by this first success, we started the same therapeutic regimen in a second patient, a 64-year-old male with a 2-year history of microhematuria and proteinuria (2-3 g/day), without dysproteinemia, sustained by an idiopathic mesangioproliferative glomerulitis. Daily protein loss was 2.9 g at the beginning, then decreased to 1.8 one month later, to 0.83 after 2 months, and is now, after 3 months, 0.12 g/day.

Sulodexide, Alfa Wassermann SpA, Bologna, Italy) was administered (30 mg oral twice daily per os; this drug is currently approved for human use in Italy for the treatment of vascular diseases with thrombotic risk). Following this treatment, we observed a progressive improvement in the nephrotic syndrome (see fig. 1). Urinary excretion of proteins tended to decrease, and in February 1991 was less than 1.60 g/day. At the same time, serum proteins were increased to 6.75 g/dl and albumin to 3.73 g/dl. Currently, the patient is still receiving GAG treatment, with no

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Obviously, we cannot rule out that the amelioration of proteinuria observed in these 2 patients is entirely due to the natural history of the underlying disease. However, there are several good reasons to suspect a favorable effect exerted by GAGs. In fact, heparan sulfate constitutes the anionic charges in glomerular basement membranes, and its removal by enzyme digestion [2] or its neutralization by specific antibodies [3] increases the perm-selectivity to proteins of the basement membrane, while GAG administration augments the negative electrical potential of the vessel wall [4] and slows down the progression to uremia in rats with subtotal renal ablation [5-7]. Moreover, it has been shown that some GAGs inhibit mesangial cell proliferation both in vitro [8] and in vivo [9,10], and exert an antimitogenic effect on glomerular epithelial cells [11]. Finally, their long-term administration prevents glomerular basement membrane thickening, glomerular anionic charge reduction, and the onset of albuminuria in streptozotocin diabetic rats [1]. Further study is needed to verify the effect of these endogenous substances on the natural history of proteinuric nephropathy.

References


Rosenzweig LJ, Kanwar YS: Removal of sulfated (heparan sulfate) or nonsulfated (hyaluronic acid) glycosaminoglycans results in increased permeability of the glomerular basement membrane to 125I-bovine serum albumin. Lab Invest 1982;47:177-184.


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