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Current evidence on vitamin D deficiency and kidney transplant: What's new?

Gerardo Sarno[1] · Riccardo Nappi[1,2] · Barbara Altieri[3] · Giacomo Tirabassi[4] · Emanuele Muscogiuri[5] · Gianmaria Salvio[4] · Stavroula A. Paschou[6] · Aristide Ferrara[1] · Enrico Russo[1] · Daniela Vicedomini[1] · Cerbone Vincenzo[1] · Andromachi Vryonidou[7] · Silvia Della Casa[3] · Giancarlo Balercia[4] · Francesco Orio[8] · Paride De Rosa[1]

Abstract Kidney transplant is the treatment of choice for end-stage chronic kidney disease. Kidneys generate 1,25-dihydroxyvitamin D (calcitriol) from 25-hydroxyvitamin D (calcidiol) for circulation in the blood to regulate calcium levels. Transplant patients with low calcidiol levels have an increased risk of metabolic and endocrine problems, cardiovascular disease, type 2 diabetes mellitus, poor graft survival, bone disorders, cancer, and mortality rate. The recommended calcidiol level after transplant is at least 30 ng/mL (75 nmol/L), which could require 1000–3000 IU/d vitamin D3 to achieve. Vitamin D3 supplementation studies have found improved endothelial function and acute rejection episodes. However, since kidney function may still be impaired, raising calcidiol levels may not lead to normal calcitriol levels. Thus, supplementation with calcitriol or an analog, alfacalcidiol, is often employed. Some beneficial effects found include possible improved bone health and reduced risk of chronic allograft nephropathy and cancer.

Keywords Kidney transplantation · Vitamin D · Kidney graft survival · Cardiovascular disease · Bone mineral density · Malignancies

✉ Gerardo Sarno
gsarno79@yahoo.it

[1] General Surgery and Transplantation Unit - "San Giovanni di Dio e Ruggi D'Aragona" University Hospital, Scuola Medica Salernitana, 84131 Salerno, Italy

[2] Nephrology and Dialisys Unit - "Santa Maria della Misericordia" Hospital, ASUIUD – Udine, Udine, Italy

[3] Institute of Medical Pathology, Division of Endocrinology and Metabolic Diseases, Catholic University, Rome, Italy

[4] Division of Endocrinology, Department of Clinical and Molecular Sciences, Umberto I Hospital, Polytechnic University of Marche, Ancona, Italy

[5] Catholic University, Rome, Italy

[6] Division of Endocrinology and Diabetes, "Aghia Sophia" Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

[7] Department of Endocrinology and Diabetes, Hellenic Red Cross Hospital, Athens, Greece

[8] Endocrinology, Department of Sports Science and Wellness, "Parthenope" University Naples, Naples, Italy

1 Introduction

Patients with end-stage chronic kidney disease have the options of being treated by kidney transplantation or by dialysis, with transplantation presenting much better outcomes regarding cardiovascular events and overall survival, as well as quality of life and health costs [1, 2]. However, graft failure, metabolic and endocrine disorders, non-fatal or fatal cardiovascular events still exist and can increase the mortality risk of patients after transplantation up to 5% per year. The mortality risk is up to 3 times greater in patients with graft failure compared to those with functioning grafts [3, 4].

Vitamin D is a steroid hormone actively involved in the metabolic regulation of mineral and bone metabolism. In humans, it is primarily formed in the skin under the influence of ultraviolet-B radiation from sunlight exposure, while only a minority comes from nutritional sources or supplements [5]. Vitamin D requires two hydroxylation steps in order to become active as 1,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol), with second hydroxylation taking place primarily in the kidney [6]. Vitamin D regulates calcium and phosphate handling in the intestine and kidney, while it also downregulates bone turnover [6, 7]. Regarding kidney

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function, it has also been shown to suppress the renin angiotensin aldosterone system [8, 9], to improve glomerular and tubular interstitial fibrosis [10] and to reduce proteinuria [11]. On the other hand, vitamin D deficiency defined by The Endocrine Society as 25-hydroxyvitamin D [25(OH)D] concentrations (levels of less than 20 ng/ml (50 nmol/l) [12], has been associated with poor outcomes and higher all-cause mortality in patients with chronic kidney disease. As identification of modifiable factors that could improve graft function and related cardiovascular outcomes is of great importance, the investigation of the role of vitamin D in kidney transplantation is indeed interesting.

Decreased levels of 25(OH)D are very common in recipients of kidney transplants with deficiency present in up to 30% and insufficiency (20–30 ng/mL) in up to 81% of them [13]. Low levels of 25(OH)D usually persist in most patients and sometimes for longer than one year after transplantation [14–16], while $1,25(OH)_2D$ reaches normal levels earlier, usually within 3–6 months [17, 18]. Additionally to vitamin D insufficiency, vitamin D metabolism is also impaired. This results from alterations in the Parathyroid Hormone-Fibroblast Growth Factor 23 (PTH-FGF23) axis, as well as from the use of immunosuppressive agents [16, 19]. Consequently, patients with kidney transplants very commonly present loss of bone quantity and quality and sustained fracture risk. Bone loss has been described in up to 15% of them within the first 6 months post transplantation with improvement at the third year, while bone mineral density needs a much longer time to improve, occasionally up to 8 years [20–22]. Osteoporosis is present in 11% to 56% of these patients, while fracture risk ranges between 5% and 44% [23].

Data from observational as well as interventional studies have suggested a beneficial role of vitamin D in patients with renal transplant including various metabolic and endocrine parameters, cardiovascular disease, type 2 diabetes mellitus, graft survival and bone disorders. Recent data from stable patients with kidney transplants revealed a clear and inverse association between low levels of 25(OH)D and all-cause mortality [16], while a previous study had not shown associations between low 25(OH)D levels and a 3-year increased risk for specific cardiovascular disease, which is the main cause of mortality in these patients [24]. Vitamin D is currently considered to have a protective effect on cardiovascular system due to its pleiotropic extra-mineral effects. Decreased levels of 25(OH)D three months after transplantation were found to be associated with worse kidney function, as expressed by lower GFR at 12 months and a further decline during follow-up [16, 17]. The aforementioned associations were observed only for 25(OH)D and not for $1,25(OH)_2D$ levels [16]. A positive association between 25(OH)D insufficiency and type 2 diabetes exists in the general population, while a recent study specifically indicated that 25(OH)D levels lower than 10 ng/ml at the time of transplantation represents an independent risk factor which doubles the risk for the presence of overt type 2 diabetes within the first post transplantation year [25].

Continuing with evidence from interventional studies, vitamin D supplementation (cholecalciferol) 3 to 12 months after transplantation did not alter the onset time of proteinuria or interstitial fibrosis nor the progression rate of GFR [26]. Two ongoing studies, one comparing high (100,000 IU) vs low doses (12,000 IU) of cholecalciferol every 2 weeks for 2 months and then monthly for 22 months (VITALE Study) [27], and another randomized, placebo-controlled, double-blinded study comparing a daily dose of 6800 IU over a time period of one year vs placebo (VITA-D Study), will elucidate the effect of native vitamin D supplementation on graft survival [28]. However, active vitamin D analogues, leading to receptor activation has already been shown to be very promising. Several randomized controlled trials (RCTs) with paricalcitol supplementation revealed a beneficial effect of this agent on proteinuria even though this was not included in the primary outcomes of these studies. Paricalcitol at low doses (3 μg/week) [29] as well as at escalating doses [30], was retrospectively associated with a significant reduction of proteinuria, at 24 and 6 months, respectively. Another RCT showed that oral paricalcitol 2 μg per day during the first post- transplantation year diminished the presence of fibrosis, compared to controls [31].

Regarding bone metabolism parameters, several studies indicated a significant effect of ergocalciferol or cholecalciferol supplementation on calcium and PTH levels normalization, in patients with kidney transplant [32–34]. However, the effects of these native forms of vitamin D on Bone Mass Density (BMD) remain controversial and the VITALE study is expected to clarify this ambiguity [27]. Compared to active vitamin D supplementation after transplantation, it has already been shown to reduce PTH levels and improve BMD [35–37]. One study reported a 30% reduction of PTH levels by paricalcitol in 78% of patients who received kidney transplant. A following study revealed an even greater reduction in PTH levels, without however any benefits on bone mass density [31]. In an already described RCT, patients who were randomized to receive paricalcitol showed improvement in vertebral BMD. Furthermore, both serum and urinary bone resorption markers were reduced compared to controls [30].

2 Vitamin D deficiency - related diseases after kidney transplantation

Vitamin D insufficiency or deficiency is common in patients after kidney transplantation and in most series 70%–90% of these patients present inadequate levels of vitamin D in short or long term follow-up after renal transplantation [25, 38–43]. Studies of the last decade

which investigated 25(OH)D levels in post-kidney transplantation are summarized in Table 1. Evidence suggests that insufficient levels of 25(OH)D in kidney transplant recipients correlate with an increased risk of poor outcome and chronic allograft nephropathy [16, 44, 45], cardiovascular diseases [46] and malignancy [47]. Moreover, hypovitaminosis D also plays an important role in the endocrine outcome of these patients, particularly in the maintenance of the mineral and bone metabolism and in the development of post-transplant diabetes mellitus (PTDM) [46].

One of the most important causes of morbidity in kidney transplant recipients is post-transplantation bone disease which is associated with high risk of fractures, hospitalization and mortality [48, 49]. There are three principal pathogenic factors which contribute to the development of post-transplantation bone disease: the pre-existing chronic kidney disease (CKD)-mineral and bone disorders (MBD) at the time of kidney transplantation, glucocorticoid (GC) and immunosuppressive therapy and the reduced renal function observed after transplantation [50]. However, in transplant recipients, vitamin D deficiency not only represents a risk of osteoporosis it-self, but is also involved in the development and progression of CKD-MBD and is worsened after GCs treatment and after the decrease of renal function (Fig. 1).

CKD-MBD is an alteration of bone and mineral metabolism presented in end stage CKD patients before kidney transplantation [51]. CKD-MBD is characterized by vitamin D deficiency, hyperphosphatemia, hyperparathyroidism, frequent hypocalcemia and elevated levels of FGF-23, which promotes renal phosphate excretion. These alterations implicate a change in bone mineralization and turnover, causing bone fragility and micro-structural deterioration and fractions, associated with a calcification of soft tissues and blood vessels [52]. CKD-MBD could have different clinical presentations, such as hyperparathyroid or adynamic bone disease, mixed osteodystrophy and osteomalacia [53]. Vitamin D deficiency represents one of the key features for the development of CKD-MBD. It is well demonstrated that patients with CKD present low serum levels of 25(OH)D and $1,25(OH)_2D$ and vitamin D resistance [52, 54]. There are several conditions that are associated with vitamin D deficiency in CKD patients, including reduced sun exposure, hyperpigmentation seen in late CKD stages, dietary restriction, but also female gender, African-American race, high latitude and winter season, low serum albumin levels and diabetes [55–58]. Moreover, the activation of calcidiol in calcitriol worsens in patients with CKD together with glomerular loss due to a reduction of the 1-α hydroxylase renal expression [50, 59]. 1-α hydroxylase is also inhibited by hyperphosphatemia, high level of FGF-23, hyperuricemia, uremia and acidosis, all conditions that are present in patients with CKD [60–62]. Vitamin D deficiency produces secondary hyperparathyroidism that, together with high levels of FGF-23, stimulates the expression of 24-hydroxylase that metabolizes calcidiol degradation [63]. The prolonged low serum of $1,25(OH)_2D$ implicate the progressive loss of vitamin D receptor (VDR) in the parathyroid glands, which causes a condition of vitamin D resistance [64].

GCs used for anti-inflammatory and immunosuppressive effects in transplanted recipients, cause the development of secondary osteoporosis in a dose-dependent manner [65, 66], which mainly damages the trabecular bone of the vertebral skeleton [67, 68]. GCs have a direct catabolic activity on bones by reducing osteoblast proliferation and differentiation, stimulating the apoptosis of both osteoblasts and osteocytes and promoting osteoclastogenesis [50, 69]. Therefore, GCs reduce the intestinal calcium absorption and increase its urine excretion, which stimulates persistent hyperparathyroidism [70], and stimulate genes codifying enzymes involved in the catabolism of 25(OH)D [71–73], contributing to a decrease of 25(OH)D levels and to as development of vitamin D deficiency status. In addition, Lee et al. showed that also immunosuppressive therapy based on calcineurin inhibitor, such as ciclosporine and tacrolimus, created a condition of vitamin D resistance suppressing the VDR, which could increase the renal calcium wasting [74].

Several studies investigate the changes in the mineral metabolism after kidney transplantation. Evenepoel et al. demonstrated that a good kidney graft function was the principal predictor of improved $1,25(OH)_2D$ serum levels [75]. The authors showed that also pre-transplantation PTH levels and a decrease of FGF-23 post-transplantation could be a predictor of higher level of $1,25(OH)_2D$ post-transplantation [75]. However, in spite of improving kidney function after transplantation, it has been demonstrated that in kidney transplant recipients, PTH decreased by 50% and 45% after 6 months and 2 years from transplantation, respectively [76]. Torres et al. described that only 23% of the studied patients presented normal level of PTH after a mean of 69 months from transplantation [77]. A persistent status of secondary hyperparathyroidism represents one of the most important factors causing bone damage after kidney transplantation [78]. Different factors contribute to a long-term secondary hyperparathyroidism in transplanted patients even with a good kidney graft function, such as the persistence of parathyroid enlargement and the development of parathyroid hyperplasia, the alteration of the calcium metabolism [79], but also polymorphisms of the VDR [79, 80] and the vitamin D deficiency status [81–83]. Giannini et al. showed that PTH serum levels were higher in patients with *bb* VDR polymorphism in comparison to *BB* VDR allele [80]. Therefore, the authors demonstrated that most patients who have a persistent secondary hyperparathyroidism, had the *bb* VDR allele. These results are in agreement with what was reported in a previous study [79]. The authors speculated that the *bb* haplotype could cause a decreased expression of the *VDR* mRNA, which could in turn decrease the

Table 1 Most relevant studies in the last 10 years which have evaluated 25(OH)D levels in renal transplant patients

Authors	Country, years	Study design	Number of patients	Time of control median (range)	Mean 25(OH)D levels ± SD or levels (range)	% insufficient 25(OH)D levels (20–29.9 ng/mL)	% deficient 25(OH)D levels (<20 ng/mL)
Querings et al. [14]	Germany, 2006	Cross-sectional study: renal transplant patients vs controls	31	7 (0.6–19) years after transplantation	10.9 vs 20.0	12.9	83.9
Stavroulopoulos et al. [38]*	UK, 2007	Cross-sectional study: short and long term follow-up	104 and 140	3.4 (1.9–12) months and 6 (1–24) years after transplantation	13.2 ± 7.6 and 16.8 ± 8	29% and 43%	68% and 51%
Sadlier et al. [15]	USA, 2007	Prospective study	112	At the time of transplantation	16.6 ± 9.6	88%	
Ewers et al. [40]*	Denmark, 2008	Cross-sectional study: female vs male	173	7.4 (3.3–12-7) years after transplantation	21.6 vs 18.2	45% vs 56%	29% vs 42%
Tripathi et al. [39]*	USA, 2008	Observational: African American patients	38	23 months after transplantation	16 ± 7.4	36.9%	57.8%
Giannini et al. [82]**	Italy, 2010	Retrospective observational study	125	44 ± 23 months after transplantation		57%	40%
Penny et al. [117]*	UK, 2012	Cross-sectional study: winter vs summer season	266	16 (12–23) years after transplantation	15.6 ± 10.8 vs 23.6 ± 12.4	32% vs 26%	59% vs 31%
Burkhalter et al. [118]	Switzerland, 2012	Cross-sectional study: winter vs summer season	50	11.1 (0.8–33.6) years after transplantation	12.4 vs 17.6	6% vs 26%	90% vs 60%
Mazzaferro et al. [119]	Italy, 2012	Cross-sectional study: chronic kidney disease patients treated with conservative therapy vs transplantation	111 vs 136	Non-transplanted vs transplanted patients	19.5 ± 13.3 vs 24.5 ± 10.9	82% vs 69.1%	
Marcén et al. [24]*	Spain, 2012	Observational prospective study	389	One year after transplantation	24.1 ± 10.7 and 13.1 ± 6.0 in insufficiency and deficiency patients	48.6%	28.7%
Yilmaz et al. [120]	Turkey, 2013	Longitudinal cohort study	161	Pre-transplantation vs 6 months after transplantation	18.1 ± 4 vs 22.0 ± 4.5	55.8%	
Beique et al. [121]	Canada, 2013	Retrospective observational study	331	After transplantation			76.5%
Bienaimé et al. [41]	France, 2013	Prospective study	634	3 (2–4) months after transplantation	13 (9–20)	18.9%	72.8%
Kulshrestha et al. [122]*	USA, 2013	Observational prospective study	74	3 months after transplantation	22.65	51.4%	29.7
Keyzer et al. [16]	Netherlands, 2014	Prospective observational single-center study	435	6.3 (3.1–11.7) years after transplantation	31.6 ± 9.1	33%	49%
Obi et al. [123]	Japan, 2014	Prospective single-center study	264	After transplantation	17.1 ± 6.5		
Lee JR et al. [124]	USA, 2014	Retrospective study	351	within the first 30 days of transplantation	20.2 ± 11.1		61.5%
Rizvi et al. [43]	Norway, 2015	Longitudinal study: winter and summer season	94	14.5 years after transplantation		67.0% in winter and 56.4% in summer	
Barros et al. [18]***	Multicenter, 2015	Longitudinal prospective observational study	98	Baseline and 6 months after transplantation	14.3 (9–22) vs 16.3 (10.1–20.6)	88.2% vs 89%	
Lee HH et al. [84]***	Korea, 2015	Retrospective study	25	Baseline and 6, 12, 24 months after transplantation	3.94 ± 0.79 vs 3.07 ± 0.63 vs 6.78 ± 1.36 vs 8.24 ± 1.65		68% (baseline) vs 40% (12 months) vs 28% (24 months)
Le Fur et al. [25]***	France, 2016	Prospective single-center study	444	At the time of transplantation	19.4 (3.4–160.0)	59.5%	19.8%

*considered insufficient 25(OH)D levels = 16–29.9 ng/ml and deficient 25(OH)D levels <16 ng/ml. **considered insufficient 25(OH)D levels = 12,4–32 ng/ml (31–80 nmol/L) and deficient 25(OH)D levels <12 ng/ml (<30 nmol/L). ***considered insufficient 25(OH)D levels = 10–29.9 ng/ml and deficient 25(OH)D levels: <10 ng/ml

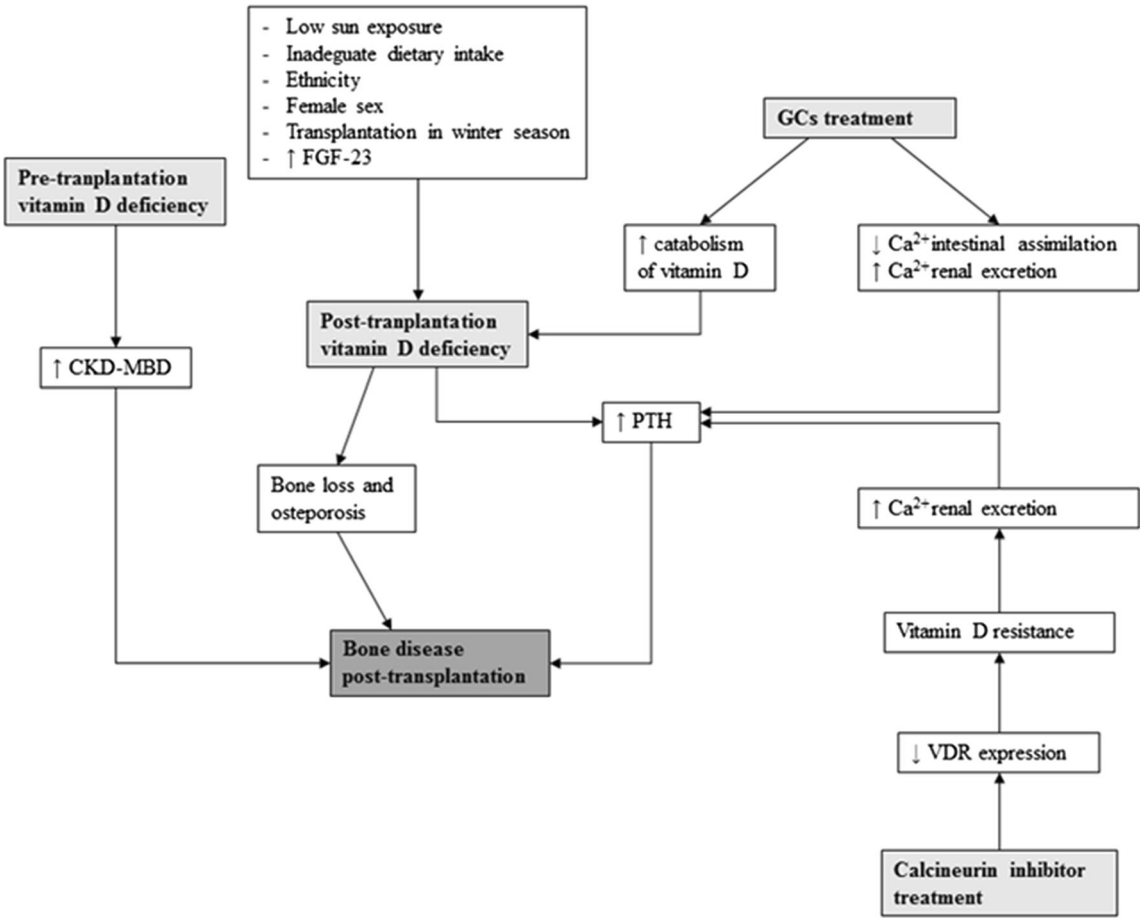

Fig. 1 Bone disease post-transplantation and vitamin D deficiency. In transplant kidney recipients, vitamin D deficiency not only represents a risk of osteoporosis itself, but is also involved in the development and progression of preexisting chronic kidney disease (CKD)-mineral and bone disorders (MBD) and worsens after glucocorticoids (GCs) treatment. In particular, vitamin D deficiency pre-transplantation improves the CKD-MDB, which is a risk factor for bone loss after transplantation. GCs treatment reduces the intestinal calcium (Ca^{2+}) absorption and increases its urine excretion, which stimulates persistent secondary hyperparathyroidism (↑PTH, elevate parathyroid hormone levels) and stimulates genes codifying enzymes involved in the catabolism of 25(OH)D contributing to a decrease of 25(OH)D. The immunosuppressive therapy based on calcineurin inhibitor created a condition of vitamin D resistance suppressing the VDR, which could increase the renal calcium wasting with a consequent stimulation of the PTH. All of these factors contribute to bone loss and the development of bone disease post-transplantation

calcitriol effects on parathyroid glands [80]. In a more recent study, the same group of authors demonstrated a negative correlation between the persistence of secondary hyperparathyroidism and 25(OH)D serum levels after kidney transplantation and that vitamin D deficiency was one of the major predictors of high PTH levels [82]. This association between low calcidiol levels and higher PTH concentrations were confirmed by Barros et al. [18]. The authors demonstrated also that in the first 6 months after kidney transplantation, $1,25(OH)_2D$ levels rapidly increased, whereas 25(OH)D levels remained low. They suggested that the increase and the normalization of calcitriol levels could be due to a decrease of FGF-23, while the persistence of low 25(OH)D levels could mainly be caused by reduced sun exposure recommended to transplant recipients to prevent skin cancer [18]. An improvement of $1,25(OH)_2D$ levels without an increase of 25(OH)D levels after 12 months from kidney transplantation was also observed by Lee et al. [84]. However, the authors, in contrast to what is reported above, but in agreement with what is described by Sezer et al. [85], did not find a correlation between 25(OH)D levels and PTH levels. Sezer et al. demonstrated also that low 25(OH)D levels can predict worsening renal graft function and an increase of proteinuria [85]. The correlation between low 25(OH)D levels and low glomerular filtration rate after 3 months from transplantation was confirmed also by a more recent study [41].

In conclusion, vitamin D plays a complex role in the regulation of mineral and bone metabolism pre- and post- renal transplantation and vitamin D deficiency or insufficiency worsens the bone-disease post-transplantation. Treatment with vitamin D supplementation before and after the kidney transplantation could improve bone metabolism.

The onset of type 2 diabetes mellitus after transplantation, defined as PTDM by a recent international consensus in 2013

[86] or defined as new-onset diabetes mellitus after transplantation (NODAT) by the American Diabetes Association (ADA) in 2003 [87], is a frequent metabolic complication that has been described in a large number of patients after solid organ transplantation. Different series reported an incidence of 10–45% in kidney transplant recipients [46, 88, 89]. Renal transplant patients which present the PTDM show the same complication that are described in the general population affected by type 2 diabetes mellitus, but at an accelerated rate [90, 91]. Thus, the PTDM is frequently associated with unfavorable outcomes, graft failure, cardiovascular events and impaired patient's survival [92, 93].

Transplanted kidney recipients have a high risk to development the PTDM for both traditional risk factors, such as age, ethnicity and obesity, and non-traditional risk factor, among which the immunosuppressive therapy, based on GCs, and cytomegalovirus infection [89]. Another important risk factor for the development of the PTDM is the status of vitamin D deficiency [25] that is frequent in a large percentage of patients after kidney transplantation [38, 41, 46]. Several *in vitro*, *in vivo* and human studies demonstrated that vitamin D could influence the β-cell function and insulin sensitivity [94]. Indeed, VDR are expressed both in pancreatic β-cells and in all insulin-responsive tissues such as liver, skeletal muscle and adipose tissue [95, 96]. Moreover, vitamin D, which could be locally activated due the expression of the 1-α-hydroxylase, improves the secretion of insulin trough the activation of the vitamin D response element (VDRE) in the insulin gene promoter of β-cells [96]. Vitamin D (25(OH)D) could also stimulate the expression of insulin receptors on target tissues, influencing directly the insulin sensitivity [97, 98].

In a very recent study by Le Fur et al. demonstrated in a large cohort of 444 patients that 25(OH)D deficiency at the time of transplantation was an independent risk factor for the development of PTDM with the first year after renal transplantation (HR 2.41, 95% CI 1.01–5.75, $P = 0.048$ in a multivariate analysis) [25]. At the time of kidney transplantation, 19.8% of recipients had vitamin D deficiency (considered as 25(OH)D < 10 ng/ml) and 59.5% had vitamin D insufficiency (considered as 25(OH)D ≥ 10 and <30 ng/ml), whereas the 13% of patients developed PTDM within one year. Le Fur et al. confirmed also the association of the known risk factors, such as age ≥ 55 years old, high body mass index (BMI), GCs and tacrolimus treatment, with the onset of PTDM. The authors speculated that 25(OH)D levels at the time of transplantation may be used as a potential marker of the risk of PTDM [25].

In conclusion, we could suppose that normal levels of 25(OH)D at the time of transplantation may preserve and maintain the β-cells function and may improve the insulin sensitivity of the responsive tissues. However, additional studies and controlled randomized trials are necessary to provide that vitamin D deficiency represents a risk for PTDM and to confirm the protective role of vitamin D supplementation.

3 Effects of vitamin D supplementation in kidney transplant patients

Several studies have evaluated the effects of vitamin D on different outcomes in renal transplant recipients (RTRs), including bone metabolism, cardiovascular disease (CVD), transplant-related results and cancer risk.

As far as bone outcome is concerned, the National Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines recommend supplementation with vitamin D in the case of 25(OH)D levels below 30 ng/ml in patients affected by stage 3–4 chronic kidney disease (CKD), whereas patients who have undergone kidney transplantation (KT) with disturbances in bone and mineral metabolism should be treated on the basis of their kidney function with the same recommendations valid for CKD patients [99].

Despite vitamin D insufficiency and even vitamin D deficiency are common findings in KT patients, most of these patients do not receive adequate supplementation, partially because of the unknown risk of inducing hypercalcemia, hypercalciuria or hyperphosphatemia [34]. In 2008, Courbebaisse et al. [34] studied a total of 94 RTRs and evaluated the effect of high doses of cholecalciferol on calcium-phosphate balance in 47 of them. The authors chose a threshold of target serum 25(OH)D of 30 ng/ml and they administered to patients in the treatment group four doses of 100,000 IU of cholecalciferol. After 12 months of follow up, they found that the regimen was not only safe but also increased serum 25(OH)D levels above the target level in most of the patients, decreasing serum PTH levels and consequently contrasting secondary hyperparathyroidism.

On the other hand, Jimenez Alvaro et al. [100] demonstrated that even low doses of cholecalciferol may be effective as much as high doses in improving vitamin D status. In fact, they compared 37 adult RTRs treated for 6–12 months with cholecalciferol (400–800 IU/d) and calcium supplements with 37 RTRs who did not receive treatment. Their data show that low doses of cholecalciferol increase significantly serum levels of 25(OH)D and help to reduce PTH levels, with no adverse effects on urinary calcium excretion.

Beyond 25(OH)D levels, patients who underwent renal transplantation are at high-risk for bone fractures. A large amount of evidence supports the use of classical osteoporosis medication in order to prevent further loss of BMD.

In this setting, El-Agroudy et al. [101] performed a 1-year single-blind trial on 60 adult RTRs who were allocated in 4 different groups of treatment: group I received alfacalcidol 0.5 mg/d PO, group II received alendronate 5 mg/d PO, group III received intranasal calcitonin (100 mcL every other day

and stopped for 1 month every 3 months) and group IV served as control group; all of them received daily calcium carbonate supplementation (500 mg/d). Even if all drugs were safe and effective in improving BMD, patients treated with alfacalcidol showed an evident reduction in PTH levels, suggesting a potential role in suppressing secondary hyperparathyroidism.

Similarly, several studies demonstrated a positive effect of vitamin D supplementation on BMD (Table 2) and calcium-phosphate balance using different metabolites, such as cholecalciferol [102, 103], 25-OH-cholecalciferol [104], alfacalcidol [101, 105] and calcitriol [37, 102, 103, 106–108]. The majority of these studies were designed to evaluate the effect of vitamin D supplementation after 12 months of treatment at least, even if some authors limited the follow up period to 6 months [102, 106, 109] and Berczi et al. [105] extended this period to 3 years. Furthermore, in 2005, El-Agroudy et al. [101] observed the greatest effect of vitamin D supplementation after 1 year of treatment with alfacalcidol, reporting a 2.1% increase of lumbar BMD on DXA (from 1.1 ± 0.12 g/cm^2 to 1.2 ± 0.11 g/cm^2) and a 3.2% increase in neck femur BMD (from 0.93 ± 0.1 g/cm^2 to 1.0 ± 0.02 g/cm^2). These data were in line with a previous study by Jeffery et al. [108], which showed a similar increase in lumbar and femur BMD (2.0% and 3.3%, respectively), but not with others [103, 106, 107] which demonstrated a protection against bone loss but stable values of BMD.

On the other hand, some authors found no advantages on BMD in treating RTRs with vitamin D supplementation. Nam et al. [109], for example, recruited 50 patients who were assigned to three groups: pamidronate treatment group, calcitriol treatment group and control group, all of them supplemented with 500 mg/d of elemental calcium. Patients treated with calcitriol (0,5 g/d for six months) had a significant reduction in BMD (−2.2 ± 1.5% at L2–4 and −1.4 ± 0.7% in femur neck), even if less pronounced than the one observed in the control group (−8.2 ± 2.3% at L2–4 and −5.1 ± 2.2% in femur neck). In the same way, Cueto-Manzano et al. [36] studied the effect of calcitriol plus calcium carbonate not only on BMD, but also on histomorphometric parameters (including osteoblast surface, osteoid surface and osteoclast surface). They recruited 30 patients who were allocated to control or treatment group and who underwent bone biopsy and densitometry at baseline and after one year of follow up. At the end of the study, they observed no difference in BMD between groups and no improvement in histomorphometric parameters in the treatment group or between groups.

Regarding cardiovascular outcomes, in 2016 Atis et al. [110], in order to investigate the potential role of vitamin D in improving the endothelial dysfunction of CKD patients and RTRs, presented a prospective single-arm study evaluating modifications in serum levels of Endocan and high-sensitivity C-reactive protein (hs-CRP) after 12 weeks from a single load of 300.000 IU cholecalciferol; they included in

Table 2 Studies investigating the efficacy of vitamin D supplementation after KT on bone disease by DEXA

Authors	Patients treated with vitamin D	Treatment(s)	Duration (months)	Effect
Talalaj et al. 1996 [104]	41	25(OH)cholecalciferol (40 μg/d) + calcium (3000 mg/d)	12	=
Nam et al. 2000 [109]	15	Calcitriol (0.5 μg/d) + calcium (500 mg/d) versus IV pamidronate (30 mg/4wk) + calcium (500 mg/d) versus calcium (500 mg/d)	6	↓
Cueto-Manzano et al. 2000 [36]	16	Calcitriol (0.25 μg/d) + calcium (500 mg/d) versus placebo	12	=
Ugur et al. 2000 [107]	Not specified	Calcitriol (0.5 μg/d) + calcium (3000 mg/d) versus calcitriol (0.5 μg/d) + calcium (3000 mg/d) + nasal calcitonin (200 IU/48 h) versus calcium (3000 mg/d) versus no treatment	12	=
De Sevaux et al. 2002 [106]	65	Calcitriol (0.25 μg/d) + calcium (1000 mg/d) versus no treatment	6	=
Berczi et al. 2003 [105]	81	Alfacalcidol (0.25–2 μ) versus calcium (1500–3000 mg/d)	36	=
Jeffery et al. 2003 [108]	51	Calcitriol (0.25 μg/d) + calcium (1500 mg/d) versus alendronate (10 mg/d) + calcium (1500 mg/d)	12	↑
Torres et al. 2004 [37]	45	Calcitriol (0.5 μg/48 h) + calcium (500 mg/d) versus placebo + calcium (500 mg/d)	12	=
El-Agroudy et al. 2005 [101]	15	Alfacalcidol (0.5 μg/d) + calcium (500 mg/d) versus alendronate (5 mg/d) + calcium (500 mg/d) versus intranasal calcitonin (100 μL every other day) + calcium (500 mg/d) versus calcium alone (500 mg/d)	12	↑
Mainra et al. 2010 [103]	58	Calcitriol (0.5 μg/d) or cholecalciferol (1000–4000 IU/d) versus alendronate (70 mg/wk) or intravenous zoledronate (4 mg)	12	=
Sikgenc et al. 2010 [102]	57	Calcitriol or cholecalciferol	6	↑

↑ improvement, ↓ worsening, = no changes

the data analysis only patients with levels of serum 25(OH)D > 30 ng/ml after treatment. They observed a significant decrease in median serum endocan levels (from 621.5 pg/ml to 538 pg/ml; $p = 0.001$), suggesting that adding vitamin D to the medication regimen in patients after KT could be useful to improve endothelial function.

Furthermore, Sikgenc et al. [102] reported a decrease in total cholesterol (from 183 ± 50 mg/dl to 173 ± 46 mg/dl) and triglycerides (from 167 ± 99 mg/dl to 143 ± 71 mg/dl) levels among patients treated with vitamin D versus placebo after a follow up of at least 6 months from KT. They also observed unchanged fasting glucose levels among patients in the treatment group. Thus, these data confirm the favorable effect of vitamin D supplementation on blood glucose and lipid parameters, supporting, consequently, the role of vitamin D in protecting against CVD in patients undergone KT.

Concerning specific transplant-related outcomes, vitamin D has been studied in the past for its immunosuppressive properties that may be useful in the clinical context of kidney transplantation. For this purpose, Ahmadpoor et al. [111] investigated the expression of co-stimulatory molecules and HLA-DR in 24 renal transplant recipients who were administered 0.5 mcg oral calcitriol daily for 4 weeks. They found that expression of HLA-DR, CD28, CD40 and CD86 was significantly decreased by treatment with vitamin D, confirming its role in regulating the immune response. Tanaci et al. [112], by conducting a retrospective study, found that RTRs affected by osteoporosis and treated with vitamin D showed a lower number of acute rejection episodes than not treated subjects. This is in line with *in vitro* results reported by Pérez et al. [113], who demonstrated that calcitriol acts on peripheral mononuclear cells decreasing proliferation and increasing apoptosis in those cells that were previously activated as a consequence of rejection. This is not surprising, since previous studies have already demonstrated the immunosuppressive effect of vitamin D and in particular on T-cell function, inhibiting production of interleukin 2 and gamma interferon [114].

In 2005, Sezer et al. [115] evaluated renal function in RTRs in a group of patients treated with calcitriol for osteoporosis compared to a group of patients not affected by osteoporosis and not treated with vitamin D. They reported that osteoporotic patients needed lower pulse steroid doses during acute rejection episodes and they had lower creatinine levels (1.6 ± 0.6 mg/dl vs 2.5 ± 2.2 mg/dl) suggesting a potential role for vitamin D in preventing chronic allograft nephropathy.

Finally, the relationship between malignancy risk in RTRs and vitamin D status is gaining increasing interest among physicians, because of the important incidence of cancer in patients who have undergone KT. In this context, Obi et al. [116] studied 262 ambulatory patients. They reported incidence rates of post-transplant malignancy of 2.1/100 patient-year in the alfacalcidol or calcitriol group and of 3.5/100 patient-year in not treated subjects, suggesting a potential role for vitamin D in chemoprevention against cancer. Also, the VITALE study [27], a prospective, multicenter, double-blind, randomized controlled trial will assess 640 RTRs who will be treated with high or low doses of vitamin D for at least 22 months to demonstrate the safety and efficacy of vitamin D supplementation on different endpoints, including *de novo* cancer.

4 Conclusion

Several studies and emerging evidences suggest an association between vitamin D deficiency and KT-related cardiovascular, metabolic and endocrine diseases. Besides bone disorders, in transplant patients low calcidiol levels are associated with an increased risk of poor graft survival, cancer, and eventually mortality rate.

Vitamin D supplementation should be considered as an effective tool to prevent or treat KT- related disease. Further studies still need to investigate the role of vitamin D in KT-related disease and the beneficial effect of vitamin D supplementation.

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Compliance with ethical standards

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