Nutrition Disturbances and Metabolic Complications in Kidney Transplant

Subjects: Transplantation

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Nutrition disturbances occur at all stages of chronic kidney disease and progress with the decrease of the kidney filtration rate. Kidney transplantation (KTx) as the best form of kidney replacement therapy poses various nutritional challenges. Prior to transplantation, recipients often present with mild to advanced nutrition disturbances. A functioning allograft not only relieves uremia, acidosis, and electrolyte disturbances, but also resumes other kidney functions such as erythropoietin production and vitamin D3 metabolism. KTx recipients represent a whole spectrum of undernutrition and obesity. Since following transplantation, patients are relieved of most dietary restrictions and appetite disturbances; they resume old nutrition habits that result in weight gain. The immunosuppressive regimen often predisposes them to dyslipidemia, glucose intolerance, and hypertension. Moreover, most recipients present with chronic kidney graft disease at long-term follow-ups, usually in stages G2–G3T. Therefore, the nutritional status of KTx patients requires careful monitoring.

kidney transplantation nutrition disturbances metabolic complications dietary treatment

1. Etiology of Nutrition Disturbances in Chronic Kidney Disease

Chronic kidney disease (CKD) affects over 10% of the worldwide population and is one of the leading causes of mortality [1]. CKD is inevitably associated with nutrition disturbances. The links between nutritional status and quality of life, psychological well-being, physical fitness, morbidity, or even mortality have been scrutinized for decades. The 2020 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for nutrition in CKD patients stress the importance of early detection and screening, recommending comprehensive nutritional assessments to be regularly performed [2]. The best treatment of end-stage kidney disease (ESKD) is kidney transplantation (KTx). The nutrition disturbances of CKD patients, including KTx recipients, are complex and depend on the glomerular filtration rate (eGFR), the cause of ESKD, the history and duration of dialysis prior to transplantation, the time since transplantation, pharmacotherapy including immunosuppression both before and after KTx, the comorbidity burden (i.e., diabetes mellitus (DM), including post-transplant DM (PTDM), hypertension, cardiovascular (CV) complications, and bone and mineral disturbances), and finally dietary habits and lifestyle choices [3].

Several subtypes of nutrition disturbances have been described in the CKD population. Despite many obese individuals in this population, undernutrition is more common in the forms of protein–energy wasting (PEW), malnutrition-inflammation-atherosclerosis syndrome (MIA syndrome), and dynapenia and uremic wasting [4];

naturally, obese individuals also suffer from these conditions. These pathologies all result from different combinations of chronic inflammation, uremic toxemia, and hypermetabolism [4]. The expert panel gathered by the International Society of Renal Nutrition and Metabolism proposed the following criteria of PEW: reduced overall body (or fat) mass, reduced muscle mass or the presence of sarcopenia, the reduced dietary intake of energy or protein, and low levels of the following serum markers: albumin, cholesterol, and transthyretin (previously known as prealbumin) [4]. Its causes include increased catabolism, dyselectrolytemia, metabolic acidosis, insulin resistance, and other endocrine disorders, such as hyperparathyroidism, hyperglucagonemia, or the deficiency of multiple vitamins including vitamin D. Patients treated with dialysis lose water-soluble micro- and macronutrients during both hemodialysis (HD) and peritoneal dialysis (PD). MIA syndrome describes the coexistence of malnutrition with chronic inflammation and atherosclerosis, all of which are poor prognostic factors for CKD. Reportedly, recipients who exhibit signs of MIA prior to transplantation have a greater risk of post-KTx CV events [3]. Aside from increasing the CV risk, it also impairs muscle function, which leads to dynapenia—a state of decreased muscle strength independent of muscle mass loss [5].

The progression of CKD and the associated toxemia exacerbate malnutrition. Diminished appetite is a common complaint of CKD patients, who often suffer from taste disturbances, delayed gastric emptying, and constipation. Uremia and anemia increase the incidences of gastropathy, Helicobacter pylori infection, and uremic gastritis [6]. Bowel edema facilitates bacterial translocation and endotoxemia, the severity of which increase with CKD progression and peak once dialysis is introduced. Through stimulating chronic inflammation, endotoxemia forms a non-traditional CV risk factor in CKD [7]. Metabolic acidosis, which occurs more frequently with CKD progression, contributes to malnutrition via appetite loss, taste distortion, and MIA exacerbation. Correcting acid–base disturbances has the potential of improving malnutrition [8]. The malnutrition burden is characteristic of ESKD patients who then undergo kidney transplantation.

KTx as the best form of kidney replacement therapy poses different nutritional challenges. A functioning allograft not only relieves uremia, acidosis, and electrolyte disturbances, but also resumes other kidney functions such as erythropoietin production and vitamin D3 metabolism. Studies suggest that kidney transplantation is protective against endotoxemia-induced chronic inflammation associated with bacterial translocation [9]. However, it is important to remember that only a small percentage of KTxs are preemptively performed; most recipients are treated before KTx with maintenance HD or rarely with PD. Moreover, most recipients present with chronic kidney graft disease long-term after KTx, usually from stages G2–G3T [10]. Hence, prior to transplantation, recipients often present with mild to advanced nutrition disturbances [10]; potential recipients rarely present with obesity, since a BMI > 35kg/m^2 is considered a modifiable exclusion criterion for KTx in most transplantation centers [11].

2. BMI in KTx Recipients

KTx recipients represent a whole spectrum of undernutrition and obesity. While a higher BMI is rarely related to adverse outcomes in HD patients [12], it appears disadvantageous in KTx patients [13]. In the perioperative period, obesity is associated with poor wound healing, prolonged hospitalization, and surgical complications including lymphoceles and delayed graft function [14]. In the late post-transplant period, obese individuals are more prone to

impaired graft function, the presence of proteinuria, PTDM, and atherosclerosis progression, which lead to hypertension and CV complications [13]. The largest increase in body mass occurs within the first 12 months following transplantation [15]. According to a study conducted in a Polish population, only about 35% of KTx recipients present with a normal BMI in a late post-transplant follow-up, 38% are overweight, and as many as 26% are obese. Overall, BMI increased in 65% of subjects and decreased in 24% after KTx. Interestingly, recipients with a normal BMI prior to KTx experienced a greater increase in BMI compared with their overweight peers; the increase in BMI was 0.6 ± 3.5 kg/m^2 for obese individuals and 1.9 ± 2.4 kg/m^2 for those with a normal BMI [15]. Weight gain in the first 12 months is associated with HD vintage; the longer the HD vintage, the greater the weight gain [16]. Although obesity remains the main focus in nutrition studies, being underweight has also been linked to poor graft function [17]. A meta-analysis showed that both BMI extremes—being obese and underweight—at the time of KTx were associated with worse survival and graft function [18].

3. Immunosuppression and the Nutritional Status

The immunosuppressive regimen alone has a disadvantageous effect on the nutritional status. Calcineurin inhibitors (CNIs: tacrolimus (TAC) and cyclosporine A) and m-TOR inhibitors (everolimus and sirolimus) included in the standard immunosuppressive regimen have an unfavorable metabolic profile. They all lead to dyslipidemia, hypertension, and hyperkalemia. CNIs (mainly TAC) and m-TOR inhibitors, as well as glucocorticosteroids (GCSs), may cause PTDM. Additionally, they may be a cause of fluid retention [19]. Cyclosporin A (CsA) also increases the risk of hyperuricemia [20]. All immunosuppressants, especially mycophenolates, also promote gastritis and intestinal erosions [6]. Mycophenolate mofetil has relatively few metabolic side-effects; however, common side-effects include gastrointestinal distress, which contributes to malabsorption and dysbiosis [21]. Reportedly, one of the most common reasons behind mycophenolate mofetil dose reduction (or rarely, discontinuation) is gastrointestinal distress [22].

Adverse effects of GCSs also include a loss of skeletal muscle mass, increased appetite, and visceral obesity [23]. Those combined with alleviated dietary restrictions cause post-KTx weight gain, which as body composition analysis shows, is mostly due to an increase in fat tissue mass. GCSs cause an unfavorable shift in body composition, with increased muscle wasting and adiposity. It was shown that early steroid withdrawal is supposedly linked to an increase in lean mass percentage [24]; however, it could increase the risk of graft rejection.

Drug–food interactions are crucial in the KTx population to maintain the desired blood trough levels of immunosuppressive medications and to avoid rejection or drug toxicity. CNIs are metabolized via the cytochrome P450 and the CYP3A4 and CYP3A5 enzymes. Restricted products include grapefruit and grapefruit juice, pomelo, and spices such as turmeric and ginger [25][26]. Herbal preparations with known interactions with CNIs include cat's claw (Uncaria tomentosa), devil's claw (grapple plant, Harpagophytum procumbens), and milk thistle (Silybum marianum). All of these inhibit the CYP3A4 cytochrome and thus increase blood levels of TAC and CsA; St John's wort on the other hand is a CYP3A4 inductor and thus decreases blood levels of CNIs [27]. Aside from direct metabolic interactions, different food groups alter the adsorption of the drug itself; high-fat meals delay TAC absorption. Hence, it is recommended to eat at least 2–3 h or 1 h after TAC ingestion [28]. Mycophenolate mofetil

on the other hand is often taken alongside meals to mitigate its gastrointestinal side-effects without decreasing the AUC of the mycophenolic acid [27].

In the early post-transplant period, symptoms such as nausea, vomiting, diarrhea, and abdominal pain are highly prevalent as medication doses are typically higher to meet target blood trough levels.

4. Dyslipidemia in KTx

Over 60% of KTx recipients suffer from dyslipidemia, with hyperlipidemia being the most common presentation. The immunosuppressive regimen is the main risk factor of the development of lipid disturbances in this population [29][30][31]. While HDL levels remain comparable or slightly decrease [32], triglyceride-rich VDL and LVDL particles, more prone to oxidation and thus more atherogenic, increase [31]. This disadvantageous shift in lipidemia is largely attributable to immunosuppressive pharmacotherapy. The negative impact of GCSs on carbohydrate metabolism and CV risk, including dyslipidemia, has been well documented [33]. Furthermore, CsA reduces cholesterol elimination associated with bile excretion through inhibiting the mitochondrial steroid 26-hydroxylase [34]. CsA reportedly increases LDL and triglycerides (TGs), while in subjects receiving TAC-based immunosuppressive schemes, dyslipidemia is less frequent; some studies report no relationship between TAC and blood lipid profiles [35]. Nevertheless, patients treated with TAC have a greater risk of developing PTDM [36]. Dyslipidemia remains one of the most common side-effects of m-TOR inhibitors. It presents as an increase of total cholesterol and LDL and TG levels and is observed in most patients treated with these kinds of immunosuppressive drugs [37]. The m-TOR signaling pathway regulates the uptake of lipids into adipose tissue, their breakdown by lipoprotein lipase [38], and the expression of hepatic LDL receptors [39]. It amounts to a 20–30% reduction in lipid storage and a 20% increase in basal lipolysis [38]. On the other hand, it has anti-atherosclerotic properties, such as improving the endothelial function, decreasing the number of macrophages in the atheromatous plaque, and inducing cholesterol efflux from macrophages, thus decreasing lipid accumulation [40]. Due to their antiproliferative effect on smooth muscle cells and their supposed atheromatous plaque stabilization, m-TOR inhibitors found another application in drug-eluting stents [41]. Ultimately, however, the results of large studies regarding m-TOR inhibitors and CV risk remain inconclusive.

5. Post-Transplant Diabetes Mellitus

PTDM is a frequent complication of KTx, affecting about 10–40% of kidney recipients [42]. Risk factors are often divided into two categories: pre- and post-transplantation. Some pre-transplant risk factors are the same as in type 2 DM: obesity with a BMI > 30 kg/m^2; an age > 40 years; a family history of DM; and Hispanic, African American, or Asian ethnicity. Several conditions, such as cystic fibrosis, polycystic kidney disease, hepatitis C, and CMV virus infection, also increase the odds of PTDM [19][43]. Post-transplant risk factors are largely associated with the immunosuppressive regimen. GCSs increase insulin resistance, hepatic gluconeogenesis, and the overall caloric intake through appetite stimulation [19]. CNIs may contribute to PTDM on many levels, including β-cell toxicity, as calcineurin regulates the survival of human β-cells in the pancreatic islets [44]. While TAC is seemingly preferable in

the context of dyslipidemia, clinical observations and many studies have shown a greater incidence of PTDM in subjects treated with TAC [45]. Wissing et al. conducted a prospective study and found that a conversion from TAC to CsA was associated with improved glucose metabolism, and in 34% of cases, a reversal of PTDM [46]. However, there are no strong recommendations for converting PTDM patients from TAC to CsA. Researchers have also stressed the role of pre-existing damage to the β-cells in cases of insulin-resistant or peridiabetic patients, which predisposes them to post-transplantation CNI-induced damage [47]. CNIs also contribute to the insulin resistance of adipose and skeletal muscle tissue [48]. Likewise, m-TOR inhibitors also contribute to PTDM (in animal models), sirolimus-inhibited β-cell proliferation, as well as the production and secretion of insulin [49]. In fact, the inhibition of the m-TOR pathway was suggested as another mechanism through which TAC induced diabetes [50]. There has been speculation about a possible link between intestinal dysbiosis and the development of PTDM [51].

There are no nutritional guidelines specifically targeted at patients with PTDM; thus, they must follow the same basic recommendations for all diabetic and CKD patients: limited monosaccharide consumption, a low salt intake, increased fiber consumption, and moderate physical activity performed for 150 min/week [2]. There are few intervention trials aimed at preventing PTDM. Interventions such as dietary counsel and the regular supervision of physical activity appear beneficial against insulin resistance [52]. The 2022 KIDGO guidelines for DM in CKD place nutrition and lifestyle at the base of the pyramid for lowering CV risk [53]. An increased vegetable intake and Mediterranean dietary patterns may prove beneficial in the prevention and management of PTDM; however, based on a 2022 systematic review, high-quality research is needed to confirm these findings [54].

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