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CASE REPORT

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Treatment of proteinuria with low-molecular-weight heparin after renal transplantation

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Abstract The development of nephrotic-range proteinuria after renal transplantation is an unfavourable prognostic factor for graft survival. In contrast to that in other nephropathies, the role of renin–angiotensin blockade in kidney transplantation is less well defined, and its anti-proteinuric effect is markedly reduced in the presence of segmental glomerulosclerosis. Here, we describe two patients who developed severe proteinuria after renal transplantation, despite effective blood pressure control with an ACE inhibitor. Histological changes were consistent with IgA-nephropathy and focal segmental glomerulosclerosis. Both patients were treated with low-molecular-weight heparin in addition to pre-existing ACE inhibition. This regimen led to a significant and long-lasting reduction of proteinuria. Our data suggest that low-molecular-weight heparin possesses strong renoprotective properties, thus confirming previous data from experimental nephropathies. This approach might represent a promising new strategy for treatment of proteinuria after kidney transplantation.

Keywords Kidney transplantation · ACE inhibition · Proteinuria · Low-molecular-weight heparin

Introduction

Proteinuria frequently develops after renal transplantation and is mainly caused by chronic allograft nephropathy and de novo or recurrent glomerulonephritis [1, 2, 3]. Glomerulitis during acute allograft rejection may, occasionally, also be complicated by nephrotic-range proteinuria [4]. Urinary protein loss of more than 3 g per day at any time in the post-transplantation period is an unfavourable prognostic factor for graft survival independent from renal function [1, 3]. ACE inhibitors and angiotensin II receptor antagonists are the mainstay of pharmacological treatment of proteinuric nephropathies, both diabetic and non-diabetic [5, 6]. However, only few studies have investigated the nephroprotective potential of ACE inhibitors in post-transplantation proteinuria.

Oka et al. were able to show that trandolapril reduced mean arterial blood pressure and urinary protein excretion in ten patients with IgA nephropathy after renal transplantation, but they provided no data on renal function and histological changes [7]. Treatment with enalapril reduced proteinuria in 64% of patients with post-transplant IgA nephropathy. The presence of segmental glomerulosclerosis markedly reduced that effect to 28% [8]. The use of renin–angiotensin blockers in renal transplantation has been quite limited so far, as nephrologists are often afraid of the possibility of inducing renal insufficiency in patients with a single kidney transplant. Thus, more-potent treatment strate-

gies are needed to prevent renal damage from increased protein excretion. Here, we report on two patients in whom proteinuria secondary to segmental glomerulosclerosis after renal transplantation was successfully treated with low-molecular-weight heparin (LMWH) in addition to pre-existing ACE inhibition.

Case report

Case 1

A 63 year-old male patient was suffering from end-stage-renal failure secondary to biopsy-proven IgA-nephropathy. After having been on maintenance haemodialysis for 3 years, he received an HLA-identical cadaveric kidney transplant, which gained immediate function. Immunosuppressive therapy consisted of basiliximab, cyclosporine A, mycophenolate mofetil and prednisone. In the first weeks after transplantation low-molecular-weight heparin (dalteparin 2500 anti-factor X units q.d.) was used for prevention of thrombosis. Several days after transplantation, diuresis decreased. Urinanalysis showed mild proteinuria (1 g/24 h). Histological examination of a renal biopsy specimen showed very mild acute interstitial rejection (borderline lesions, Banff 1A). Immunohistological investigation was negative. After pulse steroid therapy, diuresis and renal function recovered promptly. Blood pressure was effectively controlled with ACE inhibition (enalapril 10 mg b.i.d.). At the time of the patient's discharge proteinuria declined to 0.5 g/24 h. Six weeks later the patient was re-admitted to the hospital because of right-sided deep-vein thrombosis. MR venography demonstrated extension of thrombosis below the iliac veins and excluded transplant vein thrombosis. At the same time, nephrotic-range proteinuria (13 g/24 h) was detected. Treatment with low-molecular-weight heparin (nadroparin 6650 anti-factor X units b.i.d.) was started, and it was decided not to perform a renal biopsy. The addition of nadroparin to enalapril led to a gradual reduction of proteinuria to 2.5 g/24 h.

Three weeks later, however, therapy with nadroparin had to be stopped due to an episode of lower gastrointestinal bleeding, and proteinuria rose to 7.4 g/24 h. Re-institution of nadroparin decreased the proteinuria to 2.5 g/day. After the patient had been discharged, the regimen was continued for the following ten months. Twelve months after the onset of proteinuria the patient's primary care physician stopped treatment with nadroparin. At this time proteinuria was 1.0–1.5 g/24 h (Fig. 1). Four months later a renal biopsy for re-

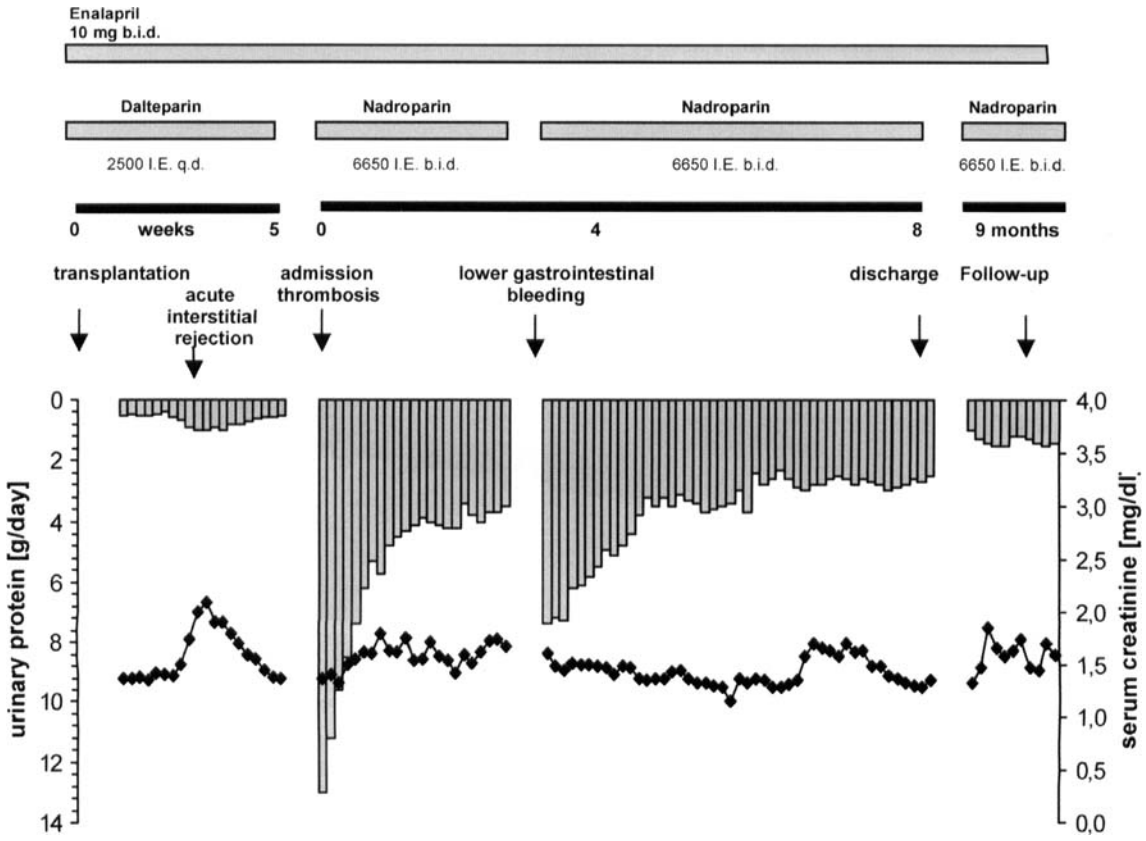


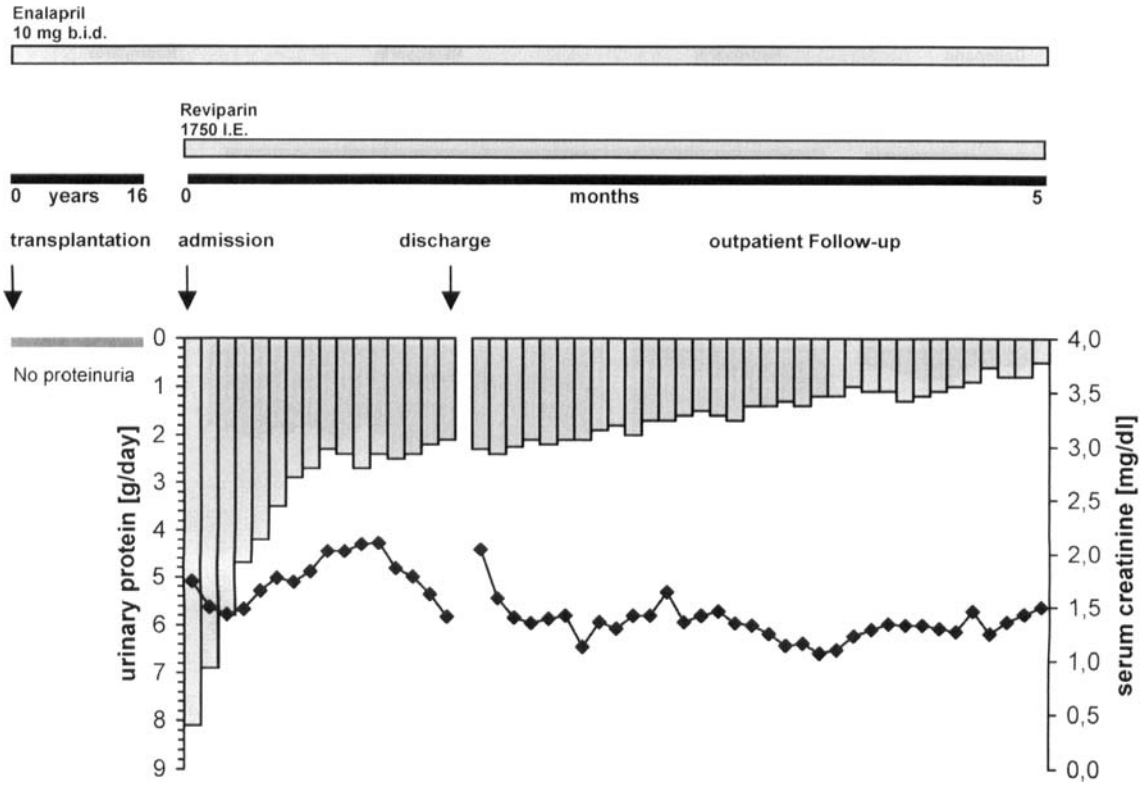
Fig. 1 Effect of nadroparin (6650 I.E. b.i.d.) on serum creatinine (mg/dl) and urinary protein (g/day)

assessment was performed. At this time renal function was stable, and proteinuria was 1.4 g/24 h. The biopsy showed recurrence of IgA-nephropathy, segmental glomerulosclerosis, and borderline interstitial rejection. Pulse steroid therapy was repeated, without a change in renal functional parameters. During the subsequent follow-up, proteinuria further decreased to 0.5 g/24 h. Twenty months after transplantation renal function was stable and proteinuria remained in the near-normal range (Fig. 1).

Case 2

A 58-year-old man, who had had insulin-dependent diabetes mellitus for 54 years, had been treated by chronic haemodialysis for end-stage diabetic nephropathy, starting in 1983. One year later he had received a cadaveric kidney graft. Immunosuppressive treatment consisted of cyclosporine and prednisone. Renal function remained stable for many years. Blood pressure was effectively controlled with ACE inhibition after transplantation. In 1996 pancreatic islet-cell transplantation was performed, resulting in sufficient glycaemic control ($Hb1A_c$ 5.6% to 6.5%). Two years later insulin therapy had to be re-instituted because of worsening blood glucose control. Four years later decline of renal function was noted. Creatinine clearance decreased from 40 to 25 ml/min, and serum creatinine levels increased from 1.6 to 2.8 mg/dl. A renal biopsy specimen revealed chronic transplant nephropathy with focal glomerular obsolescence, interstitial fibrosis and tubular fibrosis. In addition, severe hyaline vasculopathy compatible with chronic vascular cyclosporine toxicity was noted. Focal or segmental mesangial proliferation was absent. The immunosuppressive regimen was switched from cyclosporine/prednisone to mycophenolate mofetil/prednisone. Renal function immediately improved (increase in creatinine clearance from 24 to 43 ml/min, decrease of serum creatinine from 2.8 to 1.5 mg/dl), but during subsequent follow-up proteinuria progressively increased (0.2 to 8 g/24 h) despite high-dose ACE inhibition (enalapril 10 mg b.i.d.). Four months after the first biopsy, repeat renal histology revealed focal-segmental glomerulosclerosis in addition to the lesions described in the first biopsy. Immunohistology was non-specific. Because of the anti-proteinuric effect of low-molecular weight heparin observed in patient 1, treatment with low-molecular-weight heparin (reviparin 1750 anti-factor X units once per day, subcutaneously) was instituted. Five months later, proteinuria had declined to 0.5 g/day and renal function remained stable (Fig. 2).

Fig. 2 Effect of reviparin (1750 I.E. q.d.) on serum creatinine (mg/dl) and urinary protein (g/day)



Discussion

Proteinuria and nephrotic syndrome are well-known complications after renal transplantation. It is estimated that approximately 30% of kidney transplant recipients develop significant proteinuria [1, 2, 3]. After transplantation, proteinuria is a reliable early prognostic marker, predicting graft loss [1, 2] independent of underlying graft disease [4]. The spectrum of histological changes includes acute and chronic rejection, calcineurin-inhibitor toxicity, and recurrent, transmitted, or de novo glomerular disease [1, 2, 3, 4]. Proteinuria is not only a marker of renal damage, correlating with the activity of glomerular disease and/or renal scarring, but also promotes renal damage by up-regulating inflammatory and profibrotic genes [9, 10]. Thus one central therapeutic target in nephrology is the reduction of proteinuria.

The patients described in this report had nephrotic-range proteinuria from different underlying histology. In patient 1, a biopsy performed 1 year after transplantation showed recurrence of IgA-nephropathy, focal segmental glomerulosclerosis, and borderline interstitial rejection. The second kidney from the same cadaveric donor, transplanted in another patient in our centre, revealed stable allograft function without any episodes of rejection or proteinuria. In patient 2, the biopsy showed de novo focal segmental glomerulosclerosis (FSGS). The incidence of FSGS in transplanted kidneys as recurrence of primary disease is approximately 20%–30%, de-novo FSGS appears in about 8% [11, 12].

Recurrent FSGS is characterized, histologically, by mild degrees of obliterative arteriopathy and preferential involvement of the juxta-medullary glomeruli, whereas the glomerulosclerosis in de novo disease appears to be a manifestation of chronic rejection, cyclosporine nephrotoxicity, or the haemodynamic factors associated with the glomerular hypertrophy induced by reduced nephron mass [11, 13, 14]. Clinically, the onset of proteinuria is delayed and more indolent in de novo FSGS than in recurrent FSGS, generally occurring 3 months or later after transplantation. No specific treatment exists for de novo FSGS in allografts, and therapeutic intervention generally consists of strict blood pressure control and renin–angiotensin blockade. In both patients, hypertension was effectively controlled with ACE inhibition before onset of proteinuria. Addition of heparin had no effect on blood pressure level, a fact that argues against a primarily haemodynamic effect of LMWH.

Heparins represent poly-dispersed mixtures of glycosaminoglycan molecules of different chain length that have demonstrated remarkable renoprotection in a number of experimental nephropathies, i.e. anti-Thy1 mesangio-proliferative glomerulonephritis [15], chronic puromycin nephrosis [16], and streptozotocin-induced diabetic nephropathy [17], as well as in humans with diabetic nephropathy [18, 19, 20]. The observed anti-proteinuric effect of heparins has generally been associated with their well-known anti-mitogenic activity [21], but other mechanisms might also play a role: correction of balance between extracellular matrix synthesis and degradation, restoration of GBM permselectivity by modulation of composition and/or sulphation pattern of heparan sulphate proteoglycans, and inhibition of activated glomerular TGF-β axis [22].

We have previously shown that the long-term administration of the LMWH reviparin prevents development of chronic allograft nephropathy in rats that have received allogeneic transplants [23]. Both early and late-onset treatment effectively reduced proteinuria in kidney recipients, independent of any influence on blood pressure. Histologically, segmental glomerular sclerosis and thickening of glomerular basement membrane were markedly reduced by reviparin treatment. Those experimental data thus confirm the anti-proteinuric and nephroprotective effect of LMWH observed after human kidney transplantation. Although the underlying mechanisms need to be investigated in future studies, they are most probably related to the interaction of glycosaminoglycans with a broad spectrum of proinflammatory and fibrotic mediators [23].

In summary, the addition of a LMWH to pre-existing ACE inhibition resulted in marked and long-lasting reduction of nephrotic-range proteinuria following kidney transplantation in two patients. Our observation confirms the remarkable renoprotective potential of these drugs previously demonstrated in experimental nephropathies. This novel therapeutic approach should be further investigated in larger clinical trials.

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