

Special Article - Nephrology and Dialysis

Proteinuria and Everolimus. The Relevance of Knowing Urinary Sodium Excretion in a Kidney Transplant Patient

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Abstract

A sixty-four year old male with a seven-year history of kidney transplantation started with increasing amounts of proteinuria. His maintenance immunosuppression consisted on meprednisone 4 mg/day, sodium mycophenolate 720 mg/day and everolimus 1.5 mg/day for the last three years. Two years after being on this regime, he started to display increasing amounts of proteinuria and no hematuria, while his kidney function remained steady and his blood pressure was normal. A Doppler sonogram was normal; anti-HLA antibodies were negative and a kidney biopsy revealed mild mesangial expansion and 15% of interstitial fibrosis and tubular atrophy; C4d stain was negative. Twenty four urinary sodium was 385mEq/day. He was started on a 3 g sodium/day diet. Two months later urinary sodium excretion dropped to 77 mEq/day and proteinuria decreased from a maximum of 3.85 g/day to 0.7 g/day. At first glance, the initial approach to reduce proteinuria would have been to withdraw everolimus, as it is a well-known cause of proteinuria. This case report underscores the relevance sodium tubular reabsorption plays on proteinuria and on glomerular filtration, showing that urinary ionograms are mandatory when the assessment of proteinuria is undertaken. It also calls the attention of nephrologists to pursue proteinuria and to treat it accordingly in the transplant population, as it is a cardiovascular risk factor and a surrogate of chronic kidney disease and of kidney disease progression.

Keywords: Proteinuria; Everolimus; kidney transplantation; mTORi; Urinary sodium; Urinary ionogram

Case Presentation

A sixty-four male was started on chronic hemodialysis due to primary focal and segmental glomerulosclerosis. He had a past history of arterial and primary pulmonary hypertension, tobacco consumption and cocaine abuse. He was on bisoprolol 10 mg / day, enalapril 10 mg/day and sildenafil 100 mg/day. Average blood pressure control: 130/80 mmHg. Hepatitis B, hepatitis C and HIV serologies were negative. While on dialysis he withheld both toxic habits, confirmed repeatedly by toxicologic analyses. Five years afterwards he received a kidney graft from a 67 year-old male with mild hypertension. A kidney graft biopsy revealed mild mesangial matrix expansion and a mild interstitial fibrosis and tubular atrophy (5%). HLA mismatches: 1A, 1 B. Cold ischaemia was 12 hours. In the induction immunosuppressive regime basiliximab was employed; his initial maintenance therapy consisted on steroids 4 mg/day, sodium mycophenolate 1440 mg/day and tacrolimus 6 mg/day (trough levels between 4.7 and 8 ng/mL). Baseline creatinine 1.3mg/dL, proteinuria 0.4g/day. Ambulatory average blood pressure control: 120/70 mmHg. Two years later a second protocol kidney biopsy revealed no changes with respect to the previous ones. Tacrolimus was replaced by everolimus; serum creatinine 1.2 mg/dL, creatinine clearance 51 ml/min, albuminemia 4.1 g/day and proteinuria 0.8 g/day. Blood pressure control was 120/80 mmHg. The patient was in a steady state and normotensive with no oedema. During the last four years after the switching proteinuria began to increase in coincidence

with the creatinine clearance, while blood pressure registries were within normal limits (Table 1). At a proteinuria peak of 3.85 g/day a new kidney biopsy revealed mild mesangial expansion and 15% of interstitial fibrosis and tubular atrophy; C4d stain was negative. Anti-HLA antibodies were repeatedly negative. As mammalian Target of Rapamycin inhibitors (mTORi) are contraindicated when proteinuria is over 0.8 g/day, the next approach was to withdraw everolimus. However, a urinary ionogram revealed a 24-hour sodium urinary excretion of 370mEq/day, despite hyposodic diet counseling, which physicians assumed it had been followed by the patient. After a strict sodium hyposodic diet (< 3 g/day), the urinary sodium decreased in parallel with proteinuria (proteinuria was always determined by 24-hour collection); blood pressure remained normal (Table 1). Everolimus was not discontinued.

Table 1: Laboratory results.

	3 years post Tx	4 years post Tx	5 years post Tx	6 years post Tx	7 years post Tx	7 years post Tx; with low sodium diet
Creatinine mg/dL	1.3	1.27	1.23	1.27	1.4	1.4
Creatinine Clearance mL/minute	57	58	63	65	59	59
Urinary sodium mEq/day	65	83	NA	NA	370	77
Proteinuria g/day	0.40	0.45	1.44	1.9	3.85	0.7

Abbreviations: Tx: Transplantation.

Discussion

In kidney transplant patients, proteinuria is associated with renal damage and is a clinical predictor of graft loss, mortality and cardiovascular events [1-4]. Therefore, KDIGO guidelines suggest to measure proteinuria at least once in the first month posttransplant, every 3 months during the first year, and yearly thereafter [5]. At the first diagnosis of proteinuria of uncertain origin, a kidney biopsy is indicated. Unfortunately, evidence-based treatments of proteinuria in the transplant population are limited. The prevalence of proteinuria oscillates considerably between 7.5% and 45%, depending on the threshold employed to define it [6-19]. When the normal limit employed was similar to the one used in the general population (>150 mg/day) the prevalence reported was between 31% and 45% [7-9], while if proteinuria was defined when it was >1 g/day, the prevalence was lower, 19% [6,11-17]. Finally, when defined between 2-3 g/day, the prevalence lowered to 13% [6,18,19]. Regardless of the values under consideration, it is evident that proteinuria is a real, frequent and underestimated problem in the posttransplant period, with a similar prevalence to that reported in the predialysis period [20]. Finally, as remnant protein excretion during the dialysis period is generally ignored, proteinuria in a recent transplanted individual is even more difficult to interpret [21]. One of the main causes of drug-related proteinuria is the employment of mTORi, which can be used either as the *novo* agents with or without calcineurin inhibitors, or more commonly as a preventive switching or conversion strategy from calcineurin inhibitors to mTORi during the first year post transplantation to avoid cyclosporine or tacrolimus nephrotoxicity. The proteinuric proposed mechanisms are a decrease in Vascular Endothelial Growth Factor (VEGF) synthesis and an interference with the Transient Receptor Potential Cation channel 6 (TRPC6) podocyte protein, causing podocyte contraction and increased glomerular basement membrane permeability to proteins [22,23]. A proximal tubular inhibition of luminal albumin has also been reported. Regardless of the mechanism involved, when proteinuria is more than 0.8 g/day, it is generally recommended that either everolimus or rapamycin be discontinued [24,25]. However, in none of the studies in which proteinuria and mTORi were assessed, sodium excretion was taken into consideration [24,25].

In our patient, everolimus- a drug without other relevant nephrotoxic side effects besides proteinuria- ought to have been discontinued according to the accepted recommendations. This could have led to different scenarios: The possible reintroduction of tacrolimus, and its potential nephrotoxicity and shortening of the long-term graft survival; the immunosuppressant maintenance regime based on steroids and sodium mycophenolate alone, with the risk of acute rejection; the evaluation of rapamycin in replacement of everolimus, with an elevated risk of proteinuria relapse; or the introduction of belatacept, with not-yet assessed potential advantages in the switching strategy.

The urinary sodium excretion is a handful non-expensive exam that can add important information to the nephrologist. It offers a clue to diet compliance, which our patient did not comply and that our physicians had assumed the patient was following. A 3-gram daily hyposodic diet contains 51 mEq of sodium. In a compensated steady state, the daily urinary sodium excretion should be close to the

mentioned concentration intake. Our patient was excreting 370mEq/day, an equivalent to a 21.7 g of sodium daily load. Most of the filtered sodium is reabsorbed lumenally at the proximal convoluted tubule, while minor quantities are reabsorbed at the descending and ascending limbs of the loops of Henle and the distal convoluted tubule. The distal nephron is the place where the fine tuning of sodium takes place, mainly under the influence of aldosterone through active transport. Albeit proximal luminal sodium is reabsorbed passively, the driving force led by the basolateral cellular sodium reabsorption is undertaken by the sodium-potassium pump, which requires the consumption of ATP.

The relationship between urinary sodium and renal protein handling is straightforward, but it depends on the primary event, as two different scenarios exist. The first one is a primary podocyte insult, which derives in an increase in glomerular protein leakage and eventually in nephrotic syndrome, glomerular and interstitial sclerosis and chronic kidney disease. The luminal protein load that is incapable of being reabsorbed proximally due to the saturation of luminal receptors as megalin or cubilin, leads to a rise in proximal and distal tubular sodium and water reabsorption, in which ENaC and plasmin play a central role. Moreover, proteinuria itself upregulates ENaC activity and contributes to more volume expansion and salt retention [26,27]. The second mechanism, in which podocytes are damaged secondarily, - which our patient displayed- is due to a primary increased sodium load, which leads to sodium reabsorption by the stimulation of the proximal tubule NHE3 transporter. NHE3 is normally stimulated by luminal sodium, sympathetic activity, corticoids, angiotensin II and endothelin [28]. Angiotensin II causes vasoconstriction of both afferent and efferent arterioles, being its effect more potent in the latter. The resultant is an increase in volume expansion and in the filtration fraction, leading to glomerular hyperfiltration with an increased local protein trafficking, and functional and histologic damage as scarring, more protein leakage and proximal tubular reabsorption, mesangial inflammation, tubulointerstitial fibrosis, renal failure and hypertension [29]. This sodium reabsorption by NHE3 transporter is the driving force that determines the parallel proximal tubular endocytic reabsorption of albumin by megalin and cubilin [28]. The compensatory glomerular hyperfiltration per remaining nephron -augmented in the transplanted kidney- serves initially to maintain the glomerular filtration rate, which is accompanied by a parallel rise in glomerular volume that involves expansion of matrix components and an increase in the number of endothelial and mesangial cells, vascular damage, a decrease in nitric oxide secretion, glomerular hypertension, podocyte contraction and eventual detachment, leaving gaps in the glomerular basement membrane, adding another etiologic irreversible factor to proteinuria, fibrosis and progressive deterioration of renal function [29-31]. This situation, at least initially, appears to be independent of systemic hypertension. When the individual intake of sodium drops, less sodium is offered to the proximal tubule. Consequently, the NHE3 transporter action is decreased, leading to a lower reabsorption of sodium and water. As a result, the extracellular volume contracts. This decrease in total body water and sodium content leads to a decrease in hyperfiltration. Finally, as a consequence of a proximal tubule reduced sodium reabsorption and of glomerular hemodynamic normofiltration, the loss of proteins climbs down.

In summary, in this case we want to highlight the relevant role sodium chloride itself plays in the development of proteinuria. As proteinuria heralds kidney disease progression and is a marker of cardiovascular morbidity and mortality, salt intake is in the centre of the scene. The study of proteinuria should be adjusted not only to other clinical variables as blood pressure and renal function, but also to sodium chloride intake, which in turn can be easily and closely monitored employing urinary sodium excretion.

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