RETROSPECTIVE CHART REVIEW OF ELECTROLYTES DISORDERS IN POST KIDNEY TRANSPLANT PATIENTS AT KENYATTA NATIONAL HOSPITAL

PRINCIPAL INVESTIGATOR

DR. JAMES KAMAU KAHURA

H114/10162/2018

EAST AFRICA KIDNEY INSTITUTE

UNIVERSITY OF NAIROBI, KENYA

A PROJECT SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE FELLOWSHIP IN CLINICAL NEPHROLOGY OF THE UNIVERSITY OF NAIROBI

DECEMBER, 2021

APPROVAL BY MY SUPERVISORS

This proposal has been submitted with the approval of my supervisors

PROF JOSHUA K. KAYIMA

MBChB, MMED (Internal Medicine) FRCP (Edin).

Associate Professor of Internal Medicine and Nephrology

University of Nairobi, School of Medicine, Department of Clinical Medicine & Therapeutics

Signature ..... Date 08/9/2021

PROF SETH . O. McLIGEYO

MBChB, MMED (Internal Medicine), FRCP (Edin).

Professor of Nephrology of Internal Medicine and Nephrology

University of Nairobi, School of Medicine, Department of Clinical Medicine & Therapeutics

Signature ..... Date 8/9/21

DR KHALIDA B. SOKI

MBChB, MMED (Internal Medicine), FISN (UK)

Consultant Physician & Nephrologist,

Nairobi Hospital

Signature ..... Date 16/9/2021

DEDICATION

This study is dedicated to my family, loving wife Cathrine, Son Keith, daughters Faith and Beth who have given me immense support and persevered prolonged absence from home during my study and work.

TABLE OF CONTENTS **PAGE**

LIST OF TABLES

LIST OF FIGURES

CHAPTER ONE

INTRODUCTION

Kidney transplantation is the current treatment of choice for patients with end-stage renal disease. Newer and safer innovations in transplantation and immune-suppression regimens have greatly improved the renal allograft survival.

Kidney transplantation is now a common procedure in patients with chronic kidney disease. Patients undergoing solid organ transplantation require lifelong immune-suppression to prevent allograft rejection. The ideal form of immune-suppression should induce donor specific tolerance without impairing the host defenses' or increasing the susceptibility to infections and without giving toxicities that may impair the allograft or the organ system. Patients therefore trade their renal disease for a chronic, albeit less lethal, condition – that of relative immune-incompetence.

End-stage kidney disease is associated with a variety of metabolic and electrolyte derangements. In as much as most of these abnormalities resolve with kidney transplantation, a new wide spectrum of electrolytes and acid-base abnormalities are noted. The abnormalities seen in the post-transplant period are surprisingly different from those seen in chronic kidney disease. Multiple factors contribute to the high prevalence of these abnormalities that include level of allograft function, use of immunosuppressive medications and metabolic changes in the post-transplant period. These electrolyte disturbances are common in patients after renal transplantation, and several studies have tried to determine the clinical significance of these disturbances.

In a study done by Einollahi et al, the authors observed that the most frequent post-transplant electrolyte and acid-base disturbances are hyperkalemia, metabolic acidosis, hypercalcemia, hypomagnesaemia, and hypophosphatemia.

Although kidney transplantation can improve mineral disorders, it cannot completely relieve the condition. The early period after renal transplantation is a critical phase in terms of extracellular volume assessment, intravenous fluid administration, and electrolyte balance. The electrolyte levels including sodium, potassium, bicarbonate, calcium, phosphorus, and serum magnesium and parameters of renal function in Renal Transplant Recipients (RTRs) are carefully examined during this period.

CHAPTER TWO

LITERATURE REVIEW

2.1 HYPERKALEMIA

2.1.1Epidemiology

Hyperkalemia is a common complication in renal allograft recipients and is reported to have an incidence ranging from25 to 44% in kidney transplant recipients on calcineurin inhibitors [CNIs] (2, 3)**.** Dual kidney-pancreas transplant recipients with bladder drainage are reported to have more frequent hyperkalemia, with one study reporting an incidence of 73 %(3). Studies are few that describe the time course of hyperkalemia after kidney transplantation. In a small study published in 1996 in type 1 diabetics, hyperkalemia occurred up to average post-operative day of 100 for kidney transplant recipients. Only two patients had hyperkalemia beyond 8 months after transplantation (3). Patients on tacrolimus have more frequent hyperkalemia when compared to patients' on cyclosporine (4).

2.1.2 Mechanisms of hyperkalaemia

Potassium (K+) is the most abundant intracellular cation with a concentration of 150 mEq/L compared to just 4 mEq/L in the extracellular compartment. The difference in concentration between compartments is maintained by the Na- K-ATPase pump. Since the ratio between the intracellular and extracellular K+ concentration is the main determinant of the resting membrane potential then maintaining K+ homeostasis, i.e., maintaining a relatively constant plasma K+ concentration, is critical for cell function (5). Plasma K+ concentration are determined by the relationship between K+ intake, its distribution between the intracellular and extracellular compartments, and renal K+ excretion. Under normal conditions, a dietary K+ load is absorbed by the gut into the circulation followed by a rapid uptake by muscle and liver cells facilitated by the presence of insulin and beta 2 adrenergic receptors.

Thereafter the K+ load is mostly renally excreted, in a process that is primarily determined by potassium secretion by the principal cells located in the connecting tubule and cortical collecting duct. K+ secretion in these segments is tightly regulated. Adequate aldosterone secretion and responsiveness and adequate distal water and sodium delivery are key determinants of renal K+ secretion (5).

Distal sodium delivery is especially important because sodium reabsorption via the epithelial sodium channel (ENaC) in these distal nephron segments creates an electrical gradient that favors K+ secretion. Common mechanisms for hyperkalemia in the non-transplant individual are insulin deficiency, inorganic metabolic acidosis, decreased glomerular filtration rate, and decreased distal sodium delivery. Hyperkalemia in the kidney transplant recipient is usually seen in association with renal tubular acidosis and can be seen even without any of the above-mentioned factors. Insulinopenia or insulin resistance can decrease translocation of potassium and glucose from the extracellular to the intracellular compartment and cause hyperkalemia and hyperglycemia in the post-transplant setting, especially in insulin dependent diabetics.

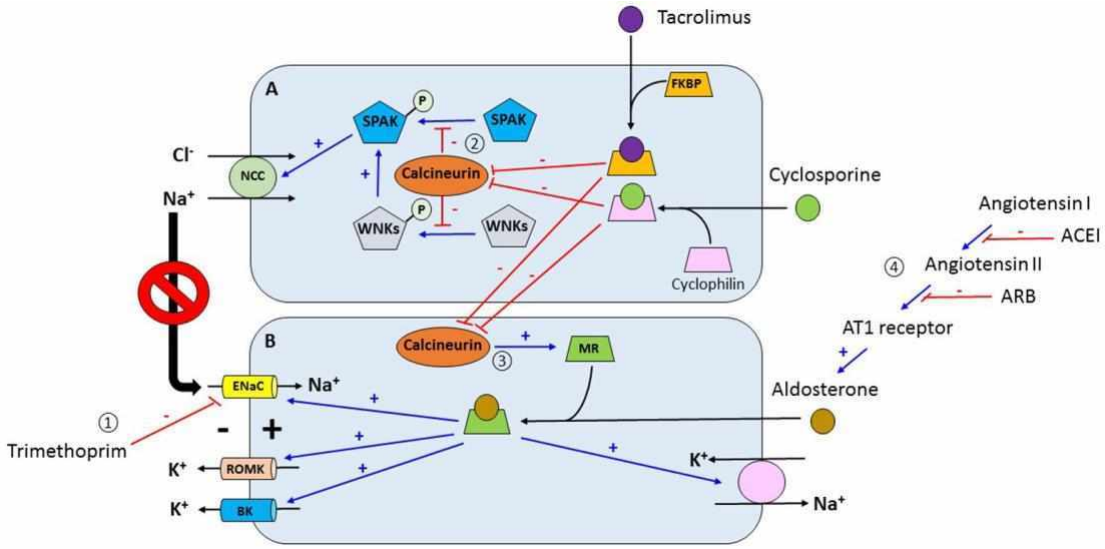


Figure 1- illustrating the most common mechanisms of hyperkalemia in the renal transplant recipient.

Medications used post-transplant are thought to be the major cause for post-transplant hyperkalemia in recipients with a well-functioning graft. Use of trimethoprim in Trimethoprim/Sulfamethoxazole (TMP/SMX) in standard doses contributes to hyperkalemia by ENaC blockade (7) but the incidence is low especially when the regimen comprises of single strength tablet three times weekly for Pneumocystis and urinary tract infection prophylaxis (8).

Use of pentamidine can also cause hyperkalemia by a similar mechanism (9). Use of renin-angiotensin system blockers is associated with better patient and graft survival in renal transplant recipients but risk of life threatening hyperkalemia is also 2-fold when compared to recipients not on these medications (10).

2.1.3. Calcineurin inhibitors

Calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporine are considered the major players in the development of hyperkalemia in the kidney transplant recipient. Deppe and Heering showed that CNIs inhibit mineralocorticoid receptor transcriptional activity, causing down regulation of mineralocorticoid expression leading to impaired mineralocorticoid function and aldosterone resistance (11, 12). Hence, patients on CNIs might show signs of hypoaldosteronism despite normal plasma aldosterone levels. Hoorn EJ et al. postulated a new mechanistic pathway of hyperkalemia in transplant recipients by demonstrating that tacrolimus activates the thiazide-sensitive sodium-chloride co- transporter (NCC) in the distal convoluted tubule (DCT) leading to hyperkalemia and hypertension similar to the ones that occur in Gordon syndrome (13). What is more, it seems that the tacrolimus causes this effect predominantly by directly inhibiting calcineurin in DCT cells (14). If this concept is further validated in future studies, thiazide diuretics may become an attractive and more targeted therapeutic option for hyperkalemia in these patients.

2.1.4. Managing hyperkalaemia

Limiting the use or lowering the dose of drugs that increase potassium levels may not always be feasible in the immediate post-transplant setting. Initial approach should include dietary modification and addition of thiazide or loop diuretic if volume status permits. Fludrocortisone has mineral corticoid properties and causes sodium re-absorption and potassium excretion in the distal nephron. Studies indicate that fludrocortisone can ameliorate persistent hyperkalemia and metabolic acidosis in transplant recipients, but it can result in fluid retention (11, 16).Sodium polystyrene sulfonate is a cation exchange resin that has been commonly used to treat chronic hyperkalemia for decades. Its use is associated with colonic perforation, which is a rare yet catastrophic complication after renal transplantation, mainly when used with sorbitol as a carrier. Hence, caution is advised in its use, especially in the immediate peri-operative period (17, 18). Patiromer, a relatively new cation exchange resin which exchanges potassium for calcium and has been approved for the treatment of chronic hyperkalemia in chronic kidney disease (19), but studies are still ongoing to assess the drug interactions between patiromer and anti-rejection

medications and to assess its efficacy in the transplant recipients (20). Renal replacement therapy is reserved for severe hyperkalemia and to patients with delayed graft function or allograft failure.

2.2 HYPERCALCAEMIA

2.2.1. Epidemiology

Hypercalcemia after kidney transplantation has been reported to occur with a very high variability from around 10 to 59% (21).

The incidence is highest within 3 months after transplant and in majority of the patients, it resolves by 1 year after transplantation. However, in 5–10% of the patients, it persists beyond 1 year (22–24). Pre-transplant parathyroid function and longer duration of dialysis, i.e., the indicators of pre-transplant bone status, are considered risk factors for post-transplant hypercalcemia.

2.2.2 Mechanisms of Hypercalcaemia

Calcium is the fifth abundant mineral in our body with greater than 99% being stored in the bone. Serum calcium is tightly regulated by parathyroid hormone (PTH) and 1, 25-dihydroxyvitamin D3 by acting on receptors in the gut, kidney, and bone. Calcium is essential for cellular signaling, nerve impulse transmission, coagulation, muscle contraction, and bone mineralization (25). The distal nephron is responsible only for the reabsorption of 5– 10% of the filtered calcium load. Yet, the distal convoluted tubule is the main regulator of calcium excretion as calcium absorption here is regulated independent of sodium absorption and is also the principal site of action of PTH, calcitonin, and vitamin D (26, 27). Tertiary hyperparathyroidism is a very common cause of post-transplant hypercalcemia. A successful kidney transplant eliminates the stimuli that usually induce parathyroid overactivity in dialysis patients. Yet parathyroid involution does not always occur immediately, especially in patients with severe pre-transplant hyperparathyroidism, probably due to the presence of underlying parathyroid hyperplasia or adenoma, causing persistent and sometimes significant hypercalcemia. The improvement in production of calcitriol post-transplant, further stimulated by the inappropriately high PTH levels and low phosphorous levels, also is considered an important factor for the development of hypercalcemia. Steroid therapy and the resorption of soft-tissue calcium phosphate deposition formed in dialysis patients are also hypothesized as potential contributors for post-transplant hypercalcemia (23, 28–30).

2.2.3. Clinical Manifestations

The clinical manifestations of hypercalcemia range from anorexia, nausea, constipation, polyuria, polydipsia, and nephrocalcinosis in mild cases to cognitive difficulties, drowsiness or obtundation in severe cases in the general population (15). Given that post-transplant hypercalcemia is usually mild to moderate and is chronic in nature, such drastic symptoms are not very common. There are conflicting results in the literature about the effect of persistent hypercalcemia on graft function. Some studies consider hypercalcemia as an innocent complication that is well tolerated (31), while others have shown association with impaired graft function (32, 33), fractures, bone disease and vascular calcification.

2.2.4. Treatment of hypercalcaemia.

KDIGO guidelines recommend that we apply the same principles for managing the mineral bone disorders in patients with chronic kidney disease stages 3–5 to managing bone mineral disorders after renal transplant. However, no specific guidelines are offered by KDIGO pertaining to the management of metabolic derangements in kidney transplant recipients with normal renal function. The first treatment option nowadays for post-transplant hypercalcemia is a calcimimetic, cinacalcet being most commonly used. Calcimimetics induce changes in conformation of the calcium receptor and thus increase sensitivity to extracellular calcium and cause reduction in PTH secretion and thereby decrease calcium levels in tertiary hyperparathyroidism (34). If there are no symptoms and patient does not have significant hypercalcemia, i.e., serum calcium greater than 11 mg/dL, most practitioners wait for at least a year for spontaneous resolution before opting for parathyroidectomy (35). Gastrointestinal side effects and cost of cinacalcet can limit the use of cinacalcet in some patients. Parathyroidectomy is more cost effective when cinacalcet duration reaches 14–16 months (36, 37).Evenepoel et al. studied the effect of cinacalcet in a placebo-controlled trial for management of post-transplant hypercalcemia due to persistent hyperparathyroidism. They demonstrated that cinacalcet normalizes serum calcium and lowers PTH levels while placebo treatment led to no significant changes in these parameters and the discontinuation rate was quite low. However, after 1 year of treatment, the cinacalcet group had several other outcomes similar to placebo treatment: no improvement in bone mineral density (BMD), no improvement in biomarkers of high bone turnover and both groups had comparable and stable estimated GFR (38). When they looked at serum calcium and PTH levels after withdrawal of cinacalcet, the levels were similar in the cinacalcet and placebo groups, suggesting

that cinacalcet did not hasten parathyroid gland involution. The follow up period in this study was relatively short; however, this study underlines the dilemma that continues when prescribing calcimimetics. There is definite improvement in PTH and calcium levels while using cinacalcet, but the studies that have shown improvement in hard outcomes like BMD are few and some studies in turn indicate a concern for low bone turnover state and decrease in BMD (39–41).Cruzado et al randomized 30 post-transplant patients with hyperparathyroid hypercalcemia to receive cinacalcet or subtotal parathyroidectomy. The surgery group in the study had greater reduction of parathyroid hormone levels and was associated with a significant increase in femoral neck BMD but also had higher incidence of hypocalcemia. No significant change in vascular calcification was seen in either group (36). Future larger and randoomized trials that assess hard clinical outcomes such as bone disease and graft function would help guide the management of hypercalcemia in the post-transplant population.

Contributors to Hypercalcemia in kidney transplant recipients include improvement in production of calcitriol post-transplant, resorption of soft-tissue calcium phosphate deposition formed in dialysis patients, steroid therapy, lack of parathyroid involution and underlying parathyroid adenoma.

2.3 HYPOMAGNESEMIA

2.3.1. Epidemiology

In renal transplant recipients, hypomagnesemia is reported with high prevalence with lowest serum magnesium concentration noticed around second month post transplantation. In 20% of the renal transplant recipients, hypomagnesemia might persist several years after transplantation (42). The incidence of hypomagnesemia and that of post-transplant diabetes (previously referred as NODAT) is reported to be higher among patients using tacrolimus than those on cyclosporine (43–45).

2.3.2. Pathophysiology

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation after potassium (46). Around 99% of body magnesium is found in bone, muscle and soft tissues. Renal excretion is the major regulator of magnesium balance of the body and plays a crucial role in magnesium homeostasis. Bulk of the reabsorption of the filtered magnesium

occurs in the thick ascending loop of Henle where magnesium is reabsorbed via the paracellular pathway facilitated by tight-junction proteins Claudin 16 and 19. Magnesium reabsorption in this segment depends on lumen-positive voltage created by potassium recycling in the thick ascending limb cells. Around 10% of the filtered magnesium is reabsorbed in the DCT via TRPM6 (transient receptor of potential melastatin 6) transporters, playing an important role in determining the final urinary magnesium concentration (47). Use of CNIs is associated with an inappropriate and significant increase in fractional excretion of calcium and magnesium. CNIs induce renal magnesium wasting by down regulation of magnesium transport proteins in the distal tubule (**Figure 2**). CNIs induce decrease in expression of the magnesium transporter TRPM6 in the distal tubule, which is the main site for active transcellular reabsorption for magnesium (48). This decrease in expression of magnesium transport proteins leads to increased magnesium excretion, causing persistently elevated fractional excretion of magnesium despite hypomagnesaemia in these patients. Some recent data suggest that cyclosporine down regulates renal epidermal growth factor (EGF) production, which in turn leads to inhibition of TRPM6 activation (49, 50). This magnesium wasting effect is seen even with use of low dose of CNIs (50).Use of steroids, hyperglycemia, diuretics, and proton pump inhibitors could be the other contributing factors to hypomagnesaemia in the early post-transplant period.

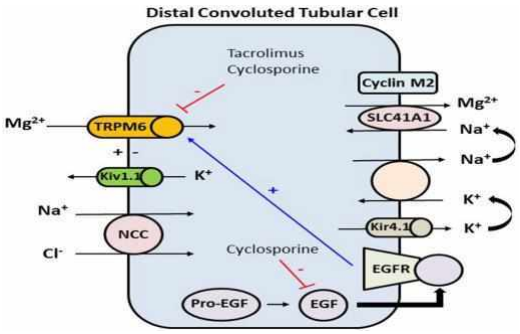


Figure 2 Illustrating mechanisms of hypomagnesaemia in post-transplant patient.

2.3.3. Clinical Manifestations

Magnesium is an essential cofactor for critical enzymatic reactions, and hence has a role in various physiological functions involving the neuromuscular and cardiovascular systems. Magnesium plays a role in PTH-induced release of calcium from bone and in severe hypomagnesemia also

might cause diminished PTH secretion (51). Hypomagnesaemia can cause tremors, tetany, and convulsions and in some cases hypokalemia. Initial EKG changes in hypomagnesemia manifest as widening of the QRS complex and peaking of T waves. Severecases can lead to prolonged PR interval, progressive widening of the QRS complex, and diminution of the T wave (52).Even mild hypomagnesemia has been associated with ventricular arrhythmias in patients with underlying cardiac disease. There are studies showing association of hypomagnesemia with vascular stiffness and decreased graft survival inpatients with CNI toxicity (53–56). Gupta et al. looked at14 hypomagnesemic non diabetic renal transplant recipients and their effect on lipid and glucose metabolism over a 6-monthperiod. This was a small and short term study, however their results suggest that correction of hypomagnesemia in renal transplant recipients was associated with reduced serum total cholesterol, LDL, and total cholesterol/HDL ratio (57).It has been well established that there is a strong association between hypomagnesemia and insulin resistance in the general population. Due to increasing awareness about post-transplant diabetes, several studies looked at hypomagnesemia after renal transplantation and its relation with post-transplant diabetes. Intracellular Magnesium regulates enzymes and ion transport channels in pancreatic beta cells and plays a role in insulin receptor phosphorylation. Conversely, insulin activates the renal magnesium channel TRMP6 that plays a role in magnesium reabsorption in the kidney and hence plays a role in magnesium homeostasis. Consequently, it is suggested that a vicious cycle may ensue in hypomagnesemic patients with diabetes in which low magnesium levels causes insulin resistance and insulin resistance reduces serum magnesium concentrations (58).Huang et al. from University of Toronto looked at 948 non diabetic kidney transplant recipients to examine the relationship between serum magnesium level and post-transplant diabetes during a median follow up of 3.4 years. Lower plasma magnesium level (defined as a plasma magnesium less than1.8mg/dL) in their study was associated with a quantitatively increased risk of post-transplant diabetes, based on time-fixed,conventional time-varying, and rolling-average time varying Cox proportional hazards models. (Hazard ratio of 1.58–1.83, $p < 0.05$) (59).

2.3.4. Treatment

Though several such studies exist that show an independent association between hypomagnesemia and post-transplant diabetes (60, 61), treating it by way of magnesium supplementation has not always translated into beneficial results in clinical studies. Van Laecke et al. conducted an open-label study to assess if magnesium supplementation improved glycemic control in renal transplant

recipients. They randomized 54 patients within 2 weeks after kidney transplantation to receive magnesium oxide supplementation (with goal serum magnesium greater than 1.9mg/dl) or no treatment. Patients on magnesium supplementation displayed lower fasting plasma glucose at 3 months post-transplant compared with controls. However, the effect was not large (104.1 mg/dl in the control group vs. 92.6 mg/dl in the treatment group, $p = 0.02$), and study had the drawback that fasting plasma glucose levels were higher in the control group already at baseline. In addition, no significant differences were noted in other measures of glycemia i.e., area under the glucose curve during an oral glucose tolerance test and in insulin resistance as expressed by Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR). The trial was also underpowered to evaluate the effect of magnesium supplementation on the risk of post-transplant diabetes. Of note, one in four patients in the treatment group had persistent hypomagnesemia despite reasonably high doses of magnesium oxide (62).There are conflicting reports about magnesium levels adequately improving with magnesium supplementation inpatients on CNIs due to high rate of renal excretion with CNIs. While some studies demonstrated that serum magnesium levels increased to normal range after magnesium oxide therapy (57, 63), other studies did not demonstrate an adequate improvement in levels despite supplementation (43, 60). While magnesium supplementation for patients with Type 2 diabetes mellitus has shown improvement in glucose metabolism and insulin sensitivity, the same results have not been demonstrated in renal transplant recipients so far. Magnesium therapy is usually well tolerated but gastrointestinal side effects are not infrequent. As there are controversies yet to be answered whether magnesium supplementation would help any of the above outcomes, it is reasonable to supplement magnesium in all patients with even mild hypomagnesemia if underlying cardiovascular disease is present. In post renal transplant patients with mild hypomagnesemia and no risk factors, it is reasonable to at least advise foods rich in magnesium and reserve supplementation for moderate (less than 1.5 mg/dl) and severe hypomagnesemia (less than 1.2 mg/dl). Intravenous magnesium supplementation followed by oral supplementation should be reserved for severehypomagnesemia and in symptomatic patients. The population in the United States does not usually meet the expected average requirement for magnesium from food consumed due to change in dietary habits and move toward more processed foods in recent years. In plants, magnesium forms the central ion of chlorophyll and hence magnesium is abundant in green leafy vegetables. It is also found in abundance in other foods such

as legumes, nuts, brown rice, unprocessed cereals such as whole grains, and whole wheat bread (46, 64).

2.4 HYPOPHOSPHATEMIA

2.4.1. Epidemiology

Hypophosphatemia in kidney transplant recipients has been reported with varying incidence from 40 to 93% in different studies (31, 65, and 67). Data indicate that the incidence of hypophosphatemia peaks at week two post-kidney transplant and renal phosphate wasting usually regresses by 1 year after successful kidney transplantation (68, 69).

2.4.2. Pathophysiology

Phosphate is a major player in energy metabolism, bone formation, nucleic acid, and cell membrane formation and in several signaling pathways. Majority of total body phosphate is stored in the bone, with less than one percent present in the extracellular fluid. Maintaining this small percentage of total body phosphate in the narrow range of 2.5 to 4.5 mg/dl in the serum is mainly achieved by the kidneys via regulation of renal phosphate reabsorption in the proximal tubule. The renal sodium phosphate co-transporters NaPiIIa and NaPiIIc in the proximal tubule use the energy derived from the transport of sodium down its gradient to move inorganic phosphate from the lumen into the cell and are responsible for reabsorbing 85% of the filtered phosphate in the tubule (27). Dietary phosphate, parathyroid hormone, vitamin D, insulin and fibroblast growth factor 23 (FGF23) are the major regulators of phosphate homeostasis and they involve a complex interplay between intestinal absorption, internal redistribution, and renal excretion of phosphate. FGF23 is a recently characterized phosphaturic hormone that is produced in osteoblasts in response to increased phosphate levels. FGF23 causes suppression of vitamin D 1a hydroxylation, increase in renal phosphate excretion, and decreases gut absorption of phosphate causing a decrease in serum phosphate levels. Vitamin D increases phosphate absorption in gut and kidney while PTH increases renal excretion of phosphate (70). FGF23 and PTH are found to be at elevated levels in chronic kidney disease and end stage renal disease patients in response to elevated phosphate levels. After successful kidney transplantation, elevated FGF23 levels and other phosphatonins might take some time to come down and this persistent elevation is considered to play a key causative role in the phosphaturia and hypophosphatemia seen in the kidney transplant recipients

(71, 72). Tacrolimus also increases renal phosphate wasting by decreasing the abundance of phosphate co-transporter NaPi-2a in the renal tubule (30, 87).Factors such as dialysis vintage, low calcitriol levels, elevated parathyroid hormone level, and tubular damage from immunosuppression are thought to be the other contributors that determine phosphate wasting after renal transplantation (81, 86, 88, 89).

2.4.3. Clinical Manifestations

Hypophosphatemia, especially in the severe forms is known to cause predisposition to hemolysis, rhabdomyolysis, respiratory failure, muscle weakness, seizures, and myocardial depression. There is growing concern that hypophosphatemia can cause muscle weakness, osteodystrophy and contribute to increased fracture risk in this patient population. However, no association exists between renal phosphate wasting and adverse graft outcomes (76). In fact, some newer studies actually show favorable outcomes in patients with hypophosphatemia likely indicating a very-well functioning graft (77).

2.4.4. Treatment

Though no specific guidelines exist for the management of post-transplant hypophosphatemia, patients are usually treated with oral phosphate supplements and the treatment is well tolerated. However, intervention studies are scarce for the treatment of post-transplant hypophosphatemia and phosphate supplementation in these patients is not always considered benign. There is a theoretical risk that phosphate supplementation can in turn increase PTH and FGF23 synthesis and hence worsen hyperparathyroidism and cause further phosphate wasting in patients with a well-functioning allograft (58, 78). This effect was not seen in the early period after kidney transplantation, but was seen in late post-transplant periods in some studies. (66, 79). Patients with persistent post-transplant hyperparathyroidism with concurrent hypercalcemia and hypophosphatemia can be treated effectively with cinacalcet (48, 52). Kidney transplant recipients should be advised to consume phosphate rich foods like whole grains, eggs, poultry, fish, and dairy products as soon as good graft function is achieved (80, 81).

2.5 METABOLIC ACIDOSIS

2.5.1. Epidemiology

Metabolic acidosis after kidney transplantation is not an uncommon finding. It has been reported with varying prevalence from 12 to 58% (82). While in patients with chronic kidney disease, it is seen mainly at glomerular filtration rates (GFR) of less than 30 mL/min, in renal transplant recipients it is seen at higher GFR and even in patients with normal renal function. Factors such as suboptimal allograft function, donor age, deceased donor transplantation, graft rejection, hyperparathyroidism, and the use of calcineurin inhibitors have been associated with post-transplant acidosis (82–83). One year post kidney transplantation, the prevalence of metabolic acidosis falls to around 13–16% (82, 85).

2.5.2. Pathophysiology

When present, metabolic acidosis is predominantly of the normal anion gap variant. In addition to the common pathogenic factors acting in any form of chronic kidney disease, there are other mechanisms specific to the kidney transplant status. Both proximal and distal (including type 4) renal tubular acidosis can be seen in kidney transplant recipients (86). Diarrhea causing bicarbonate loss from the gut is also a common cause of normal anion gap acidosis in post-transplant patients. Diarrhea in the post-transplant setting can also constitute a side effect of medications like mycophenolate, from known underlying bowel disease or enteric pathogens like Clostridium difficile, Cytomegalovirus infections, parasites etc. Various mechanisms have been suggested for high prevalence of renal tubular acidosis in the kidney transplant recipient, which include immunological injury from rejection, subclinical tubular dysfunction from ischemia, reduced nephron mass from the single kidney processing the acid load and effect of various medications (CNIs, TMP/SMX, etc.) (87, 88). Tubulitis seen in rejection, the reduced activity of H+-V-ATPase pumps and anion exchanger (AE1) and decrease in renal function are postulated to be the factors responsible for association between rejection and metabolic acidosis (89). Experimental data suggests that calcineurin inhibitors impair mineralocorticoid transcriptional activity in the distal tubular cells and can thus cause aldosterone resistance contributing to hyperkalemia and metabolic acidosis in the post-transplant setting (12). Cyclosporine and tacrolimus can produce metabolic acidosis but by different mechanisms also.

In the cortical collecting duct, the intercalated cell exists as a beta form that secretes bicarbonate in exchange for chloride and the alpha intercalated cell that secretes acid. Work by Watanabe et al

suggests that cyclosporine produces distal renal tubular acidosis by blocking peptidyl prolyl cis-trans isomerase activity of cyclophilin and thus inhibiting this remodeling of the intercalated cell from the bicarbonate secreting beta form to the acid secreting alpha form, especially in times of acid loading (90) (**Figure 2**). Animal studies by Mohebbi et al. demonstrated that tacrolimus can impair urinary acidification especially in the setting of acid load by dysregulation of many acid-base transporters in the proximal and distal nephron including H+-ATPase, sodium bicarbonate cotransporter and anion exchangerAE1 (91). TMP/SMX can cause type 4 renal tubular acidosis often seen in association with hyperkalemia. Kidney transplantation, unrelated to immunosuppressive therapy or transplant related histologic changes, also has been shown to cause a generalized decrease in H+-ATPase expression and hence impaired proton handling (92).

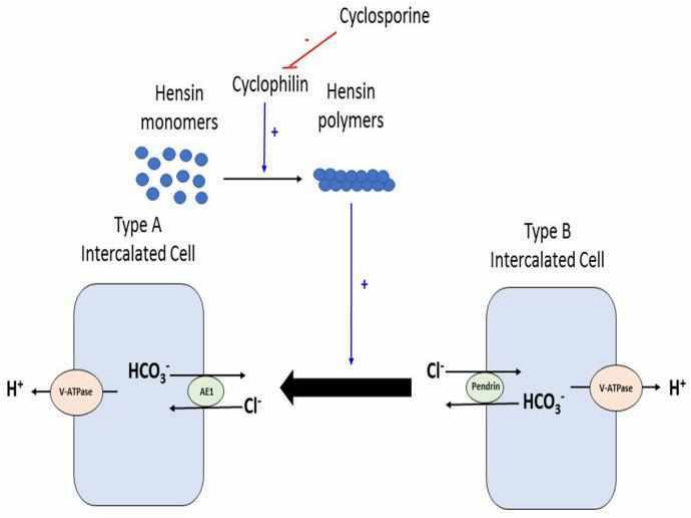


Figure 3. Illustrating mechanisms of metabolic acidosis

2.5.3. Clinical Manifestations

Metabolic acidosis in the non-transplant population affects growth in children, causes progression of nephrocalcinosis, bone disease and is an indicator of poor outcome in chronic kidney disease at all ages (80). In the past, post-transplant renal tubular acidosis was considered asymptomatic and subclinical; however, various studies have now implicated it as a factor in bone disease, mineral metabolism and now consider it as a marker of poor renal outcome in the renal transplant recipient (83, 84, 87, 93). In a recently published retrospective cohort study of 2318 adult kidney transplant recipients, a strong detrimental association between low bicarbonate levels(less than 22 mEq/L)

and graft function as well as death censored graft failure was noted even after adjusting for estimatedGFR (87).

2.5.4. Treatment

Starke et al performed a one-year study to assess the effect of improving bicarbonate levels on bone health in 30 kidney transplant recipients. Nineteen patients treated with potassium citrate were able to achieve bicarbonate levels of greater than 24 mEq/L and had better bone histology and markers of bone turnover when compared to 11 patients in the control group treated with potassium chloride. However, no relevant changes were seen in the DEXA scans at the end of 1 year and the study was limited by the small number of patients. In addition, this study did not comment on graft function/graft survival. Currently, given that alkali therapy is inexpensive and relatively safe, bicarbonate supplementation is recommended at least to protect the bone, if the condition is prolonged (94). It is unknown whether this supplementation will have a positive effect on renal outcomes in this population. Attention should also be paid to dietary factors, as diet might have an influence on the post-transplant acidosis. Modification of diet by higher intake of fruits and vegetables and lower animal protein intake can improve the acidosis by a small extent even in transplant recipients (95).

2.6. SODIUM

Studies have shown that CNI cause NA reabsorption via thiazide sensitive Sodium Chloride co-Transporter and Na - K - 2CL co-transporter (NKCC - 2) which is made possible through prevention of inhibitory effects of Calcineurin on “with no lysine kinases” (WNK), Glucocorticoid regulated kinases1, STEZO; SPSI related Proline alanine rich Kinases (SPAK) and oxidative - stress responsive protein type 1 kinases (OSR1) that activate NCC.

NCC and NKCC-2 are specifically found in different portions of nephron. The NKCC - 2 is expressed in the apical membrane of the thick ascending loop of Henle and in macula densa while NCC is expressed in the late portion of the distal convoluted tubule.

By inhibiting calcineurin, CNIs prevent its inhibitory effect on the kinases and consequently increase activation of NCC. This effect causes increased Sodium -absorption and causes Hypertension.

2.7. URIC ACID

Reduced uric acid excretion can occur after renal transplantation leading to Hyperuricaemia and in some cases gout. This is more common in patients treated with CNI -cyclosporin. Other co-morbities common in kidney transplant recipients such as CKD, Hypertension, diabetes Mellitus and other cardiovascular diseases may also contribute to the increased risk of hyperuricaemia.

Uric acid levels in patients with cyclosporine induced hyperuricaemia ranges from 8-14 mg/dl and approximately 10% of them develop gout.

Hyperuricaemia occurs early after transplantation and is associated with decreased GFR, Diuretic use, cyclosporine therapy and a preexisting history of gout or hyperuricaemia.

Diuretics used in post-transplant period may contribute to hyperuricaemia especially the thiazide type antihypertensives.

These drugs interfere with urate clearance and by inducing a certain degree of hypovolemia,they induce tubular urate absorption.

With cyclosporin, over 50% of patients develop hyperuriceamia and about 10% develop gout.

The mechanism of cyclosporine induced hyperuricaemia include increased net tubular urate absorption as well as decreased glomerular filtration rate with a decrease in filtered load of uric acid.

This effect is not restricted to renal transplant recipients receiving cyclosporine but was also observed in different groups of patients receiving cyclosporine independent of the presence of impaired renal function before the initiation of treatment.

Tacrolimus has also been reported to cause hyperuricaemia but with no reported cases of gout.

2.8 Study question

This study will attempt to characterize and quantify the extent of electrolyte derangements in post kidney transplant patients.

2.9 Study objective

To do a chart review of patients file so as to establish and describe the prevalence and patterns of electrolytes disorders in kidney transplant recipients with stable graft function at different stages after kidney transplantation at Kenyatta National Hospital

2.10 Specific objectives

1. To determine and identify trends in measured electrolytes in post kidney transplant recipients
2. To correlate the electrolytes derangements with immunosuppressive and other drug regimens in post kidney transplant recipients.
3. To correlate the electrolyte derangements with demographic patterns of post kidney transplant recipients

2.11 Study justification

At KNH, there are about 200 post kidney transplant patients on follow up at the transplant clinic. These patients are invariably at various stages post transplantation and are on various immunosuppressive drugs.

There is no documentation of various electrolytes disorders and acid base derangements that may be expected in these patients.

There are also no guidelines that have been laid down on how to manage these electrolyte or acid base disorders when they occur.

This study will help in raising doctor's awareness and attention in picking these electrolyte disorders.

It will also help in designing guidelines on management of such disorders when they occur.

It will also provide baseline data on expected electrolyte and acid base disorders and inform on individualization of immunosuppressive therapy.

CHAPTER THREE

METHODOLOGY

3.1 STUDY DESIGN

Retrospective and descriptive chart review Study

3.2 STUDY AREA

The study was carried out at Kenyatta National Hospital transplant clinic within the renal unit. Kenyatta National Hospital is the largest tertiary referral hospital in Eastern and Central Africa located in the capital city of Kenya, Nairobi. It was established in 1900 and it has a capacity of 2600 beds. It serves as the teaching hospital for the University of Nairobi, College of Health Sciences, Kenya Medical Training College, neighboring Health colleges and institutions such as KEMRI, Kenyatta University, and The Nairobi hospital. It serves as a referral hospital for Kenya and East Africa. It runs general and specialized clinics and in-patients services in surgical, medical, obstetrics and gynaecology, ophthalmology and paediatrics. Renal unit is one of the specialized units in Kenyatta National Hospital. The main services offered in the unit are haemodialysis and kidney transplantation. The renal unit has a weekly kidney transplant clinic that caters for pre- and post-transplant patients as well as kidney donors. The Transplant clinic runs every Tuesday overseen by Consultant Nephrologists, EAKI Fellows of Nephrology, Internal Medicine Registrars and a Transplant Coordinator nurse. An average of 15 – 20 patients are seen at every clinic

3.3 Study population

The study population included adult kidney transplant patients who are on follow-up in the transplant clinic. There are about 200 patients on follow up majority of them transplanted in KNH with a few others transferred in from India and also from neighbouring transplant centres such as Agha Khan University hospital -Nairobi, The Nairobi Hospital and Moi Teaching and Referral Hospital in Eldoret, Kenya. The study involved study of all the sampled files of these patients and extracting all the data needed in this study.

3.4 Sampling

All Kidney transplant patients attending the transplant clinic had their files numbered and sampled randomly. The sampled files had relevant data extracted and entered into the study questionnaire.

CHAPTER FOUR

RESEARCH FINDINGS

4.1 Introduction

The main objective of the study was to do a retrospective chart review to establish and describe the prevalence and trends of electrolytes disorders in kidney transplant recipients at different stages after kidney transplantation at Kenyatta National Hospital. A total of 156 recipients files were selected for the study and of these 106 files were reviewed and analyzed.

4.2 Patient characteristics

This section describes the characteristics of kidney transplant recipients whose files were studied at Kenyatta National Hospital.

Table 1: Patient characteristics

	Frequency n	**Percent %**
Gender (n=106)		
Male	67	63.2
Female	39	36.7
Age (n=106)		
13-25	9	8.4
26-35	19	17.9
36-45	28	26.4
46-55	25	23.5
>55	25	23.5

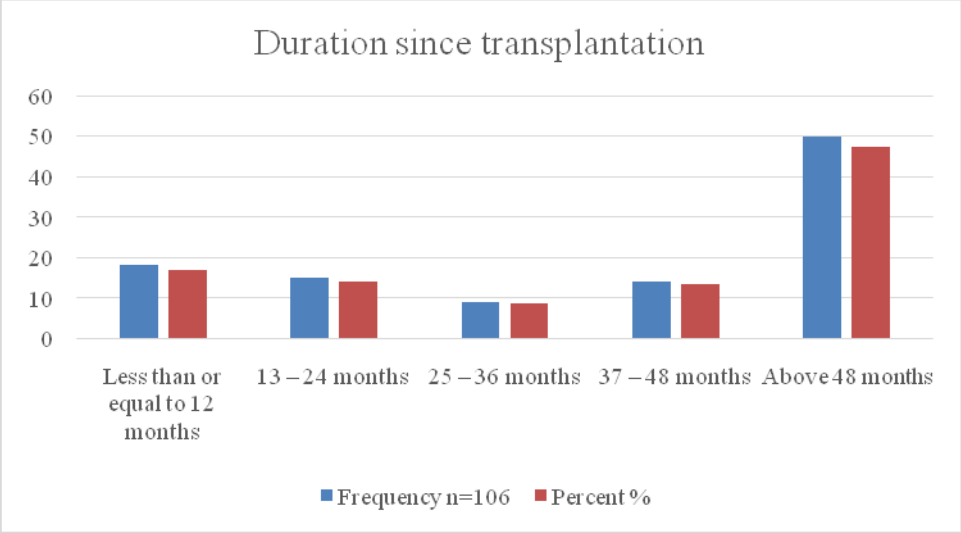
63.2% of the patients studied were males.

The mean age of the patients was 44.4 (SD=14.2) years, while the median age was 43.0 (IQR=21) years. The lowest age was 13 years, while the highest was 73 years.

Table 2: Duration since transplantation

	Frequency n=106	**Percent %**
Less than or equal to 12 months	18	16.9
13 – 24 months	15	14.1
25 – 36 months	9	8.4511
37 – 48 months	14	13.2
Above 48 months	50	47.16

Figure 4: Duration since transplantation



All the 106 recipients' source of allograft was from a living related kidney donor. The table below shows the relationship of the recipient's donor.

Table 3: Relationship with Donor

	Frequency n=106	**Percent %**
Brother	30	28.3
Sister	21	19.8
Father	1	.9
Mother	6	5.7
Wife	4	3.8
Husband	2	1.9
Cousin	1	.9
Nephew	2	1.9
Son	8	7.5
Daughter	1	0.9
Others	4	3.8
Unknown	24	22.6

Figure 5: Relationship with Donor

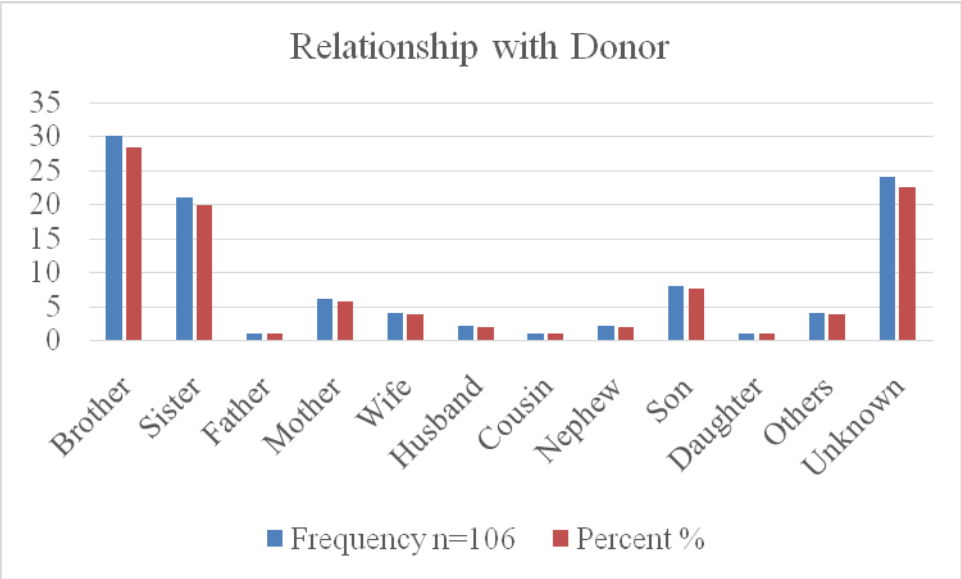
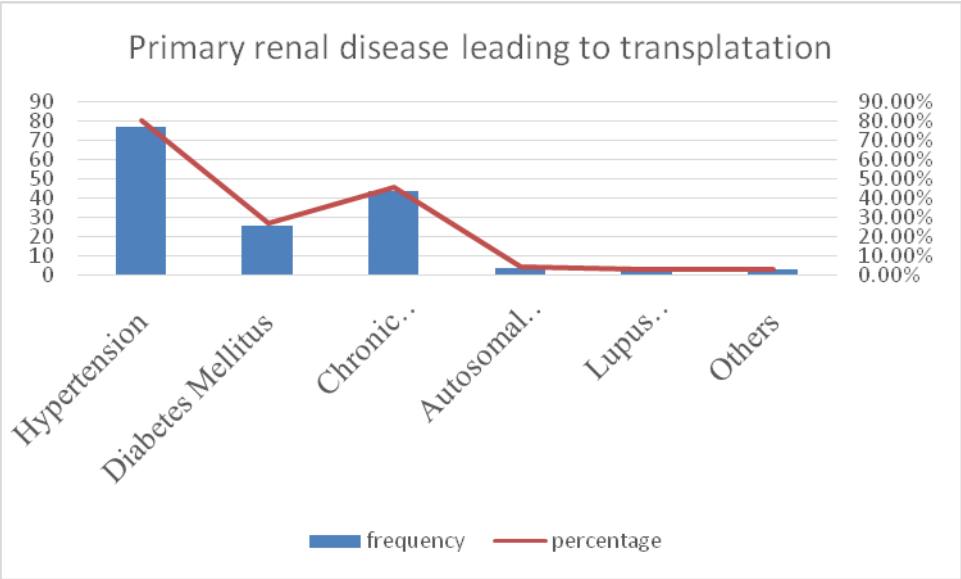


Table 4: Primary renal disease leading to transplantation

	Frequency	%
Hypertension	77	80.2%
Diabetes Mellitus	26	27.1%
Chronic Glomerulonephritis	44	45.8%
Autosomal Dominant Polycystic Kidney Disease	4	4.2%
Lupus Nephritis/Connective Tissue Disease	3	3.1%
Others	3	3.1%

Figure 6: Primary renal disease leading to transplantation



Majority of the patients had hypertension as the primary disease leading to transplantation.

However many patients had multiplicity of conditions leading to transplantation.

Table 5: Immunosuppressive medications

	Frequency	**Percent of patients % (n=106)**
Cyclosprin-A	19	20.4%
Tacrolimus	71	76.3%
Mycophenolate Mofetil/Mycophenolate Sodium	87	93.5%
Glucocorticoids	101	95.2%
Everolimus	1	2.2%
Azathiopurine	9	8.4%

Figure 7:Immunosuppressive medications

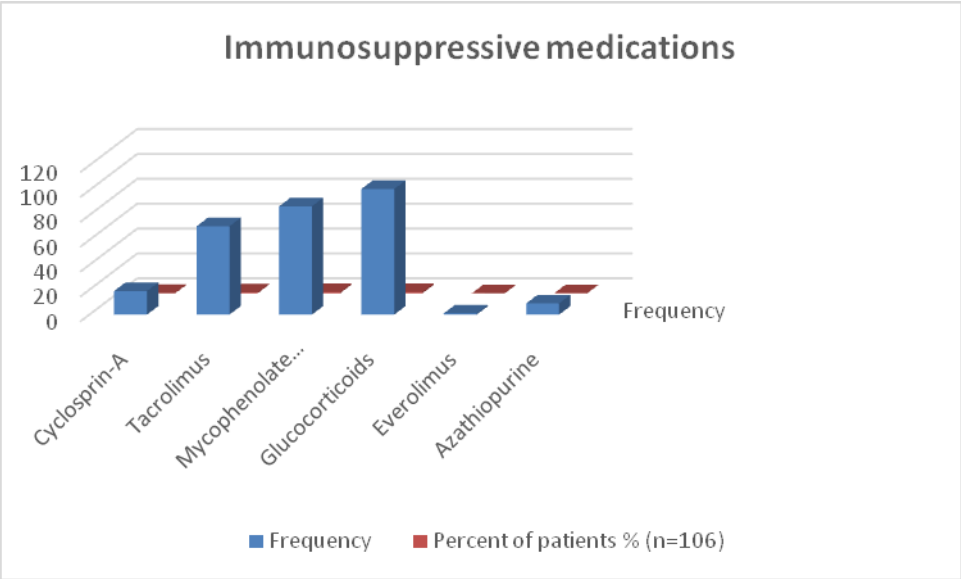


Table 6: Proton pump inhibitors

	Frequency (n=65)	**Percent %**
Pantoprazole	50	76.9
Omeprazole	2	3.06
Esomeprazole	12	18.4
Ranitidine	1	1.53

Figure 8: Proton pump inhibitors

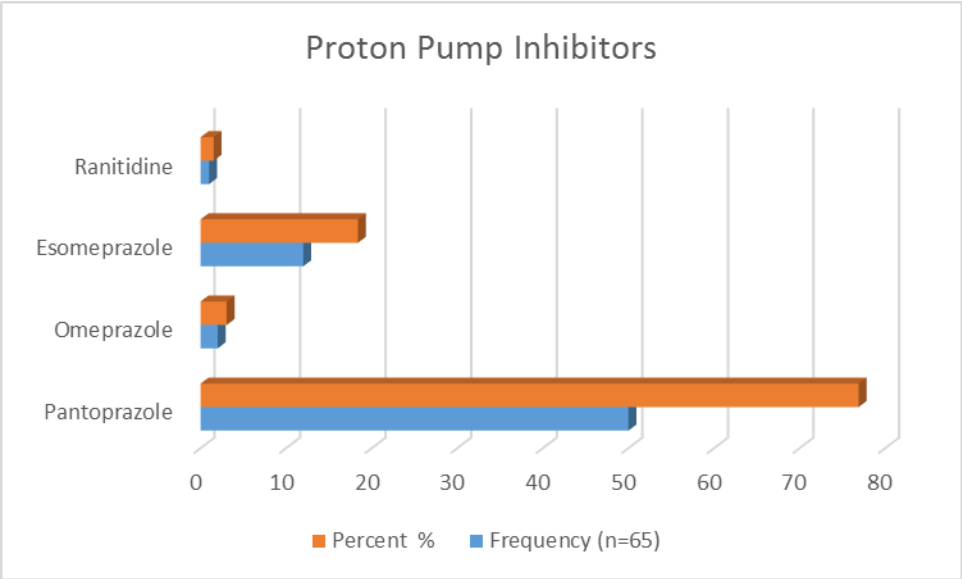


Table 7: Oral glucose lowering agents

	Frequency	**Percent of patients % (n=15)**
Metformin	9	60.0%
Sulphonylureas	3	20.0%
DPP4 Inhibitors	8	56.7%
Others	9	60.0%

Figure 9: Oral glucose lowering agents

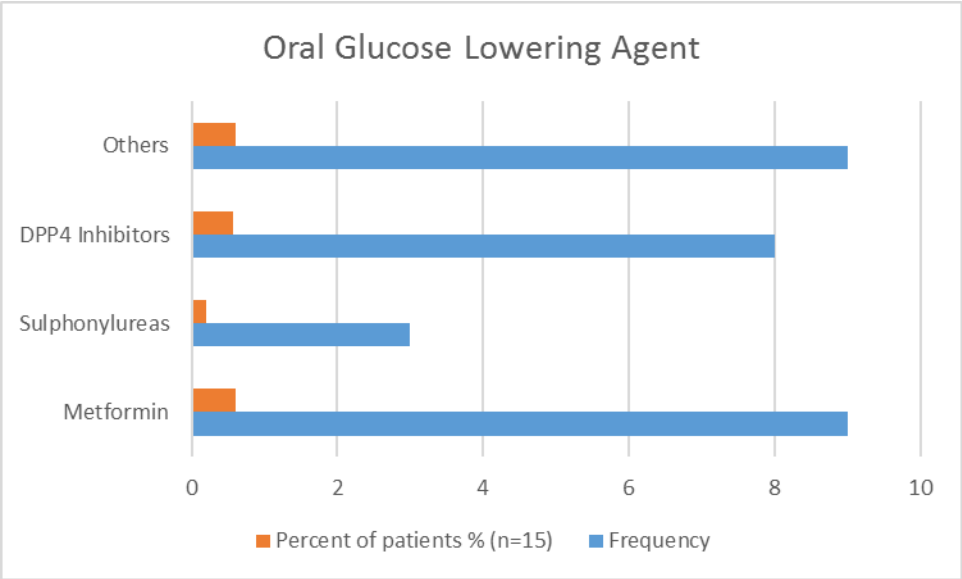


Table 8: Diuretics

	Frequency (n=2)	**Percent %**
Frusemide	11	100.0

Figure 10**: Diuretics**

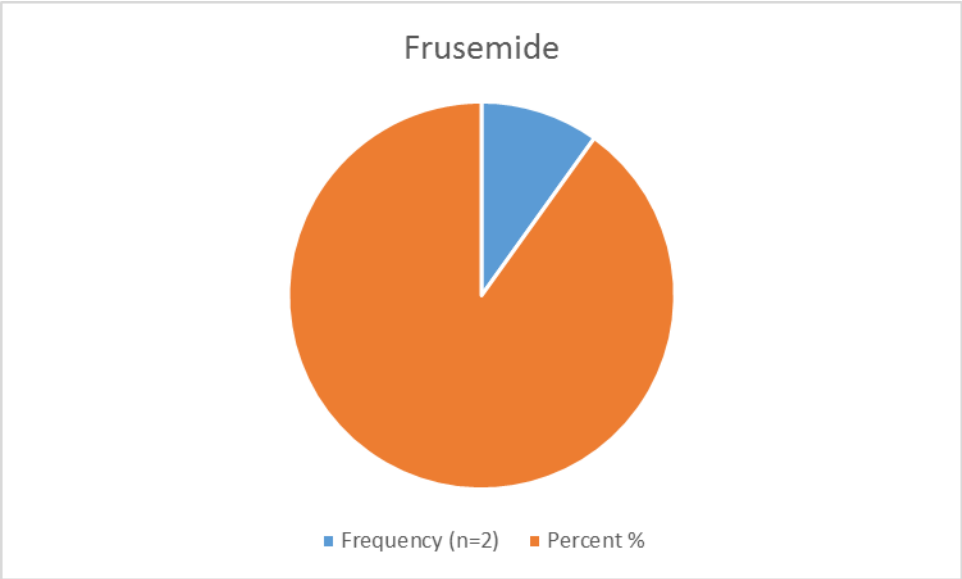


Table 9: Angiotensin converting enzyme inhibitors

	Frequency (n=7)	**Percent %**
Enalapril	6	85.7
Ramipril	1	14.3

Figure 11: Angiotensin converting enzyme inhibitors

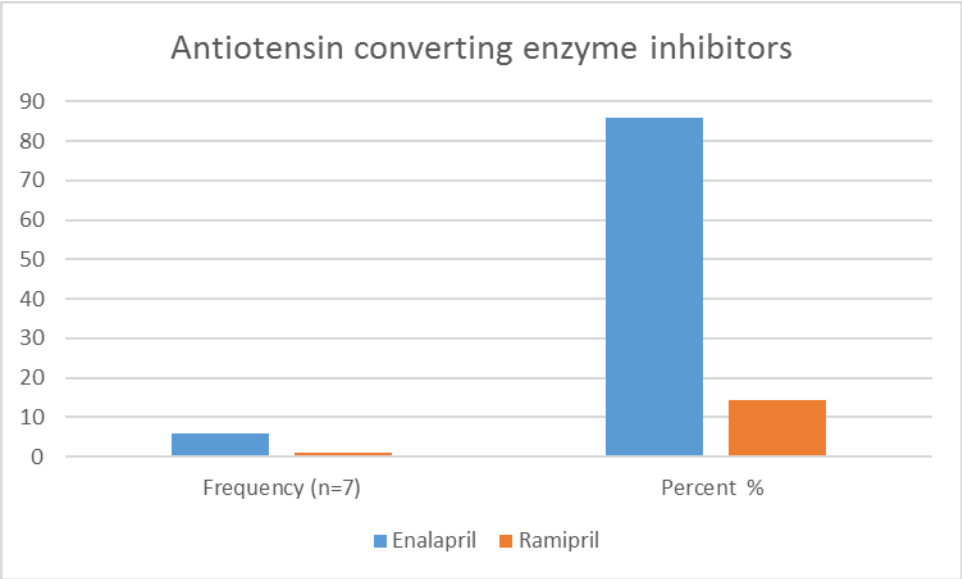


Table 10: Angiotensin receptor blockers

	Frequency (n=11)	**Percent of %**
Losartan	6	54.5
Candesartan	1	9.1
Telmisartan	2	18.2
Irbersartan	2	18.2

Table 11: Beta blockers

	Frequency	Percent of patients % (n=44)
Atenolol	6	13.6%
Nebivolol	18	40.9%
Carvedilol	6	13.6%
Metoprolol	15	34.1%

Figure 12: Beta blockers

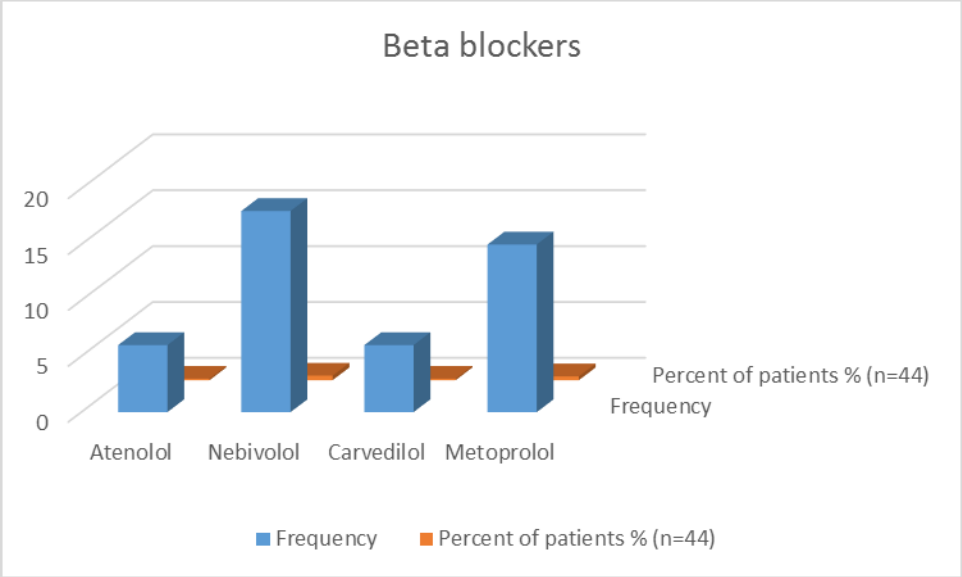
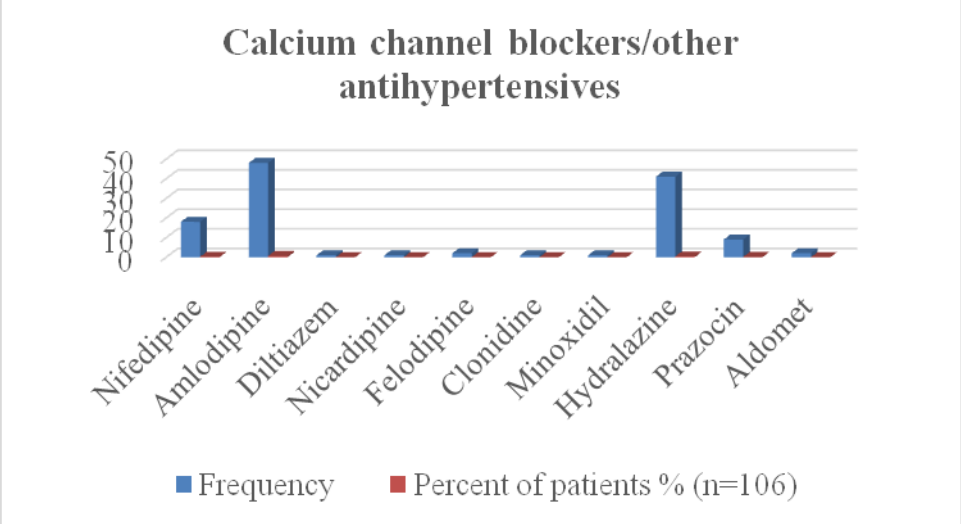


Table 12: Calcium channel blockers/other antihypertensives

	Frequency	Percent of patients % (n=106)
Nifedipine	18	23.1%
Amlodipine	48	61.5%
Diltiazem	1	1.3%
Nicardipine	1	1.3%
Felodipine	2	2.6%
Clonidine	1	1.3%
Minoxidil	1	1.3%
Hydralazine	41	38.6%
Prazocin	9	11.5%
Aldomet	2	2.6%

Figure 13: Calcium channel blockers/other antihypertensives



4.3 ESTIMATED GLOMERULAR FILTRATION RATE

Table 13: Estimated Glomerular Filtration Rate (eGFR) as per MDRD FORMULA

The parameters in the table below were used for classification of eGFR into the various stages as shown in table 13.

Stage	GFR*	Description
1	**90+**	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease
2	**60-89**	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease
3A **3B**	**45-59** **30-44**	Moderately reduced kidney function
4	**15-29**	Severely reduced kidney function
5	**<15 or on dialysis**	Very severe, or **end-stage** kidney failure

eGFR = 186 x (Creatinine/88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black)

Table 14: EGFR (n=106)

Stage	GFR*	Frequency n (%)
1	**90+**	24 (22.6)
2	**60-89**	53 (50.0)
3A **3B**	**45-59** **30-44**	17 (16.0) 8 (7.5)
4	**15-29**	4 (3.8)

CHAPTER FIVE

5.1 RESULTS

Trends in measured electrolytes

This section presents the results of the trends in measured electrolytes in post kidney transplant recipients.

A one-way repeated measures analysis of variance (ANOVA) was conducted to evaluate the null hypothesis that there is no change in the recipients measured electrolytes when measured in intervals of 3 months for 1 year. The results of the ANOVA indicated a significant time effect for Potassium, thus, there is significant evidence to reject the null hypothesis.

Follow up comparisons for Potassium indicated that the pair wise difference was observed to be significant only between K1 and K12, p = .005. There was a significant decrease in Potassium levels over time.

Trend analysis for Chloride, Calcium, Phosphate, Magnesium, and Uric acid cannot be performed due to the few observations and inconsistent readings.

5.2 POTASSIUM

Table 15: Potassium levels

Potassium	**N**	**Mean (SD)**	**p-value**
Male	67	4.05 (0.6)	0.530
Female	38	4.07 (0.3)	

An independent-samples t-test was run to determine if there were differences in potassium levels between the genders. The female had a higher mean (4.07 ± 0.3) than male (4.05 ±0.6), a not statistically significant difference of 0.02 (95% CI, -0.18 to 0.21), t (103) = 0.146, p = .866.

		Potassium
age	Pearson Correlation	.058
	p-value	0.559
	N	105

A Pearson's product-moment correlation was run to assess the relationship between age and potassium. There was a weak positive correlation between age and potassium (r = .058), but this was not statistically significant (p = .559).

5.3 HYPERKALAEMIA

Incidence of Hyperkalaemia (high potassium >5.0mmol/L) at different stages after kidney transplantation

Month	**1**	**3**	**6**	**9**	**12**
n / N	**19/106**	**11/106**	**7/106**	**7/106**	**6/106**
%	**17.9**	**12.6**	**7.86**	**7.86**	**6.7**

The incidence of hyperkalaemia was highest in the first month after transplantation and appears to stabilize over time. The average prevalence of hyperkalaemia was found to be **10.5%**

5.4 PREVALENCE OF HYPERKALAEMIA BASED ON GENDER OF RECIPIENT

Table 16: Prevalence of Hyperkalaemia Based On Gender of Recipient

Month	1	3	6	9	12
M (n, %)	11/19(57.8)	6/11(54.5)	4/7(57.1)	3/7(43.9)	1/6(16.6)
F (n, %)	8/19(42.1)	5/11(45.5)	3/7(43.9)	4/7(57.1)	5/6(83.3)

Males were found to have a higher prevalence of hyperkalaemia than females.

5.5 HYPOKALAEMIA

Table 17: Prevalence of hypokalaemia (low potassium <3.5mmol/L) Electrolytes derangements with demographic patterns

month	1	3	6	9	12
n / N	18/106	15/106	10/106	14/106	13/89
%	16.9	14.1	9.4	13.2	12.3

Average prevalence of hypokalemia was found to be 13.18**%**

Table 18: Prevalence of Hypokalaemia Based On Gender of Recipient

	1	3	6	9	12
M (n, %)	8/18(44.4)	13/15(86.6)	5/10(50)	11/14(78.5)	12/13(92.3)
F (n, %)	10/18(55.6)	2/15(13.3)	5/10(50)	3/14(21.4)	1/13(7.6)

5.6 SODIUM

MONTHS	3	6	9	12
N	38/106	25/106	26/106	25/106
%	35.8	23.5	24.5	23.5

Of 106 patients studied, hyponatraemia (sodium levels <135mmol/L) was the only sodium disorder that was evident at different times after transplantation.

Table 19: Prevalence of Hyponatraemia Based On Gender of Recipients

	3	6	9	12
M (n, %)	26/38(68.4)	19/25(76)	17/26(65.3)	15/25(60)
F (n, %)	12/38(31.57)	6/25(24)	9/26(34.6)	10/25(40)

Hyponatraemia was found to be more prevalent in male recipients.

Sodium	**N**	**Mean (SD)**	**p-value**
Male	67	136.0 (4.0)	0.829
Female	39	136.2 (5.0)	

An independent-samples t-test was run to determine if there were differences in sodium levels between the genders. The females had a higher mean (136.2 ± 5.0) than males (136.0 ±4.0), a not statistically significant difference of 0.2 (95% CI, -1.6 to 1.9), t (103) = .217, p = .829.

		Sodium
Age	Pearson Correlation	-.060
	p-value	.540
	N	105

A Pearson's product-moment correlation was run to assess the relationship between age and sodium. There was a very weak negative correlation between age and sodium (r = -.060), but this was not significant (p = .540).

5.7 CALCIUM.

Table 20: PREVALENCE OF HYPOCALCAEMIA (LOW CALCIUM<2.2mmol/L) AT DIFFERENT STAGES POST TRANSPLANTATION

MONTH	1	3	6	9	12
N	4/58	6/20	3/14	5/16	5/13
%	6.8	30.0	21.42	31.25	38.46

Hypocalcaemia was found to have unpredictable variability within the year after transplantation. The prevalence appears to decrease with increased number of observations. Of note there were a decreasing number of recipients who had their calcium measured over time.

Table 21: PREVALENCE OF HYPERCALCAEMIA (HIGH CALCIUM>2.6mmol/L) AT DIFFERENT STAGES POST TRANSPLANTATION

MONTH	1	3	6	9	12
N	6/58	3/20	3/14	1/16	2/13
%	10.3	15.0	21.4	6.2	15.3

Similarly, prevalence of hypercalcemia showed variability over the months after transplantation. Note also very few patients had their calcium done as they approached 12 months post transplantation.

5.8 PHOSPHATES

Table 22: Prevalence of Hypophosphataemia

MONTH	1	3	6	9	1 2
N	58	20	12	16	13
Hyperphosphataemia (%)	1(1.7)	0(0.0)	0(0.0)	3(18.75)	1(7.6)
Hypophosphataemia (%)	13(22.3)	4(25)	2(16.6)	6(37.5)	4(30.7)

A high prevalence of hypophosphataemia was demonstrated in the study population compared to hyperphosphataemia.

5.9 URIC ACID

Table 23: Prevalence of Hyperuricaemia (High Uric Acid Levels) Male>420, Female >390

month	1	3	6	9	12
N	28	14	7	10	7
MALE>420,FEMALE >390	6/16,4/12	3/12, 0/2	3/4, 0/3	2/6, 1/4	3/4, 1/3

We found hyperuricaemia in **30.4%**and low uric acid levels in **21.3%** of our study patients.

PREVALENCE OF HYPOMAGNAESIMIA/HYPERMAGNAESIMIA

	LOW	HIGH
N,%	11/37(29.7%)	1/37(2.7%)

Only 37 patients had their magnesium done in the first year postransplantation.

In the studied patients 29.7% had hypomagnesaemia.

CHAPTER SIX

DISCUSSION

6.1 POTASSIUM-

Our study found an incidence of hyperkalaemia 9.3**%.**

Hyperkalemia is described as a common complication in renal allograft recipients and is reported to have an incidence ranging from 25 to 44% in kidney transplant recipients on calcineurin inhibitors [CNIs].

The low incidence in our study may be explained by the low numbers of study subjects and the high number of patients on loop diuretics. In our study it was not possible to compare rates of hyperkalaemia in patients on different CNIs.

Very few patients were on cyclosporine.

Patients on tacrolimus have been reported to have more frequent hyperkalemia when compared to patients on cyclosporine. A very weak positive correlation between Potassium and age, duration or age of allograft was noted. Also, a weak negative correlation between potassium levels and tacrolimus level was noted. There was no difference in potassium levels across gender.

6.2 SODIUM-

We found hyponatraemia in 13% in our study. This is not widely reported in studies. The low levels in our study could be explained by possibility of low salt intake in many of the patients who had hypertension, weight gain, possibility of coexistent dyslipidaemia, use of steroids, and use of diuretics.

6.3 CALCIUM

We found an incidence of hypercalcaemia of **8.3%**.Hypercalcemia after kidney transplantation has been reported to occur with a very high variability from around 10 to 59%. Usually related to treatment of CKD -Mineral bone disorders, improved production of calcitriol post-transplant and steroid therapy.

6.4 PHOSPHATES

We found an incidence of hypophosphataemia **of 22.9%**.Hypophosphatemia in kidney transplant recipients has been reported with varying incidence from 40 to 93% in different studies. Data indicate that the incidence of hypophosphatemia peaks at week two post-kidney transplant and renal phosphate wasting usually regresses by 1 year after successful kidney transplantation

6.5 MAGNESIUM

We found an incidence of 36.4% of hypomagnaesimia. Hypomagnesemia is reported with high prevalence with lowest serum magnesium concentration noticed around second month post transplantation. In 20% of the renal transplant recipients, hypomagnesemia might persist several years after transplantation. The small number of patients studied could not allow further interrogation of the hypomagnaesemia i.e.-relation to diabetes,age or immunosuppressant drugs

6.6 URIC ACID

We found hyperuricaemia in **30.4%**and low uric acid levels in **21.3%** of our study patients. This could be explained by the fact that very few of our patients are on cyclosporin which has been found to cause hyperuricaemia and gout.Tacrolimus has minimal effect on uric acid metabolism

7.7 CONCLUSION

There are significant electrolyte imbalances in our post-transplant population with hypomagnesaemia being the commonest electrolyte imbalance.

APPENDIX 1

Study timelines

s/n	Activity	Timeline						
		May‘19	Jun‘19	Jul ‘19	Aug ‘19	Sept ‘19	Oct ‘19	Nov‘19
1	Protocol presentation and corrections	⇒						
2	Submission of protocol for ethics for approval		⇒					
3	Data collection		⇒	⇒				
4	Data analysis				⇒			
5	Results presentation					⇒		
6	Corrections and write up submission						⇒	
7	Final write up submission							⇒

APPENDIX 2

NORMAL RANGES

Urea and electrolytes (U&Es)

Na^+ – 133–146 mmol/ L

K^+ – 3.5–5.3 mmol/ L

Ca^{2+} (adjusted) – 2.2-2.6 mmol/L

Mg^{2+} – 0.7–1.0 mmol/ L

Urea – 2.5 – 7.8 mmol/L

Creatinine – (MALE 59–104 µmol/ L) // (FEMALE 45–84 µmol/ L)

Uric acid (umol/litre) MALE 150-420,FEMALE-120-390

APPENDIX 3
STUDY PROFORMA

1. SOCIODEMOGRAPHIC DATA

DATE OF INTERVIEW……..

STUDY NUMBER……..

FILE NUMBER……

SEX/GENDER MALE FEMALE

YEAR OF BIRTH….. ….. ……

AGE……..

BP…../…….,HEIGHT……CM WEIGHT…….KG BMI…….

2. DATE OF TRANSPLANT…….. …… ……..

3. DURATION SINCE TRANSPLANTATION…… (Months)

4. SOURCE OF ALLOGRAFT

1. CADAVERIC

2. LIVING RELATED KIDNEY DONOR

5. IF LIVING RELATED DONOR, RELATIONSHIP

1. SIBLING: BROTHER

SISTER

2. PARENT. FATHER……..MOTHER…….

3. SPOUSE WIFE…. HUSBAND……..

4. COUSIN

5. NIECE…… NEPHEW……..

6. OTHER…….

6. PRIMARY RENAL DISEASE LEADING TO TRANSPLANTATION

1. HYPERTENSION

2. DIABETES MELLITUS

3. CHRONIC GLOMERULONEPHRITIS

4. AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

5. LUPUS NEPHRITIS/CONNECTIVE TISSUE DISEASE

6. UNKNOWN

7. OTHERS

7. IMMUNOSUPPRESSION MEDICATIONS

1. CYCLOSPRIN-A

2. TACROLIMUS

3. MYCOPHENOLATE MOFETIL/MYCOPHENOLATE SODIUM

4. GLUCOCORTICOIDS

5. SIROLIMUS

6. EVEROLIMUS

7. AZATHIOPURINE

8. PROTON PUMP INHIBITORS

1. PANTOPRAZOLE

2. OMEPRAZOLE

3. LANSOPRAZOLE

4. ESOMEPRAZOLE

5. RABEPRAZOLE

9. ORAL GLUCOSE LOWERING AGENTS

1. METFORMIN

2. SULPHONYLUREAS: GLICLIZIDE

GLIMEPIRIDE

GLIBENCLAMIDE

3. DPP4 INHIBITORS

4. OTHERS

9. ANTIHYPERTENSIVES

1. DIURETICS-

1.FRUSEMIDE

2.HYDROCHLOROTHIAZIDE

3.TORASEMIDE

4.METOLAZONE

5.BENDROFLUTHIAZIDE

2. ANGIOTENSIN CONVERTING ENZYME INHIBITORS

1. ENALAPRIL
2. CAPTOPRIL
3. RAMIPRIL
4. LISINOPRIL
5. PERINDOPRIL

10. ANGIOTENSIN RECEPTOR BLOCKERS

1. LOSARTAN

2. VALSARTAN

3. CANDESARTAN

4. TELMISARTAN

5. IRBERSARTAN

11. BETA BLOCKERS

a. ATENOLOL
b. NEBIVOLOL
c. CARVEDILOL
d. METOPROLOL
e. LABETALOL

12. CALCIUM CHANNEL BLOCKERS

NIFEDIPINE

AMLODIPINE

NICARDIPINE

DILTIAZEM

VERAPAMIL

FELODIPINE

OTHERS: CLONIDINE

MINOXIDIL

HYDRALLAZINE

APPENDIX 4

BIOCHEMICAL PARAMETERS

1. UREA
2. CREATININE…….ESTIMATED GLOMERULAR FILTRATION RATE (MDRD)……..
3. SERUM SODIUM
4. SERUM POTASSIUM
5. SERUM CHLORIDE
6. SERUM IONIC CALCIUM
7. SERUM PHOSPHATE
8. SERUM MAGNESIUM
9. URIC ACID LEVELS

REFERENCES

1. Einollahi B, Nemati E, Rostami Z, Teimoori M, Ghadian AR. Electrolytes disturbance and cyclosporine blood levels among kidney transplant recipients. Int J Organ Transplant Med. (2012) 3:166–75.

2. Jones JW, Gruessner RW, Gores PF, Matas AJ. Hypoaldosteronemic hyporeninemic hyperkalemia after renal transplantation. Transplantation (1993) 56:1013–5.

3. Kaplan B, Wang Z, Abecassis MM, Fryer JP, Stuart FP, Kaufman DB. Frequency of hyperkalemia in recipients of simultaneous pancreas and kidney transplants with bladder drainage. Transplantation (1996) 62:1174–5. doi: 10.1097/00007890-199610270-00025

4. Higgins R, Ramaiyan K, Dasgupta T, Kanji H, Fletcher S, Lam F, 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) 19:444–50. doi: 10.1093/ndt/gfg515

5. Palmer BF. Regulation of potassium homeostasis. Clin J Am Soc Nephrol. (2015) 10:1050–60. doi: 10.2215/CJN.08580813

6. Rosenbaum R, Hoffsten PE, Cryer P, Klahr S. Hyperkalemia after renal transplantation. Occurrence in a patient with insulindependent diabetes. Arch Intern Med. (1978) 138:1270–2. doi: 10.1001/archinte.1978.03630330070020

7. Choi MJ, Fernandez PC, Patnaik A, Coupaye-Gerard B, D'Andrea D, Szerlip H, et al. Brief report: trimethoprim-induced hyperkalemia in a patient with AIDS. N Engl J Med. (1993) 328:703–6. doi: 10.1056/NEJM199303113281006

8. Zmarlicka M, Martin ST, Cardwell SM, Nailor MD. Tolerability of lowdose sulfamethoxazole/trimethoprim for Pneumocystis jirovecii pneumonia prophylaxis in kidney transplant recipients. Prog Transplant. (2015) 25:210–6. doi: 10.7182/pit2015153

9. Kleyman TR, Roberts C, Ling BN. A mechanism for pentamidine-induced hyperkalemia: inhibition of distal nephron sodiumtransport. Ann InternMed.

(1995) 122:103–6. doi: 10.7326/0003-4819-122-2-199501150-00004
10. Shin JI, Palta M, Djamali A, Kaufman DB, Astor BC. The association between Renin-angiotensin system blockade and long-term outcomes in renal transplant recipients: the Wisconsin Allograft Recipient Database (WisARD). Transplantation (2016) 100:1541–9. doi: 10.1097/TP.0000000000000938
11. Heering PJ, Kurschat C, Vo DT, Klein-Vehne N, Fehsel K, Ivens K. Aldosterone resistance in kidney transplantation is in part induced by a downregulation
of mineralocorticoid receptor expression. Clin Transplant. (2004) 18:186–92. doi: 10.1046/j.1399-0012.2003.00154.x
12. Deppe CE, Heering PJ, Viengchareun S, Grabensee B, Farman N, Lombes M. Cyclosporine a and FK506 inhibit transcriptional activity of the human mineralocorticoid receptor: a cell-based model to investigate partial aldosterone resistance in kidney transplantation. Endocrinology (2002) 143:1932–41. doi: 10.1210/endo.143.5.8821
13. Hoorn EJ, Walsh SB, McCormick JA, Furstenberg A, Yang CL, Roeschel T, et al. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. Nat Med. (2011) 17:1304–9. doi: 10.1038/nm.2497
14. Lazelle RA, McCully BH, Terker AS, Himmerkus N, Blankenstein KI, Mutig K, et al. Renal deletion of 12 kDa FK506-Binding protein attenuates Tacrolimus-induced hypertension. J Am Soc Nephrol. (2016) 27:1456–64. doi: 10.1681/ASN.2015040466
15. Skorecki K, Chertow GM, Marsden PA, Brenner BM, Rector FC. Brenner & Rector's the Kidney. Philadelphia, PA: Elsevier (2016).
16. Marfo K, Glicklich D. Fludrocortisone therapy in renal transplant recipients with persistent hyperkalemia. Case Rep Transplant. (2012) 2012:586859. doi: 10.1155/2012/586859
17. Scott TR, Graham SM, Schweitzer EJ, Bartlett ST. Colonic necrosis following sodiumpolystyrene sulfonate (Kayexalate)-sorbitol enema in a renal

transplant patient. Report of a case and review of the literature. Dis Colon Rectum. (1993) 36:607–9. doi: 10.1007/BF02049870
18. Pirenne J, Lledo-Garcia E, Benedetti E, West M, Hakim NS, Sutherland DE, et al. Colon perforation after renal transplantation: a single-institution review. Clin Transplant. (1997) 11:88–93.
19. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. (2015) 372:211–21. doi: 10.1056/NEJMoa1410853
20. Lee J. Pharmacokinetic Study of Tacrolimus and Mycophenolate Mofetil in Kidney Transplant RecipientsWith Hyperkalemia Receiving Patiromer. (2017). Available online at: https://ClinicalTrials.gov/show/NCT03229265
21, Messa P, Cafforio C, Alfieri C. Clinical impact of hypercalcemia in kidney transplant. Int J Nephrol. (2011) 2011:906832. doi: 10.4061/2011/906832
22. Evenepoel P, Van Den Bergh B, NaesensM, De Jonge H, Bammens B, Claes K,et al. Calcium metabolism in the early posttransplantation period. Clin J Am Soc Nephrol. (2009) 4:665–72. doi: 10.2215/CJN.03920808
23. Reinhardt W, Bartelworth H, Jockenhovel F, Schmidt-Gayk H, Witzke O, Wagner K, et al. Sequential changes of biochemical bone parameters after kidney transplantation. Nephrol Dial Transplant. (1998) 13:436–42. doi: 10.1093/oxfordjournals.ndt.a027843
24. Massari PU. Disorders of bone and mineral metabolism after renal transplantation. Kidney Int. (1997) 52:1412–21. doi: 10.1038/ki.1997.469
25. PeacockM. Calciummetabolismin health and disease. Clin J Am Soc Nephrol. (2010) 5(Suppl. 1):S23–30. doi: 10.2215/CJN.05910809
26. Seldin DW. Renal handling of calcium. Nephron (1999) 81(Suppl. 1):2–7. doi: 10.1159/000046292
27. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol. (2015) 10:1257–72. doi: 10.2215/CJN.09750913
28. Evenepoel P, Claes K, Kuypers D, Maes B, Bammens B, Vanrenterghem Y. Natural history of parathyroid function and calcium metabolism after

kidney transplantation: a single-centre study. Nephrol Dial Transplant. (2004) :1281–7. doi: 10.1093/ndt/gfh128
29. Schwartz GH, David DS, Riggio RR, Saville PD, Whitsell JC, Stenzel KH, et al. Hypercalcemia after renal transplantation. Am J Med. (1970) 49:42–51. doi: 10.1016/S0002-9343(70)80112-7
30. Torres A, Lorenzo V, Salido E. Calcium metabolism and skeletal problems after transplantation. J Am Soc Nephrol. (2002) 13:551–8.
31. Kim YJ, Kim MG, Jeon HJ, Ro H, Park HC, Jeong JC, et al. Clinical manifestations of hypercalcemia and hypophosphatemia after kidney transplantation. Transplant Proc. (2012) 44:651–6. doi: 10.1016/j.transproceed.2011.12.050
32. David DS, Sakai S, Brennan BL, Riggio RA, Cheigh J, Stenzel KH, et al. Hypercalcemia after renal transplantation. Long-term follow-up data. N Engl J Med. (1973) 289:398–401. doi: 10.1056/NEJM197308232890804
33. Ozdemir FN, Afsar B, Akgul A, Usluogullari C, Akcay A, Haberal M. Persistent hypercalcemia is a significant risk factor for graft dysfunction in renal transplantation recipients. Transplant Proc. (2006) 38:480–2. doi: 10.1016/j.transproceed.2005.12.065
34. Morales E, Gutierrez E, Andres A. Treatment with calcimimetics in kidney transplantation. Transplant Rev. (2010) 24:79–88. doi: 10.1016/j.trre.2010.01.001
35. Torregrosa JV, Barros X. Management of hypercalcemia after renal transplantation. Nefrologia (2013) 33:751–7. doi: 10.3265/Nefrologia.pre2013.Aug.11888
36. Cruzado JM, Moreno P, Torregrosa JV, Taco O, Mast R, Gomez-Vaquero C, et al. A Randomized study comparing parathyroidectomy with cinacalcet for treating hypercalcemia in kidney allograft recipients with hyperparathyroidism. J Am Soc Nephrol. (2016) 27:2487–94. doi: 10.1681/ASN.2015060622
37. Narayan R, Perkins RM, Berbano EP, Yuan CM, Neff RT, Sawyers ES, et al. Parathyroidectomy versus cinacalcet hydrochloride-based medical

therapy in the management of hyperparathyroidism in ESRD: a cost utility analysis. Am J Kidney Dis. (2007) 49:801–13.doi: 10.1053/j.ajkd.2007.03.009
38. Evenepoel P, Cooper K, Holdaas H, Messa P, Mourad G, Olgaard K, et al. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. Am J Transplant. (2014) 14:2545–55. doi: 10.1111/ajt.12911
39. Borchhardt K, Sulzbacher I, Benesch T, Fodinger M, Sunder-Plassmann G, Haas M. Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation. Am J Transplant. (2007) 7:2515–21. doi: 10.1111/j.1600-6143.2007.01950.x
40. Borchhardt KA, Diarra D, Sulzbacher I, Benesch T, Haas M, Sunder-Plassmann G. Cinacalcet decreases bone formation rate in hypercalcemic hyperparathyroidism after kidney transplantation. Am J Nephrol. (2010) 31:482–9. doi: 10.1159/000304180
41. Bergua C, Torregrosa JV, Fuster D, Gutierrez-Dalmau A, Oppenheimer F, Campistol JM. Effect of cinacalcet on hypercalcemia and bone mineral density in renal transplanted patients with secondary hyperparathyroidism. Transplantation (2008) 86:413–7. doi: 10.1097/TP.0b013e31817c13e1
42. Van Laecke S, Van Biesen W. Hypomagnesaemia in kidney transplantation. Transplant Rev. (2015) 29:154–60. doi: 10.1016/j.trre.2015.05.002
43. Osorio JM, Bravo J, Perez A, Ferreyra C, Osuna A. Magnesemia in renal transplant recipients: relation with immunosuppression and posttransplant diabetes. Transplant Proc. (2010) 42:2910–3. doi: 10.1016/j.transproceed.2010.08.016
44. Margreiter R, European tacrolimus vs ciclosporin microemulsion renal transplantation study G. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. Lancet (2002) 359:741–6. doi: 10.1016/S0140-6736(02)07875-3
45. Trompeter R, Filler G, Webb NJ, Watson AR, Milford DV, Tyden G, et al. Randomized trial of tacrolimus versus cyclosporin

microemulsion in renal transplantation. Pediatr Nephrol. (2002) 17:141–9. doi: 10.1007/s00467-001-0795-9
46. Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J. (2012) 5(Suppl. 1):i3–14. doi: 10.1093/ndtplus/sfr163
47. Topf JM, Murray PT. Hypomagnesemia and hypermagnesemia. Rev Endocr Metab Disord. (2003) 4:195–206. doi: 10.1023/A:1022950321817
48. Nijenhuis T, Hoenderop JG, Bindels RJ. Downregulation of Ca2+ and Mg2+ transport proteins in the kidney explains tacrolimus (FK506)-induced hypercalciuria and hypomagnesemia. J Am Soc Nephrol. (2004) 15:549–57. doi: 10.1097/01.ASN.0000113318.56023.B6
49. Ledeganck KJ, De Winter BY, Van den Driessche A, Jurgens A, Bosmans JL, Couttenye MM, et al. Magnesium loss in cyclosporine-treated patients is related to renal epidermal growth factor downregulation. Nephrol Dial Transplant. (2014) 29:1097–102. doi: 10.1093/ndt/gft498
50. Lote CJ, Thewles A, Wood JA, Zafar T. The hypomagnesaemic action of FK506: urinary excretion of magnesium and calcium and the role of parathyroid hormone. Clin Sci. (2000) 99:285–92. doi: 10.1042/cs0990285
51. Agus ZS. Hypomagnesemia. J Am Soc Nephrol. (1999) 10:1616–22.
52. Dyckner T. Serum magnesium in acute myocardial infarction. Relation to arrhythmias. Acta Med Scand. (1980) 207:59–66. doi: 10.1111/j.0954-6820.1980.tb09676.x
53. Van Laecke S, Marechal C, Verbeke F, Peeters P, Van Biesen W, Devuyst O, et al. The relation between hypomagnesaemia and vascular stiffness in renal transplant recipients. Nephrol Dial Transplant. (2011) 26:2362–9. doi: 10.1093/ndt/gfq728
54. Holzmacher R, Kendziorski C,Michael Hofman R, Jaffery J, Becker B, Djamali A. Low serum magnesium is associated with decreased graft survival in patients with chronic cyclosporin nephrotoxicity. Nephrol Dial Transplant. (2005) 20:1456–62. doi: 10.1093/ndt/gfh831
55. Miura K, Nakatani T, Asai T, Yamanaka S, Tamada S, Tashiro K, et al. Role of hypomagnesemia in chronic cyclosporine nephropathy. Transplantation

(2002) 73:340–7. doi: 10.1097/00007890-200202150-00005
56. Asai T, Nakatani T, Yamanaka S, Tamada S, Kishimoto T, Tashiro K, et al. Magnesium supplementation prevents experimental chronic cyclosporine a nephrotoxicity via renin-angiotensin system independent mechanism. Transplantation (2002) 74:784–91. doi: 10.1097/00007890-200209270-00009
57. Gupta BK, Glicklich D, Tellis VA. Magnesium repletion therapy improved lipid metabolismin hypomagnesemic renal transplant recipients: a pilot study. Transplantation (1999) 67:1485–7. doi: 10.1097/00007890-199906150-00017
58. Gommers LM, Hoenderop JG, Bindels RJ, de Baaij JH. Hypomagnesemia in type 2 diabetes: a vicious circle? Diabetes (2016) 65:3–13. doi: 10.2337/db15-1028
59. Huang JW, Famure O, Li Y, Kim SJ. Hypomagnesemia and the risk of newonset diabetes mellitus after kidney transplantation. J Am Soc Nephrol. (2016) 27:1793–800. doi: 10.1681/ASN.2015040391
60. Van Laecke S, Van Biesen W, Verbeke F, De Bacquer D, Peeters P, Vanholder R. Posttransplantation hypomagnesemia and its relation with immunosuppression as predictors of new-onset diabetes after transplantation. Am J Transplant. (2009) 9:2140–9. doi: 10.1111/j.1600-6143.2009.02752.x
61. Cheungpasitporn W, Thongprayoon C, Harindhanavudhi T, Edmonds PJ, Erickson SB. Hypomagnesemia linked to new-onset diabetes mellitus after kidney transplantation: a systematic review and meta-analysis. Endocr Res. (2016) 41:142–7. doi: 10.3109/07435800.2015.1094088
62. Van Laecke S, Nagler EV, Taes Y, Van Biesen W, Peeters P, Vanholder R. The effect of magnesium supplements on early post-transplantation glucose metabolism: a randomized controlled trial. Transpl Int. (2014) 27:895–902. doi: 10.1111/tri.12287
63. Van Laecke S, Caluwe R, Huybrechts I, Nagler EV, Vanholder R, Peeters P, et al. Effect of Magnesium supplements on insulin secretion after kidney transplantation: a randomized controlled trial. Ann Transplant. (2017) 22:524–31. doi: 10.12659/AOT.903439
64. Rosanoff A, Weaver CM, Rude RK. Suboptimal magnesium status in the

United States: are the health consequences underestimated? Nutr Rev. (2012) 70:153–64. doi: 10.1111/j.1753-4887.2011.00465.x
65. Seifi S, Pezeshki ML, Khatami MR, Mazdeh MM, Ahmadi F, Maziar S. Postrenal
transplantation hypophosphatemia. Transplant Proc. (2003) 35:2645–6. doi: 10.1016/j.transproceed.2003.08.056
66. Ambuhl PM, Meier D, Wolf B, Dydak U, Boesiger P, Binswanger U. Metabolic aspects of phosphate replacement therapy for hypophosphatemia after renal transplantation: impact on muscular phosphate content, mineral metabolism, and acid/base homeostasis. Am J Kidney Dis. (1999) 34:875–83. doi: 10.1016/S0272-6386(99)70045-4
67. Messa P, Cafforio C, Alfieri C. Calcium and phosphate changes after renal transplantation. J Nephrol. (2010) 23(Suppl. 16):S175−81.
68. Evenepoel P, Meijers BK, de Jonge H, Naesens M, Bammens B, Claes K, et al. Recovery of hyperphosphatoninism and renal phosphorus wasting one year after successful renal transplantation. Clin J Am Soc Nephrol. (2008) 3:1829–36. doi: 10.2215/CJN.01310308
69. Wolf M, Weir MR, Kopyt N, Mannon RB, Von Visger J, Deng H, et al. A Prospective cohort study of mineral metabolism after kidney transplantation. Transplantation (2016) 100:184–93. doi: 10.1097/TP.0000000000
00823
70. Baia LC, Heilberg IP, Navis G, de Borst MH, Investigators N. Phosphate and FGF-23 homeostasis after kidney transplantation. Nat Rev Nephrol. (2015) 11:656–66. doi: 10.1038/nrneph.2015.153
71. Evenepoel P, Naesens M, Claes K, Kuypers D, Vanrenterghem Y. Tertiary ‘hyperphosphatoninism’ accentuates hypophosphatemia and suppresses calcitriol levels in renal transplant recipients. Am J Transplant. (2007) 7:1193–200. doi: 10.1111/j.1600-6143.2007.01753.x
72. Han SY, Hwang EA, Park SB, Kim HC, Kim HT. Elevated fibroblast growth factor 23 levels as a cause of early post-renal transplantation hypophosphatemia. Transplant Proc. (2012) 44:657–60.

doi: 10.1016/j.transproceed.2011.11.046
73. Sakhaee K. Post-renal transplantation hypophosphatemia. Pediatr Nephrol. (2010) 25:213–20. doi: 10.1007/s00467-009-1252-4
74. Tomida K, Hamano T, Ichimaru N, Fujii N, Matsui I, Nonomura N, et al. Dialysis vintage and parathyroid hormone level, not fibroblast growth factor-23, determines chronic-phase phosphate wasting after renal transplantation. Bone (2012) 51:729–36. doi: 10.1016/j.bone.2012.06.027
75. Barros X, Torregrosa JV, Martinez de Osaba MJ, Casals G, Paschoalin R, Duran CE, et al. Earlier decrease of FGF-23 and less hypophosphatemia in preemptive kidney transplant recipients. Transplantation (2012) 94:830–6. doi: 10.1097/TP.0b013e318264fc08
76. Ghanekar H, Welch BJ, Moe OW, Sakhaee K. Post-renal transplantation hypophosphatemia: a review and novel insights. Curr Opin Nephrol Hypertens. (2006) 15:97–104. doi: 10.1097/01.mnh.0000203187.49890.cc
77. van Londen M, Aarts BM, Deetman PE, van der Weijden J, Eisenga MF, Navis G, et al. Post-transplant hypophosphatemia and the risk of death-censored graft failure and mortality after kidney transplantation. Clin J Am Soc Nephrol. (2017) 12:1301–10. doi: 10.2215/CJN.10270916
78. Sanchez Fructuoso AI, Maestro ML, Calvo N, De La Orden V, Perez Flores I, Vidaurreta M, et al. Role of fibroblast growth factor 23 (FGF23) in the metabolism of phosphorus and calcium immediately after kidney transplantation. Transplant Proc. (2012) 44:2551–4. doi: 10.1016/j.transproceed.2012.09.070
79. Caravaca F, Fernandez MA, Ruiz-Calero R, Cubero J, Aparicio A, Jimenez F, et al. Effects of oral phosphorus supplementation on mineral metabolism of renal transplant recipients. Nephrol Dial Transplant. (1998) 13:2605–11. doi: 10.1093/ndt/13.10.2605
80. Bishop L. Nutritional tips for managing electrolyte imbalances in post-renal transplant patients. J Ren Nutr. (2012) 22:e37–8. doi: 10.1053/j.jrn.2012.04.001

81. Chadban S, Chan M, Fry K, Patwardhan A, Ryan C, Trevillian P, et al. The CARI guidelines. Nutritional management of hypophosphataemia in adult kidney transplant recipients. Nephrology (2010) 15(Suppl. 1):S48–51. doi: 10.1111/j.1440-1797.2010.01234.x
82. Messa PG, Alfieri C, Vettoretti S. Metabolic acidosis in renal transplantation: neglected but of potential clinical relevance. Nephrol Dial Transplant. (2016) 31:730–6. doi: 10.1093/ndt/gfv098
83. Golembiewska E, Ciechanowski K. Renal tubular acidosis–underrated problem? Acta Biochim Pol. (2012) 59:213−7.
84. Keven K, Ozturk R, Sengul S, Kutlay S, Ergun I, Erturk S, et al. Renal tubular acidosis after kidney transplantation–incidence, risk factors and clinical implications. Nephrol Dial Transplant. (2007) 22:906–10. doi: 10.1093/ndt/gfl714
85. Schwarz C, Benesch T, Kodras K, Oberbauer R, Haas M. Complete renal tubular acidosis late after kidney transplantation. Nephrol Dial Transplant. (2006) 21:2615–20. doi: 10.1093/ndt/gfl211
86. Rodriguez Soriano J. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol. (2002) 13:2160–70. doi: 10.1097/01.ASN.0000023430.92674.E5
87. Park S, Kang E, Park S, Kim YC, Han SS, Ha J, et al. Metabolic acidosis and long-term clinical outcomes in kidney transplant recipients. J AmSoc Nephrol. (2017) 28:1886–97. doi: 10.1681/ASN.2016070793
88. Tanrisev M, Gungor O, Kocyigit I, Kurtulmus Y, Tugmen C, Colak H, et al. Renal tubular acidosis in renal transplant patients: the effect of immunosuppressive drugs. Ann Transplant. (2015) 20:85–91. doi: 10.12659/AOT.892320
89. Cho BS, Kim HS, Jung JY, Choi BS, Kim HW, Choi YJ, et al. Severe renal tubular acidosis in a renal transplant recipient with repeated acute rejections and chronic allograft nephropathy. Am J Kidney Dis. (2003) 41:E6. doi: 10.1053/ajkd.2003.50063
90. Watanabe S, Tsuruoka S, Vijayakumar S, Fischer G, Zhang Y, Fujimura A, 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:F40–7. doi: 10.1152/ajprenal.00218.2004
91. 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:F499–509. doi: 10.1152/ajprenal.90489.2008
92. Probst P, Soleiman A, Zbornay V, Benesch T, Haas M. The effect of kidney transplantation on distal tubular vacuolar H+-ATPase. Transplantation (2008) 85:391–7. doi: 10.1097/TP.0b013e3181622f7d
93. Yakupoglu HY, Corsenca A, Wahl P, Wuthrich RP, Ambuhl PM. Posttransplant acidosis and associated disorders of mineral metabolism in patients with a renal graft. Transplantation (2007) 84:1151–7. doi: 10.1097/01.tp.0000287430.19960.0e
94. Heering P, Degenhardt S, Grabensee B. Tubular dysfunction following kidney transplantation. Nephron (1996) 74:501–11. doi: 10.1159/000189443
95. Van den Berg E, Engberink MF, Brink EJ, van Baak MA, Joosten MM, Gans RO, et al. Dietary acid load and metabolic acidosis in renal transplant recipients. Clin J Am Soc Nephrol. (2012) 7:1811–8. doi: 10.2215/CJN.04590512