



CKJ REVIEW

Hyponatremia in kidney transplant patients: its pathophysiologic mechanisms

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ABSTRACT

Kidney transplant patients (KTPs), and particularly those with advanced chronic kidney rejection, may be affected by opportunistic infections, metabolic alterations and vascular and oncologic diseases that promote clinical conditions that require a variety of treatments, the combinations of which may predispose them to hyponatremia. Salt and water imbalance can induce abnormalities in volemia and/or serum sodium depending on the nature of this alteration (increase or decrease), its absolute magnitude (mild or severe) and its relative magnitude (body sodium:water ratio). Hyponatremia appears when the body sodium:water ratio is reduced due to an increase in body water or a reduction in body sodium. Additionally, hyponatremia is classified as normotonic, hypertonic and hypotonic and while hypotonic hyponatremia is classified in hyponatremia with normal, high or low extracellular fluid. The main causes of hyponatremia in KTPs are hypotonic hyponatremia secondary to water and salt contraction with oral hydration (gastroenteritis, sepsis), free water retention (severe renal failure, syndrome of inappropriate antidiuretic hormone release, hypothyroidism), chronic hypokalemia (rapamycin, malnutrition), sodium loss (tubular dysfunction secondary to nephrocalcinosis, acute tubular necrosis, tubulitis/rejection, interstitial nephritis, adrenal insufficiency, aldosterone resistance, pancreatic drainage, kidney-pancreas transplant) and hyponatremia induced by medication (opioids, cyclophosphamide, psychoactive, potent diuretics and calcineurinic inhibitors). In conclusion, KTPs are predisposed to develop hyponatremia since they are exposed to immunologic, infectious, pharmacologic and oncologic disorders, the combinations of which alter their salt and water homeostatic capacity.

Keywords: hyponatremia, immunosuppressant, kidney transplant, low serum sodium, pathophysiology

INTRODUCTION

Renal transplantation is currently the most effective treatment for patients with end-stage renal disease [1]. However, this group of patients, and particularly those with advanced chronic kidney rejection, are sometimes affected by opportunistic infections, metabolic alterations and vascular and oncologic diseases that require

treatments, the combination of which predisposes them to hyponatremia [2]. Hyponatremia is considered an important risk factor for high morbidity and mortality because it can decrease brain function, compromise cardiac contractility, increase insulin resistance and induce neuromuscular dysfunction. Han et al. [3] documented that hyponatremia is related in kidney transplant patients (KTPs) to overall mortality and graft loss, although it had

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Table 1. Mechanisms of hyponatremia in kidney transplant, their prevalence and clinical relevance

Hyponatremia	Prevalence	Clinical relevance	Treatment
Normotonic	–	–	–
Intravenous immunoglobulin	High	Low	Resolves after stopping drug
Hypertonic	–	–	–
Hyperglycemia	High	Low	Glycemic control
Hypotonic with low ECF	–	–	–
Renal sodium loss (rejection, diuretics)	High	High	Sodium replacement and treat cause
Extrarenal sodium loss (diarrhea)	High	High	Sodium replacement and treat cause
Adrenal insufficiency	High	High	Hormone replacement
Immunosuppressant drugs	High	Low	Fludrocortisone
Hypotonic with high ECF	–	–	–
Heart failure	Low	High	Salt and water restriction/diuretics
Cirrhosis	Low	High	Salt and water restriction/diuretics
Nephrotic syndrome	High	High	Salt and water restriction/diuretics/treat cause
Renal insufficiency	High	High	Salt and water restriction/diuretics/dialysis treat cause
Hypotonic with normal ECF	–	–	–
SIADH	High	High	Water restriction/diuretics
Hypothyroidism	Low	Low	Hormone replacement
Glucocorticoid deficiency	Low	High	Hormone replacement
Psychoactive drugs	High	Low	Replace drug

no correlation with acute rejection. Thus serum sodium should be monitored posttransplant in order to prepare physicians for potentially poorer outcomes. Moreover, pediatric kidney transplant recipients are at a significantly higher risk than adults for developing hyponatremic encephalopathy and death associated with serum sodium levels ≤ 120 mmol/L, thus meticulous postoperative fluid management is exceptionally important to minimize the risk of neurologic complications in this population [4]. Salt and water imbalance can induce abnormalities in volemia and/or serum sodium depending on the nature of this alteration, its absolute magnitude and how they alter the relative body sodium:water ratio [5]. It is known that significant salt and water depletion may generate real hypovolemia, and if this depletion involves a loss of salt in excess of water it may generate hyponatremia [3]. Also, salt and water retention induces an increase in extracellular fluid (ECF) that, depending on its pathophysiologic mechanism, may occur with hypervolemia and edema (e.g. hyponatremia in immediate posttransplant anuric patient) or effective arterial hypovolemia and edema (hyponatremia in a KTP suffering from cirrhosis secondary to hepatitis C virus or hyponatremia secondary to posttransplant nephrotic syndrome most frequently induced by focal and segmental glomerular sclerosis or membranoproliferative glomerulonephritis) [5, 6]. The sodium:water ratio can also be modified by body potassium content since its intracellular depletion induces low serum sodium levels by at least two mechanisms [5]: a shift of sodium to the intracellular compartment and by inappropriate antidiuretic hormone release.

This concept is summarized by the Edelman equation [5]: serum sodium = body (exchangeable) sodium + body (exchangeable) potassium/total body water. For instance, hyponatremia secondary to hypokalemia in KTPs on rapamycin, loop diuretics (e.g. furosemide) or suffering from renal tubular acidosis (primary or secondary to graft rejection) [7–12]. Additionally, two infrequent causes of hyponatremia in KTPs should be mentioned: first, a low serum sodium level due to excessive water intake (>14 L/day), which overcomes the free water excretion capacity of the kidneys and characteristically occurs with suppressed antidiuretic hormone and low osmolar urine [1, 5]; second, a reset osmostat hyponatremia, which can be observed in malnourished chronically ill KTPs

[5]. Based on the above-mentioned pathophysiological mechanisms, hyponatremia is currently classified depending on the patient's plasma tonicity level as hypertonic, normotonic or hypotonic hyponatremia. In addition, hypotonic hyponatremia is classified depending on the patient's ECF status as low, normal or high ECF [5]. It is worth mentioning that hyponatremia in KTPs usually results from a combination of hyponatremia-inducing mechanisms. All the hyponatremia-inducing mechanisms in KTPs that are described here are summarized in Table 1 along with their prevalence and clinical significance [3, 4, 7, 10–12].

HYPONATREMIA

Normotonic hyponatremia

Normotonic hyponatremia is an artifact due to an increase in the solid fraction of plasma, which can be documented in KTPs who received intravenous (IV) immunoglobulin (hypersensitive patients) or in those who have severe hypergammaglobulinemia secondary to hepatitis C [13–19]. It is worth mentioning that it is important to identify pseudohyponatremia because treating this entity as hypotonic hyponatremia may lead to dehydration [16, 17]; a direct ion-sensitive electrode potentiometry-based estimation can avoid this mistake [20].

Hypertonic hyponatremia

Hyperglycemia increases extracellular tonicity and extracts free water out of the intracellular compartment, diluting the extracellular compartment and consequently inducing hyponatremia [3]. Thus this sort of hyponatremia can be observed in a setting of drug-induced diabetes mellitus decompensation (high doses of methylprednisolone, high serum levels of calcineurinic inhibitors or a combination of both drugs), sepsis in kidney transplant diabetic patients (predisposed by immunosuppressant treatment) or pancreas graft rejection in kidney-pancreas transplant patients [20–22]. Additionally, even though hyponatremia induced by IV immunoglobulin has been interpreted as a pseudohyponatremia, other reports have documented that this

therapy can result in true hyponatremia, resulting from sucrose-induced translocation of water from the intracellular compartment to the extracellular compartment, as well as a large volume of hypotonic fluid in patients who have altered urinary free water excretion [14].

Hypotonic hyponatremia

Hypotonic hyponatremia can be induced by an excess of water, impaired free water urine excretion because of reduced fluid delivery (heart failure) to the thick ascending limb of the loop of Henle (TALH), altered TALH segment function (tubular necrosis or inflammation), inappropriate or appropriate antidiuretic hormone release or a combination of these [5]. Thus patients with lung (pneumonia, etc.), cardiac (cardiac failure), kidney (renal insufficiency), hepatic (cirrhosis), endocrine (hypothyroidism, adrenal insufficiency) and encephalic diseases [psychiatric disorders, syndrome of inappropriate antidiuretic hormone release (SIADH), cerebral salt wasting syndrome] can develop hypotonic hyponatremia [5].

Normal ECF hyponatremia. *SIADH.* SIADH is a condition induced by inappropriate free water retention because of inappropriate antidiuretic hormone release or an excessive response of vasopressin receptors in the distal tubules in a setting of normal glomerular filtration rate, thyroid and adrenal function and no hyponatremia-inducing medication [5]. SIADH has been described in this population as secondary to infection (tuberculosis, etc.), mainly in the central nervous system (cerebral nocardiosis, etc.) [23–25]. Other mechanisms of hyponatremia with normal ECF that should be taken into account in this population are hypothyroidism-induced hyponatremia and glucocorticoid deficiency-induced hyponatremia

Hypothyroidism-induced hyponatremia. Hypothyroidism can induce low serum sodium levels by different mechanisms: renal hypoperfusion due to heart failure, inappropriate vasopressin secretion and high sodium loss in urine [26–32]. It is worth mentioning that it should be ruled out in persistently hyponatremic-immunosuppressed individuals the presence of a hypothyroidism secondary to a decrease in hypothalamic thyrotropin-releasing hormone (TRH) induced by a masked wasting syndrome [32, 33].

Glucocorticoid deficiency-induced hyponatremia. Cortisol exerts a negative effect on antidiuretic hormone secretion, thus a cortisol deficit can promote inappropriate antidiuretic hormone release, in turn increasing the risk of developing hyponatremia [5]. The isolated cortisol deficit can be induced by any glucocorticoid axis damage [34].

Low ECF hyponatremia. Hypovolemia may induce low serum sodium levels by stimulating nonosmotic antidiuretic hormone release in a setting of adequate or excessive oral water intake [5]. Sodium losses lead to volume depletion inducing adequate antidiuretic hormone secretion. Thus low serum sodium level is promoted by two mechanisms: sodium loss and water retention. Moreover, sodium loss is worsened when there is reduced renin-angiotensin-aldosterone system (RAAS) activity (e.g. tubular damage or adrenal failure) [5].

Pancreatic sodium loss. Low ECF hyponatremia is common in pancreas-kidney transplant patients and is usually attributed to sodium loss in the pancreatic exocrine secretion drained in the bladder [21]. Genitourinary tract (GT) drainage compared with the

alternatives (pancreatic duct ligation or enteric drainage) is less prone to develop pancreatitis or microbial contamination, respectively, and also provides the opportunity to monitor urine pH and amylase levels for detecting pancreas rejection. However, GT drainage may induce cystitis, balanitis and/or hyperchloremic metabolic acidosis and hyponatremia secondary to increased sodium bicarbonate urinary loss [21, 22, 35]. At least two pathophysiologic mechanisms have been postulated for this sort of hyponatremia: total body sodium depletion through urinary volume and altered free water clearance secondary to renal failure. In this setting, hyponatremia usually gets worst if the kidney is simultaneously suffering from tubular damage (necrosis, rejection, etc.) and therefore is unable to maximally conserve sodium [22].

Massive posttransplant polyuria. Polyuria after kidney transplantation is not a rare condition, but massive polyuria is not common [34]. This entity can lead to significant sodium wasting and consequently to hyponatremia, and eventually to cerebral edema and seizure activity [26]. This sodium loss is secondary to tubular dysfunction induced by hypoxic-ischemic graft injury and aldosterone resistance in a context of a rapid normalization of the glomerular filtration rate [26, 36]. In these cases, the high fractional excretion of sodium reported in the graft urine is characteristically associated with ischemic changes on the graft biopsy [26].

Sodium-losing nephropathy. Altered tubular function in the transplanted kidney is common (more so in cadaveric donors than in living donors) and most is ascribed to tubular necrosis or graft rejection; this can improve if the acute process resolves. Other proposed pathophysiologic mechanisms are the presence of RAAS resistance, graft nephrocalcinosis (tubular necrosis or rejection) or a carryover effect of pre-transplantation ‘third factor’. Sodium-losing nephropathy is characterized by severe sodium loss (fractional excretion of sodium ~38%) with nonoliguric (neither polyuric) renal failure that responds to large amounts of normal saline and a high sodium diet but not to mineralocorticoid therapy [36].

Fanconi syndrome (FS). FS is another source of urine sodium loss inducing hyponatremia. FS can appear in children or adult transplant patients who have received a cadaveric or living donor kidney. FS can be induced by hyperparathyroidism, tubular disease or rejection [8, 9, 37–41].

Adrenal insufficiency. The hypothalamic-pituitary-adrenal axis (HPAA) can be activated by severe illness and trauma, since HPAA controls the maintenance of homeostasis and general adaptation to stress by increasing corticotropin and cortisol serum concentrations. However, in KTPs on chronic corticoid therapy, adrenal gland function is suppressed due to exogenous steroids and cannot resume steroid synthesis. Thus, relative adrenal insufficiency must be considered in patients who have received prolonged glucocorticoid therapy and have symptoms such as hypotension and/or hyponatremia, even in the context of normal serum cortisol levels, since they can be relatively low [42, 43].

High ECF hyponatremia. This condition is observed in KTPs when they are suffering from severe edematous status, which could be secondary to nephrotic syndrome, and renal, heart or liver failure. In these settings of effective hypovolemia, low

Table 2. Hyponatremia-inducing mechanisms secondary to drugs

Salt wasting	Water retention	Undefined mechanism
a. Tubular toxicity (tacrolimus, cyclosporine)	a. Severe renal insufficiency (tacrolimus, cyclosporine)	a. Amphotericine B, pentamidine
b. Interstitial nephritis (trimethoprim, loop diuretics, thiazide)	b. Cortisol deficiency (rifampicin, ketoconazol)	
	c. SIADH effect (opioids, antidepressants, cyclophosphamide)	

serum sodium is induced because of impaired circulatory delivery to diluting segments combined with adequate antidiuretic hormone release [5]. In hypervolemic states, low serum sodium level is induced by impaired free water excretion due to glomerular filtration rate reduction ($<5 \text{ mL/min/1.73 m}^2$) [5]. Renal insufficiency is one of the kidney transplant complications that can be secondary to tissue necrosis, intratubular obstruction (luminal accumulation of necrotic tubular cells) and tubulointerstitial and vascular damage (kidney rejection). In this setting, hypotonic solution overload contributes to the appearance of hyponatremia [21, 44].

Drug-induced hyponatremia. Drug-induced hyponatremia is one of the main causes of hyponatremia in KTPs and therefore this type of hyponatremia is described here separately [5]. Medication can induce hyponatremia by different mechanisms that promote water retention and/or sodium loss (Table 2) [7, 22, 38, 45–49]. High-dose IV cyclophosphamide (30–50 mg/kg), opioids and psychoactive drugs, which are usually used in transplantation, may cause water intoxication [7, 49]. Regarding calcineurinic inhibitors (tacrolimus and cyclosporine), 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, while tacrolimus has a more profound effect on distal tubular function, where it alters tubular sodium handling, which is responsible for aldosterone resistance, and can cause salt-losing nephropathy [21, 47, 49–51]. This phenomenon explains why hyponatremia was reported as significantly more common under tacrolimus therapy than cyclosporine treatment in transplant patients, and also the ineffectiveness of fludrocortisone for treating tacrolimus-induced hyponatremia [21, 22].

CONCLUSION

KTPs are predisposed to develop hyponatremia since they are exposed to immunologic, infectious, pharmacologic and oncologic disorders, the combination of which alters their salt and water homeostatic capacity.

CONFLICT OF INTEREST STATEMENT

None declared.

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