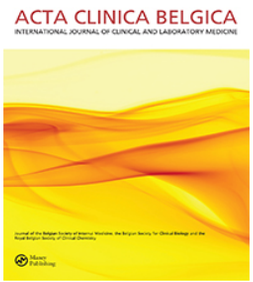
Taylor & Francis
Taylor & Francis Group



Acta Clinica Belgica
International Journal of Clinical and Laboratory Medicine

ISSN: 1784-3286 (Print) 2295-3337 (Online) Journal homepage: http://www.tandfonline.com/loi/yacb20

Electrolytes disturbances after kidney transplantation

Liesbeth De Waele, Pieter-Jan Van Gaal & Daniel Abramowicz

To cite this article: Liesbeth De Waele, Pieter-Jan Van Gaal & Daniel Abramowicz (2018): Electrolytes disturbances after kidney transplantation, Acta Clinica Belgica, DOI: 10.1080/17843286.2018.1549193

To link to this article: https://doi.org/10.1080/17843286.2018.1549193

Published online: 27 Nov 2018.

Submit your article to this journal

Article views: 1

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=yacb20

ACTA CLINICA BELGICA
https://doi.org/10.1080/17843286.2018.1549193

Taylor & Francis
Taylor & Francis Group

Check for updates

Electrolytes disturbances after kidney transplantation

Liesbeth De Waele[a], Pieter-Jan Van Gaal[b] and Daniel Abramowicz[c]

[a]Antwerp University Hospital, Antwerp; [b]ZNA Stuivenberg, Antwerp; [c]Antwerp University Hospital and University of Antwerp, Edegem

ABSTRACT

Objectives: Water and electrolytes disturbances often occur in renal transplant recipients. The objective is to describe the pathophysiology and the treatment of the most prevalent abnormalities.

Methods: We screened PubMed for the following words in various combination: kidney transplantation and (disturbances or abnormalities) of (electrolytes or sodium or potassium or phosphate or calcium or acid-base).

Results: We found abnormalities in all major electrolytes, as a consequence of tubular dysfunction caused by both rejection episodes and toxic effects of calcineurin inhibitors (CNIs; cyclosporine or tacrolimus). The renal tubular acidosis found in kidney transplant recipients is characterized by a normal anion gap and normal or high serum chloride levels. The incidence of hyperkalemia is 5–40% of patients treated with CNIs. The majority of kidney transplant recipients develop hypomagnesemia within the first weeks and months. Both cyclosporine and tacrolimus do induce hypomagnesemia by several mechanisms. Severe magnesium depletion may include clinical manifestations such as confusion, muscle weakness, tremor, dysphagia, tetany and convulsions. The immediate posttransplant period (first 3 months) is often accompanied by a decline in serum phosphate. Phosphate substitution is needed when serum levels fall below 0.5 mmol/l, or in patients with clinical symptoms and serum levels between 0.5 and 1.0 mmol/l. Hypercalcemia is also a common disorder in the chronic posttransplant phase, and is most often due to persistent hyperparathyroidism.

Conclusions: Patients with kidney transplants display electrolytes abnormalities more frequently than non-transplanted patients with the same levels of renal function. A good knowledge of their physiopathology and treatment is important in the care of those patients.

KEYWORDS
Kidney transplantation; potassium; calcium; magnesium; phosphate

Introduction

Kidney transplantation is the best strategy for patients who reach terminal renal failure. Each year, more than 400 kidney transplantations are performed in Belgium. It is thus likely that general practitioners and internal medicine physicians will come across one of those patients during their career.

Water and electrolyte abnormalities frequently occur in kidney transplant patients. They most commonly occur as consequence of tubular dysfunction caused by acute and/or chronic rejection, or by the direct toxic tubular effects of calcineurin inhibitors (CNIs; cyclosporine or tacrolimus). Although acute and/or chronic reduction in renal function is the most common and significant renal adverse effect induced by CNI, tubular dysfunctions are also described and are manifested by metabolic acidosis, magnesium loss, hyperkalemia, hypercalciuria, phosphate wasting and hyponatremia. In addition, failing grafts (eGFR <30 ml/min/1.73 m^2) are also susceptible to the electrolyte disturbances encountered with advanced renal failure.

Here, we describe the mechanisms and treatment of the most common electrolyte and acid–base disturbances observed after kidney transplantation.

Metabolic acidosis

There are three major types of renal tubular acidosis (RTA): type I, resulting from a defect in distal tubular acid excretion as a result of decreased H+ secretion or back leak of secreted hydrogen; Type II, resulting from proximal tubule HCO_3 wasting; and Type IV, resulting from decreased aldosterone action either due to a reduced hormone level or a functional resistance. Three major forms of distal RTA have been described in transplant recipients, the classic type Ia, the hyperkalemic type Ib (voltage-dependent) and a mixed form with additional bicarbonate wasting (type III) [1–4].

RTA is a common complication after kidney transplantation but information about its prevalence, clinical importance and risk factors in long-term allograft recipients is scarce. The form usually found in kidney transplant patients is characterized by a normal anion gap and normal or high serum chloride levels. RTA, especially in the early posttransplant period, is due to

CONTACT Daniel Abramowicz daniel.abramowicz@gmail.com; erik.snelders@uza.be Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem.
© 2018 Acta Clinica Belgica

suboptimal allograft function, CNI nephrotoxicity, acute rejection or ischemic tubular dysfunction [5–7]. Description of the incidence and prevalence of the different subtypes is still uncertain and needs further research (see below). Among all the immunosuppressive drugs, CNIs are considered to be the main contributors to RTA in kidney transplant recipients. Indeed, no study has reported on the involvement of the other immunosuppressive drugs in causing RTA, except for some cases of metabolic acidosis owing to diarrhea-associated intestinal bicarbonate loss secondary to mycophenolate toxicity [6].

CNIs might induce functional tubular damage, which is responsible for the occurrence of disturbances of the electrolyte tubular transport, including RTA. Watanabe et al. [8] demonstrated that cyclosporine induces RTA by blocking the peptidyl prolyl cis-trans isomerase activity, through a specific cyclophilin-dependent mechanism, but not involving calcineurin inhibition. Mohebbi et al. [9] demonstrated that tacrolimus may affect several major transport proteins involved in the renal control of acid–base balance, such as H+-ATPase transport protein and AE1 (anion exchanger).

While type I RTA has been most frequently reported, types II and IV have also been observed. For instance, type II RTA seems to prevail during the early course posttransplantation (first 6 months). This form of RTA is characterized by bicarbonate wasting due to the toxic effects of CNIs or persistent hyperparathyroidism [10,11]. As the tubular damage recovers and hyperparathyroidism resolves, proximal RTA improves [1,11]. In addition, the high doses of CNI used in the early period may lead to type IV RTA. The mechanism behind this CNI effect is the suppression of renin–angiotensin–aldosterone axis [5].

In the long-term, distal type I RTA seems to be more prevalent due to chronic CNI nephrotoxicity or to chronic transplant rejection [1]. In addition, acute transplant rejection seems to have an influence on the subtype of RTA present posttransplantation [1]. The number of acute rejections was significantly higher in type I RTA.

The evidence supporting the beneficial effects of correcting acidosis has been described in all chronic kidney disease stages except in kidney transplant patients [12,13].

Most data indicate that the RTA-inducing effects of CNI are dependent on the drug dose, because a reduction of the dosage has been reported to be often associated with a recovery of the RTA [14,15]. There is some evidence that RTA is more frequent in patients on tacrolimus than on cyclosporin treatment [1,16]. RTA seen in kidney transplant recipients receiving CNI is often associated with high potassium serum levels. The presence of this association can be useful not only for a correct diagnosis but also for a proper correction of the metabolic acidosis [6].

Hyperkalemia

The incidence of hyperkalemia is 5–40% of the patients treated with CNIs [17]. CNIs impair renal potassium excretion through different mechanisms. First, they decrease the activity of the renin–angiotensin–aldosterone system due to a tubular insensitivity to aldosterone [18]. Second, CNI can act through direct inhibition of ROMK (the renal outer medullary K^+ channel), Na-K ATPaseand direct activation of chloride shunt mechanism [19].

In patients treated with a beta-blocker, cyclosporine may exert a secondary effect on potassium homeostasis. In these patients, transient hyperkalemia may occur as a result of increasing potassium efflux from the intracellular to the extracellular fluid space through an as yet undefined mechanism [20].

The potassium level is most often only slightly elevated (around 5.5 mmol/l), and rarely requires treatment [17].

Hypomagnesemia

Data on the incidence of hypomagnesemia after transplantation are limited, although the majority of kidney transplant recipients seem to develop hypomagnesemia within the first weeks and month posttransplantation. Both cyclosporine and tacrolimus do induce hypomagnesemia [21–24]. CNIs induce a downregulation of the renal expression of epidermal growth factor and the distal magnesium absorber Transient Receptor Potential Melastatin 6 in the distal collecting tubule [23–25]. This leads to renal magnesium wasting associated with an increased absolute and fractional urinary excretion of magnesium.

In more than 20% of the kidney transplant patients, the hypomagnesemia persists for many years after transplantation [26,27]. However, CNIs-induced hypomagnesemia is often asymptomatic. Severe magnesium depletion in this setting is rare but has been reported and may include clinical manifestations such as confusion, muscle weakness, tremor, dysphagia, tetany and convulsions [28–30]. Studies by Van Laecke et al. [30] and Tin et al. [31] suggest a possible role of magnesium deficiency in graft dysfunction.

Hypophosphatemia

The immediate posttransplant period (first 3 months) is often accompanied by a decline in serum phosphate. In a study by Evenepoel et al., 90% of patients experience a temporary hypophosphatemia (defined as serum phosphate ≤2.3 mg/dl [≤0.74 mmol/l]). Mild-to-moderate hypophosphatemia (serum phosphate >1.5 and

≤2.3 mg/dl [>0.48 and ≤0.74 mmol/l]) was seen in 24% of the patients and severe hypophosphatemia (serum phosphate ≤1.5 mg/dl [≤0.48 mmol/l]) was encountered in 66% of patients [32]. This is due to the fact that when a patient undergoes transplantation, he/she is still under the influence of an hormonal 'phosphaturic climate' (high levels of serum phosphate, PTH and FGF-23 and low levels of 1,25-dihydroxyvitamin D), causing renal phosphate wasting. Furthermore, Cyclosporine has been shown to cause a decrease in fractional tubular phosphate reabsorption. Although the exact mechanism is not known, in the rat, cyclosporine inhibits the proximal tubular brush border membrane Na/Pi cotransport activity [33]. A study by Falkiewicz et al. showed a faster recovery of impaired phosphate reabsorption by the proximal tubule in patients treated with tacrolimus compared to cyclosporine [34].

Because of the rapid changes in serum phosphate after kidney transplantation, KDIGO (Kidney Disease Improving Global Outcomes)guidelines recommend to measure serum calcium and phosphate levels at least weekly, until stabilization [35]. In patients with moderate hypophosphatemia (0.5–1.0 mmol/l), substitution of phosphate, either orally or parenterally, is generally not necessary. Substitution of phosphate may even lead to nephrocalcinosis in the kidney allograft [36,37]. We suggest phosphate substitution should only be considered when serum levels fall below 0.5 mmol/l, or in patients with clinical symptoms and serum levels between 0.5 and 1.0 mmol/l.

Hyperphosphatemia

In case of impaired graft function, hyperphosphatemia might recur, which needs dietary and/or pharmacological interventions. KDIGO guidelines suggest to manage these abnormalities as for patients with CKD G3a–G5 without kidney transplantation [35]. It should be taken into account that the phosphate binder sevelamer has been shown to reduce the peak plasma concentration and area under the curve of mycophenolate mofetil reflecting interference with its gastrointestinal uptake [38]. Because of this, phosphate binders should be used with caution in patients taking immunosuppressive drugs, including renal transplant recipients.

Hypocalcemia

A decline in serum calcium levels may be seen in the immediate posttransplant period. A study by Nobata et al. shows an average drop in serum calcium of 7%, mainly due to a temporary increase in urinary calcium excretion [39]. Other possible reasons for this immediate drop in serum calcium levels are the abrupt discontinuation of calcium-containing phosphate binders and active vitamin D supplements, as well as glucocorticoid-induced calcium loss. Along this line, CNIs also induce osteopenia and bone loss by accelerating bone remodeling [40]. Furthermore, Yang et al. [41] and Steiner et al. [42] demonstrated a decreased renal calbindin – D28K expression (a vitamin D-dependent calcium binding protein) in the kidneys of cyclosporine-treated rats, which was accompanied by a significant decrease in serum calcium concentration and an increase in urinary calcium excretion.

A few studies show that tacrolimus has a more favorable bone protective profile than cyclosporine, most probably indirectly related to their steroid-sparing effect [43,44].

Finally, the presence of metabolic acidosis (as seen further) can also result in hypercalciuria.

Hypercalcemia

Despite the higher mentioned early drop in serum calcium, hypercalcemia is also a common disorder in the chronic posttransplant phase. In a Canadian cohort, hypercalcemia (defined as a serum calcium >2.60 mmol/l) was seen in 16%, 13%, 10% and 10% of patients at 12, 24, 36 and 48 months after successful transplantation, respectively [45]. Of the patients with hypercalcemia, >90% had parathyroid hormone (PTH) levels above the upper limit of normal (ULN), and >75% had PTH levels >2× ULN [45]. One of the most important determinants of posttransplantation hyperparathyroidism is the pre-transplantation PTH level, especially in patients with good graft function [parathyroid]. Thus, hypercalcemia is mainly due to secondary hyperparathyroidism persisting after transplantation (tertiary hyperparathyroidism).

Initially, in case of asymptomatic, mild hypercalcemia, watchful waiting is an option, mainly in the first year after transplantation. In case of severe, persistent or symptomatic hypercalcemia, treatment options are calcimimetics (cinacalcet) or parathyroidectomy (subtotal vs. total with or without autotransplantation) [47]. Bisphosphonates, used in the classical treatment of hypercalcemia, is not a preferred choice in renal transplant recipients, as it may lead to adynamic bone disease despite preservation of bone mineral density [48]. A systematic review and meta-analysis demonstrated that the use of cinacalcet appeared to be safe and effective for treatment of posttransplant hyperparathyroidism [49]. Parathyroidectomy is a very efficient treatment to correct hypercalcemia and treat hyperparathyroidism. A retrospective review demonstrated that near total parathyroidectomy leads to resolution of hypercalcemia in 97% of patients at a median follow-up of 3 years. In 80% of patients, PTH levels fell to <250 pg/ml [50]. Optimal timing of parathyroidectomy is a matter of discussion. Some centers opt to perform a parathyroidectomy during the time on the waiting list in patients with pre-transplant hypercalcemia or severe secondary hyperparathyroidism.

Hyponatremia

Kidney transplant patients are predisposed to develop hyponatremia since they are exposed to immunologic, infectious and pharmacologic changes, the combination of which alters their salt and water homeostasis. Studies have suggested that cyclosporine reduces proximal tubular sodium reabsorption by decreasing sodium–hydrogen exchanger activity, which is responsible for reabsorbing 30–60% of the filtered sodium [51].

Tacrolimus alters distal tubular sodium handling by inducing aldosterone resistance, thereby causing a salt-losing nephropathy [52–56]. This explains why hyponatremia appears to be more common under tacrolimus than cyclosporine therapy. Furthermore, it explains the ineffectiveness of fludrocortisone for treating tacrolimus-induced hyponatremia [51,52,57].

Conclusions

Patients with kidney transplants display electrolyte abnormalities more frequently than non-transplanted patients at the same levels of renal function. This is due to the specific consequences of tubular dysfunctions caused by either rejection episodes or the use of CNIs. A good knowledge of their physiopathology and treatment is important in the care of those patients.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Daniel Abramowicz http://orcid.org/0000-0002-6556-9199

References

[1] Schwarz C, Benesch T, Kodras K, et al. Complete renal tubular acidosis late after kidney transplantation. Nephrol Dial Transplant. 2006;21:2615–2620.
[2] Heering PJ, Kurschat C, Vo DT, et al. Aldosterone resistance in kidney transplantation is in part induced by a down-regulation of mineralocorticoid receptor expression. Clin Transplant. 2004;18:186–192.
[3] Wilson DR, Siddiqui AA. Renal tubular acidosis after kidney transplantation. Natural history and significance. Ann Intern Med. 1973;79:352–361.
[4] Rodriguez Soriano J. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol. 2002;13:2160–2170.
[5] Kenan K, Ramazan O, Sule S, et al. Renal tubular acidosis after kidney transplantation incidence, risk factors and clinical implications. Nephrol Dial Transplant. 2007;22:906–910.
[6] Messa PG, Alfieri C, Vettoretti S. Metabolic acidosis in renal transplantation: neglected but of potential clinical relevance. Nephrol Dialysis Transplantation. 2016;31(5):730–736.
[7] Yakupoglu HY, Corsenca A, Wahl P, et al. Posttransplant acidosis and associated disorders of mineral metabolism in patients with renal graft. Transplantation. 1997;84:1151–1157.
[8] Watanabe S, Tsuruoka S, Vijayakumar S, et al. Cyclosporin A produces distal renal tubular acidosis by blocking peptidyl prolyl cis-trans isomerase activity of cyclophilin. Am J Physiol Renal Physiol. 2005;288:40–47.
[9] Mohebbi N, Mihailova M, Wagner CA. The calcineurin inhibitor FK506 (tacrolimus) is associated with transient metabolic acidosis and altered expression of renal acid–base transport proteins. Am J Physiol Renal Physiol. 2009;297:499–509.
[10] Bank N, Aynediian HS. A micropuncture study of the effect of parathyroid hormone on renal bicarbonate reabsorption. J Clin Invest. 1976;58:336–344.
[11] Better OS. Tubular dysfunction following kidney transplantation. Nephron. 1980;25:209–213.
[12] Kovesdy CP. Metabolic acidosis and kidney disease: does bicarbonate therapy slow the progression of CKD? Nephrol Dial Transplant. 2012;27:3056–3062.
[13] De Brito-Ashurst I, Varagunam M, Raftery MJ, et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol. 2009;20:2075–2084.
[14] Kocyigit I, Unal A, Kavuncuoglu F, et al. Renal tubular acidosis in renal transplantation recipients. Ren Fail. 2010;32:687–690.
[15] Stahl RA, Kanz L, Maier B, et al. Hyperchloremic metabolic acidosis with high serum potassium in renal transplant recipients: a cyclosporine A associated side effect. Clin Nephrol. 1986;25:245–248.
[16] Keven K, Ozturk R, Sengul S, et al. Renal tubular acidosis after kidney trans- plantation: incidence, risk factors and clinical implications. Nephrol Dial Transplant. 2007;22:906–910.
[17] Kaplan B, Wang Z, Abecassis MM, et al. Frequency of hyperkalemia in recipients of simultaneous pancreas and kidney transplants with bladder drainage. Transplantation. 1996;62:1174–1175.
[18] Kamel KS, Jh E, Quaggin S. Studies to determine the basis of hyperkalemia in recipient of renal transplant treated with cyclosporine. J Am Soc Nephrol. 1991;2:1279–1284.
[19] Chang HL, Electrolyte G-HK. Acid-nase disturbances induced by calcineurin inhibitors. Electrolyte Blood Press. 2007;5(2):126–130.
[20] York P, Richardson R, Greenwood C, et al. Extrarenal effect of cyclosporine A on potassium homeostasis in renal transplant recipients. Am J Kidney Dis. 1993;2:314–319.
[21] Ch B, Nd V, Dc M, et al. Hypomagnesemia and renal magnesium wasting in renal transplant recipients receiving cyclosporine. Am J Med. 1987;83 (4):693–699.
[22] Sd N, Sankarasubbaiyan S, Gros S, et al. Tacrolimus-associated hypomagnesemia in renal transplant recipients. Transplant Proc. 2006;38 (5):1320–1322.
[23] Van Laecke S, Van Biesen W. Hypomagnesemia in kidney transplantation. Transplantation Rev. 2015;29:154–160.
[24] Ledeganck KJ, De Winter BY, Van Den Driessche A, et al. Magnesium loss in cyclosporine-treated patients is related to renal epidermal growth factor

downregulation. Nephrol Dial Transplant. 2014;29:1097–1102.
[25] Nijenhuis T, Hoenderop JGJ, Bindels RJM. Downregulation of Ca2+ and Mg2+ transport proteins in the kidney explains tacrolimus (FK506)-induced hypercalciuria and hypomagnesemia. J Am Soc Nephrol. 2004;15:549–557.
[26] Vannini SD, Mazzola BL, Rodoni L, et al. Permanently reduced plasma ionized magnesium among renal transplant recipients on cyclosporine. Transpl Int. 1999;12:244–249.
[27] Van de Cauter J, Sennesael J, Haentjens P. Long term-evolution of the mineral metabolism after renal transplantation: a prospective, single-center cohort study. Transplant Proc. 2011;43:3470–3475.
[28] Atsmon J, Dolev E. Drug-induced hypomagnesaemia: scope and management. Drug Saf. 2005;28:763–788.
[29] Agus ZS. Hypomagnesemia. J Am Soc Nephrol. 1999 (10):1616–1622.
[30] Van Laecke S, Nagler EV, Verbeke F, et al. Hypomagnesemia and the risk of death and GFR decline in chronic kidney disease. Am J Med. 2013;126:825–831.
[31] Tin A, Grams ME, Maruthur NM, et al. Results from the Atherosclerosis Risk in Communities study suggest that low serum magnesium is associated with incident kidney disease. Kidney Int. 2015;87:820–827.
[32] Evenepoel P, Naesens M, Claes K, et al. 'hyperphosphatoninism' accentuates hypophosphatemia and suppresses calcitriol levels in renal transplant recipients. Am J Transplant. 2007;7(5):1193–1200.
[33] Demeule M, Béliveau R. Cyclosporin inhibits phosphate transport and stimulates alkaline phosphatase activity in renal BBMV. A J Physiol. 1991;260:518–524.
[34] Falkiewicz K, Kamińska D, Nahaczewska W, et al. Renal function and tubular phosphate handling in long-term cyclosporine- and tacrolimus-based immunosuppression in kidney transplantation. Transplant Proc. 2006;38:119–122.
[35] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017;7(1):1–59.
[36] Sakhaee K. Post-renal transplantation hypophosphatemia. Pediatr Nephrol. 2010;25 (2):213–220.
[37] Singh N, Qadir M. Do no harm: calcium and phosphate supplementation in kidney transplant recipients. Transplantation. 2013;96(11):e81–82.
[38] Pieper AK, Buhle F, Bauer S, et al. The effect of sevelamer on the pharmacokinetics of cyclosporin A and mycophenolate mofetil after renal transplantation. Nephrol Dial Transplant. 2004;19(10):2630–2633.
[39] Nobata H, Tominaga Y, Imai H, et al. Hypocalcemia immediately after renal transplantation. Clin Transplant. 2013;27(6):644–648.
[40] Epstein S. Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. J Bone Miner Res. 1996;11:1–7.
[41] Yang CW, Kim J, Kim YH, et al. Inhibition of calbindin D28K expression by cyclosporin A in rat kidney: the possible pathogenesis of cyclosproin A-induced hypercalciuria. J Am Soc Nephrol. 1998;9:1416.
[42] Steiner S, Aicher L, Raymackers J, et al. Cyclosporine A decreases the protein level of the calcium-binding protein calbindin-D 28 kDa in rat kidney. Biochem Pharmacol. 1996;51:253.
[43] Goffin E, Devogelaer JP, Lalaoui A, et al. Tacrolimus and low-dose steroid immunosuppression preserves bone mass after renal transplantation. Transpl Int. 2002;15:73–80.
[44] Goffin E, Devogelaer JP, Depresseux G, et al. Evaluation of bone mineral density after renal transplantation under a tacrolimus based immunosuppression: A pilot study. Clin Nephrol. 2003;59:190–195.
[45] Muirhead N, Zaltman JS, Gill JS, et al. Hypercalcemia in renal transplant patients: prevalence and management in Canadian transplant practice. Clin Transplant. 2014;28(2):161–165.
[46] Torres A, Rodríguez AP, Concepción MT, et al. Parathyroid function in long-term renal transplant patients: importance of pre-transplant PTH concentrations. Nephrol Dial Transplant. 1998;13 (Suppl 3):94–97
[47] Torregrosa JV, Barros X. Management of hypercalcemia after renal transplantation. Nefrologia. 2013;33 (6):751–757.
[48] Coco M, Glicklich D, Faugere MC, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. J Am Soc Nephrol. 2003;14(10):2669–2676.
[49] Cohen JB, Gordon CE, Balk EM, et al. Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients: a systematic review and meta-analysis. Transplantation. 2012;94(10):1041–1048.
[50] Dewberry LK, Weber C, Sharma J. Near total parathyroidectomy is effective therapy for tertiary hyperparathyroidism. Am Surg. 2014;80(7):646–651.
[51] Musso CG, Castaneda A, Giordani M, et al. Hyponatremia in kidney transplant patients: its pathophysiologic mechanisms. CKJ. 2018;11 (4):581–585.
[52] Bagchi S, Husain Zaidi S, Prasad Mathur R. Severe symptomatic hyponatremia-an uncommon presentation of tacrolimus nephrotoxicity. Nephrol Dial Transplant. 2011;26:2042–2044.
[53] Burdmann EA, Bennett WM. Nephrotoxicity of calcineurin and mTOR inhibitors. In: De Broe M, Porter G, Bennett Weditors. Clinical nephrotoxins. Renal injury from drugs and chemicals. New York: Springer; 2008. p. 617–682.
[54] Bressler RB, Huston DP. Water intoxication following moderate-dose intravenous cyclophosphamide. Arch Intern Med. 1985;145:548–549.
[55] Musso CG, Navarro M, Mombelli C, et al. Furosemide test in stage III-chronic kidney disease and kidney transplant patients on tacrolimus. Int Urol Nephrol. 2013;45:1471–1474.
[56] Einollahi B, Nemati E, Rostami Z, et al. Electrolytes disturb- ance and cyclosporine blood levels among kidney transplant recipients. Int J Organ Transplant Med. 2012;3:166–175.
[57] Higgins R, Ramaiyan K, Dasgupta T, et al. Hyponatraemia and hyperkalaemia are more frequent in renal transplant recipients treated with tacrolimus than with cyclosporin. Further evidence for differences between cyclosporin and tacrolimus nephrotoxicities. Nephrol Dial Transplant. 2004;19:444–450.