

## Vascular calcification, bone and mineral metabolism after kidney transplantation

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### Abstract

The development of end stage renal failure can be seen as a catastrophic health event and patients with this condition are considered at the highest risk of cardiovascular disease among any other patient groups and risk categories. Although kidney transplantation was hailed as an optimal solution to such devastating disease, many issues related to immune-suppressive drugs soon emerged and it became evident that cardiovascular disease would remain a vexing problem. Progression of chronic kidney disease is accompanied by profound alterations of mineral and bone metabolism that are believed to have an impact on the cardiovascular health of patients with advanced degrees of renal failure. Cardiovascular risk factors remain highly prevalent after kidney transplantation, some immune-suppression drugs worsen the risk profile of graft recipients and the alterations of mineral and bone metabolism seen in end stage renal failure are not completely resolved. Whether this complex situation promotes progression of vascular calcification, a hall-mark of advanced chronic kidney disease, and whether vascular calcifications contribute to the poor cardiovascular outcome of post-transplant patients is reviewed in this article.

**Key words:** Morbidity; Chronic kidney disease-mineral bone disorder; Cardiovascular disease; Chronic kidney

disease; Mortality; Bone fractures

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**Core tip:** Despite partial restoration of glomerular function many bone and vascular abnormalities that develop during dialysis persist after kidney transplantation. Cardiovascular risk factors are also highly prevalent after kidney transplantation and some immune-suppressive drugs worsen the risk profile of graft recipients. As a result kidney transplant recipients continue to demonstrate a high cardiovascular risk in part due to the effect of vascular calcification.

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## INTRODUCTION

Despite a significant improvement in recent years, cardiovascular (CV) morbidity and mortality remain highly incident in recipients of kidney transplant. The reported annual risk of fatal or non-fatal cardiovascular events is 3.5%-5% even after adjustment for traditional risk factors<sup>[1]</sup>. This represents a very high CV risk against the 10-year risk benchmark of 20% in the general population as stigmatized by the ATP-III guidelines<sup>[2]</sup>. In addition to conventional cardiovascular disease (CVD) risk factors (such as diabetes, hypertension, obesity, smoking and dyslipidemia), several patient and graft related factors seem to influence the high incidence of cardiovascular events post-transplantation<sup>[3,4]</sup>. These include, among others, the duration of prior dialysis, graft function after transplantation, hyperhomocysteinemia, elevated inflammatory markers, proteinuria, acute rejection episodes, new onset diabetes mellitus post-transplant, and the toxic effects of immunosuppressant drugs. However, the effect of residual bone and mineral metabolism abnormalities commonly seen in patients with chronic kidney disease (CKD) must also be taken into account. Vascular and valvular calcifications feature prominently as conditions tied with a poor outcome in patients with CKD<sup>[5,6]</sup>. In this review we discuss how persistent alterations of mineral metabolism and bone remodeling typical of end stage renal failure may affect the long-term CV health of patients after kidney transplantation.

## CV RISK PROFILE AFTER TRANSPLANTATION: TRADITIONAL RISK FACTORS

Diabetes mellitus (DM) is one of the most common

causes of CKD and dialysis in Western countries and carries a high risk of CV complications even after transplantation. New onset DM has been described in approximately 25% of non-diabetic kidney-transplant recipients years after surgery<sup>[7,8]</sup>. Immunosuppression regimen may have a part in inducing new onset DM; steroids as well as tacrolimus have been identified as agents linked with a high incidence of *de-novo* DM and an associated increased risk of atherosclerotic cardiovascular events<sup>[9]</sup>. An observational analysis from the Norwegian Renal Registry that included 201 consecutive renal allograft recipients demonstrated that patients with post-transplant DM have a three-fold increased risk of major cardiac events (cardiac death or non-fatal myocardial infarction) compared with non-diabetic patients (HR = 3.27, 95%CI: 1.22-8.80,  $P = 0.019$ )<sup>[10]</sup>. Of interest, pre-transplant DM (HR = 5.09, 95%CI: 2.60-9.96,  $P < 0.001$ ) and age (HR = 1.03, 95%CI: 1.01-1.05,  $P = 0.016$ ), but not post-transplant DM (HR = 1.20, 95%CI: 0.58-2.49,  $P = 0.621$ ), were independent predictors of death in the multivariable regression model.

Recent estimates assess the prevalence of hypertension in post-renal transplant recipients at 40%-90%<sup>[11]</sup>. The prevalence is particularly high in the first 3 mo after surgery, but it appears to remain elevated even after the first and second year after surgery<sup>[12]</sup>. In a recent report<sup>[11]</sup>, hypertension persisted despite a definite improvement in serum urea and creatinine levels and progressive increase in urinary volume. Hypertension in the post-renal transplant patients carries a greater risk of cardiovascular events and death than it does in the general population and it plays a major role in the chronic deterioration of graft function<sup>[13]</sup>. Many factors may contribute to the development of post-transplant hypertension; among others the use of immunosuppressive drugs, donor-recipient mismatch, hypercalcemia and recurrence of glomerular nephritis<sup>[13]</sup>.

Dyslipidemia is mainly characterized by increased levels of triglycerides and low levels of apoA1 associated lipoproteins (namely HDL) while LDL levels, a well-established risk factor for CVD in the general population, are not typically elevated or only mildly elevated. Immunosuppressive drugs can adversely affect a patient's lipid profile in the post-transplantation period. Steroids can cause insulin resistance and hyperinsulinemia with the attendant dyslipidemia<sup>[14]</sup>. Cyclosporine has been known to decrease hepatic clearance of LDL as well as increase the synthesis of VLDL and decrease the secretion of bile salts<sup>[15]</sup>. Mammalian target of rapamycin (mTOR) inhibitors reduce the activity of circulating lipases and decrease fatty acids uptake into the adipose tissue leading to a decrease in plasma lipid clearance<sup>[16]</sup>. All of these mechanisms contribute to an increase in the serum level of various lipoprotein subfractions. Statins lower CV morbidity and mortality in patients with early stages of CKD, have little or no effect in patients receiving dialysis<sup>[17]</sup>, and have uncertain effects in kidney transplant recipients<sup>[18]</sup>. Based on limited available data

such as the ALERT study<sup>[19]</sup>, the members of the KDIGO panel on dyslipidemia recommended use of statins in renal transplant recipients (weak recommendation with moderate quality of evidence)<sup>[20]</sup>.

Approximately 25% of renal transplant recipients are smokers. Tobacco use is an independent risk factor for CVD and confers a 30% risk of graft loss as a consequence of early CVD<sup>[21]</sup>. Of note, smoking has been shown to confer a risk of death with a functioning graft as great as DM<sup>[22]</sup>. Smoking cessation can reverse the risk; patients who stopped smoking for at least 5 years prior to transplantation had a 34% risk reduction in CV events<sup>[23]</sup>. Thus, physicians are expected to provide a strong recommendation for smoking cessation prior to transplantation<sup>[24]</sup>.

## IMMUNOSUPPRESSIVE DRUGS

Endothelial cells play a vital role in the success or failure of a transplant graft. As a result of a succession of insults suffered during explantation and reimplantation the inflammatory cascade is triggered and may activate the proliferative and fibrotic processes characteristic of chronic graft vasculopathy. Immunosuppressive drugs are used to minimize acute rejection and maximize graft survival although they have the potential to induce nephrotoxicity and increase CV risk. Of note, episodes of acute rejection have been reported as an additional risk factor for incident CV events post-transplantation<sup>[3]</sup>. As discussed previously, corticosteroids and calcineurin inhibitors (CNIs) can promote or aggravate the severity of hypertension, induce lipid abnormalities and transplant related DM. The main cardiovascular toxicity of steroids and CNIs is inhibition of inducible nitric oxide, thus promoting endothelial dysfunction, one of the first steps in the development of atherosclerosis<sup>[25]</sup>. mTOR inhibitors have different vascular effects. Rapamycin inhibits smooth muscle cells proliferation, while everolimus impairs the vasoactive and antithrombotic function of endothelial cells<sup>[26]</sup>.

## NONTRADITIONAL RISK FACTORS: BIOMARKERS OF BONE AND MINERAL DISORDERS

Bone and mineral disorders are frequent in patients who have undergone kidney transplantation<sup>[27]</sup>. Pre-existing alterations of mineral metabolism and bone remodeling acquired during CKD progression and dialysis, such as hyperparathyroidism, often persist and are compounded by the effects of immunosuppressive agents. Typical laboratory abnormalities post-transplant include hypercalcemia and hypophosphatemia. Hypercalcaemia is a severe complication reported in up to 53% of kidney transplant patients that can affect graft function both acutely, owing to vasoconstriction, and chronically by mediating calcification of the tubulointerstitium<sup>[28-30]</sup>. Hypercalcemia can also increase the

risk of soft-tissue and vascular calcification, which in turn can adversely affect patients' outcome<sup>[31]</sup>. In kidney transplant recipients persistent hyperparathyroidism is largely dependent on parathyroid gland hyperplasia. Parathormone (PTH) enhances calcium re-absorption and phosphorus excretion leading to hypercalcemia and hypophosphatemia<sup>[32]</sup>. In addition, the restoration of active vitamin D [1,25(OH)<sub>2</sub>D] synthesis by the transplanted kidney and the progressive improvement of skeletal resistance to PTH may accelerate hypercalcemia. The negative impact of hypercalcemia and persistent secondary hyperparathyroidism (SHP) on outcome of transplanted patients has been demonstrated in several observational studies. Altered calcium and PTH homeostasis have been linked to renal calcinosis and loss of graft function as documented by serial biopsies in a cohort of 213 patients<sup>[29]</sup>. Persistent SHP is associated with a poor prognosis in kidney transplant recipients. Bleskestad *et al.*<sup>[33]</sup> reported that high PTH levels (greater than the fourth quartile, > 14.4 pM) were associated with a significant 2.6 fold increase (HR = 2.60, 95%CI: 1.10-6.16, *P* = 0.03) in the risk of the composite endpoint of all-cause mortality, cardiovascular events and graft loss, independent of confounders.

Hypophosphataemia is very common and is seen in the majority (> 90%) of transplant recipients 3 mo after transplantation. Although it is usually seen shortly after transplantation, phosphate levels may remain low for longer than a year post-transplantation<sup>[34]</sup>. Persistent hyperparathyroidism is not the only mechanism subtending post-transplantation hypophosphatemia and fibroblast growth factor 23 (FGF-23) may play an important role as well<sup>[35]</sup>. FGF-23 levels increase early and continue to rise with CKD progression in an attempt to maintain serum phosphorus levels in the normal range. FGF-23 is mainly synthesized by osteocytes and is involved in the bone-kidney axis and the regulation of calcium phosphate metabolism. It acts primarily on the proximal renal tubule as a phosphaturic agent through the downregulation of sodium-phosphate co-transporters. Additionally, it blocks the generation of 1,25(OH)<sub>2</sub>D through inhibition of the renal 1- $\alpha$ -hydroxylase enzyme and stimulation of the 24-hydroxylase enzyme that is responsible for the degradation of activated vitamin D<sup>[36]</sup>. Through down-regulation of production of 1,25(OH)<sub>2</sub>D, FGF-23 can also promote the development of secondary hyperparathyroidism<sup>[37]</sup>. Investigators have suggested that some patients develop a syndrome of tertiary FGF-23 hypersecretion post-transplant that may justify their persistent hypophosphatemia<sup>[38,39]</sup>. FGF-23 has been independently associated with risk of all-cause death, heart failure and cardiovascular events in dialysis and CKD patients<sup>[40]</sup>. Available data, also suggest that elevated levels of FGF-23 post-transplant are independently associated with all-cause mortality and graft loss. In a large prospective cohort of 984 stable kidney transplant recipients (mean estimated glomerular filtration rate 51  $\pm$  21 mL/min per 1.73 m<sup>2</sup>), elevated FGF-23 levels (median level 28 RU/mL; interquartile range: 20-43 RU/mL) were independently

associated with a significantly increased risk of all-cause mortality and graft loss (adjusted HR = 1.46 per SD increase in log FG-F23, 95%CI: 1.28-1.68,  $P < 0.001$ ). Notably, the results were similar for each components of the composite endpoint and, at least in this study cohort, none of the other biomarkers of CKD-MBD were linked with the outcome of interest after adjustment for confounders<sup>[41]</sup>.

## RENAL OSTEODYSTROPHY AFTER KIDNEY TRANSPLANTATION: PECULIARITIES AND CLINICAL RELEVANCE

As discussed above, SHP persists in many cases after renal transplantation<sup>[42]</sup>. Parathyroid glands from transplant recipients show increased expression of both vitamin D and calcium sensing receptors when compared to glands from patients on maintenance dialysis, indicating an increased sensitivity to circulating levels of vitamin D and calcium. Importantly, persistent SHP is a major determinant of bone disease in the post-transplant period. Although bone histology has been reported rarely in these patients, limited evidence suggests that bone histologic parameters are mostly abnormal. The prevailing findings are reduced bone volume, low bone turnover and generalized or focal defective mineralization (osteomalacia)<sup>[43]</sup>. Biochemical markers like PTH and alkaline phosphatase are of limited diagnostic utility to recognize the presence of bone disease<sup>[44]</sup>. Similarly, the information obtainable with non-invasive radiologic techniques like Dual-energy X-ray absorptiometry (DEXA) is weakly correlated with bone histology. As an example, in a study that enrolled only patients with markedly reduced bone mineral density (BMD), defined as a DEXA T-score  $< 4.0$ , bone histology confirmed the presence of osteoporosis only in 25% of the cases<sup>[45]</sup>. Furthermore, while reduced BMD is a frequent finding after renal transplantation, little is known about the associated risk of bone fracture. A recent systematic review of the literature (10 studies that enrolled 262678 transplant recipients were included), aiming at assessing the incidence and the risk factors associated with bone fracture after kidney transplant, concluded that incidence rates ranged from 3.3 to 99.6 fractures per 1000 person-years (5-year cumulative incidence: 0.85%-27%), depending on fracture site and case-mix. Common factors linked with increased fracture risk were older age, female sex, diabetes mellitus, dialysis duration before transplantation, previous history of fracture and cadaveric kidney (vs living) donor<sup>[46]</sup>. Unfortunately, poor consensus on data reporting in different studies hampers a more accurate assessment of the relationship between fracture rate and risk factors post-transplantation. Immunosuppressive drugs contribute to bone disease. A recent publication described a decrease in the incidence of hip fractures in more recent years, with a potential

positive influence on this favorable trend exerted by improved immunosuppressive strategies<sup>[47]</sup>. The case-mix adjusted HR for hip fracture was 0.56 (95%CI: 0.47-0.99) in 2010 compared to 1997; when the model was adjusted for baseline immunosuppressive therapy the HR increased slightly to 0.68 (95%CI: 0.47-0.99), suggesting that part of the effect may be attributable to post-transplant immunosuppressive regimens. Of interest, the observed 30-d mortality risk after a hip fracture was relatively low when compared to the general population (event rate: 2.2 per 100 events, 95%CI: 1.3-3.7)<sup>[48]</sup> possibly reflecting the younger age of the study subjects (median age 51 years) and/or the favorable trend toward hip fracture reduction. In summary, transplant recipients, like advanced CKD and dialysis patients, suffer from persistent renal osteodystrophy that is linked with morbidity and mortality risk.

## BONE-VASCULAR AXIS AND VASCULAR CALCIFICATION IN TRANSPLANTS PATIENTS

In recent years there has been an increasing appreciation of the existence of a "bone-vascular axis". This term refers to the existence of a bidirectional flow of information between bone and vessels through exchange of cells, hormones and other metabolic signals<sup>[49]</sup>. Although a close bone-vascular interaction is present in the general population, it is particularly active in CKD patients<sup>[50]</sup>, and very likely in kidney transplant recipients. Investigators proposed that promoters and inhibitors of bone mineralization, such vitamin D, PTH, phosphorus, fetuin-A, matrix-Gla protein and others, are also involved in the pathogenesis of vascular calcification<sup>[51]</sup>. FGF-23 has been linked with increased mortality and graft loss after kidney transplantation<sup>[41]</sup>, but its role as a promoter of vascular calcification warrants further elucidation. Drugs with immunosuppressive activity may modulate the expression, regulation, and function of the RANKL, RANK, and OPG system both at the skeletal and vascular level. In particular, sirolimus inhibits osteoclast formation, steroids can induce apoptosis of osteoblasts and osteocytes, and reduce osteoblast replication and differentiation<sup>[25,52]</sup>. However, current data are limited and at times conflicting. For instance, experimental studies suggest that mycophenolate mofetil inhibits vascular smooth cells proliferation and improves endothelial dysfunction when compared to steroids or calcineurin inhibitors<sup>[26]</sup>. Similarly, mTOR inhibitors (rapamycin and everolimus) interfere with vascular smooth muscle cells proliferation and endothelial cell function<sup>[51]</sup>. These observations may explain the results documented by Nguyen *et al.*<sup>[53]</sup> of a protective role of mycophenolate mofetil on aortic calcification in recipients of kidney allografts. Nonetheless, the concomitant effect of various immunosuppressive drugs on lipid metabolism, diabetes mellitus, and hypertension may



**Table 1** Summary of findings of prospective studies that investigated the progression of coronary artery calcium and aortic calcium after kidney transplantation, and studies that assessed the prognostic significance of coronary artery calcium after transplantation; all imaging studies were performed with cardiac computed tomography

Ref.	Size	Follow-up	Main findings
Risk factors associated with vascular calcification progression in KTR			
Maréchal <i>et al</i> <sup>[56]</sup> , 2012	281 enrolled, 197 analyzed	4.4 yr	CAC increase: 11%/yr AoC increase: 4%/yr Risk factors for CAC progression: Baseline CAC, history of CVD, statin use, 25OH vit D levels Risk factors for AoC progression: Baseline AoC, higher pulse pressure, statin therapy, older age, serum phosphate level, use of aspirin, and male sex
Mazzaferro <i>et al</i> <sup>[55]</sup> , 2009	41 KTR compared to 31 matched dialysis patients	2 yr	KTR blunts but does not halt CAC progression (12.2% <i>vs</i> 56.6% CAC progression in KTR <i>vs</i> dialysis patients) Factors associated with CAC progression: Parathyroid hormone serum levels, modality of renal replacement therapy (dialysis <i>vs</i> transplantation), erythrocyte sedimentation rate
Seyahi <i>et al</i> <sup>[57]</sup> , 2012	150 prevalent KTR without history of CVD	2.8 yr	Baseline CAC prevalence 35.3% (mean CAC: 60 ± 174) Follow-up: CAC prevalence 64.4% (mean CAC: 94 ± 245) Individual CAC progression: 28%-38% Median annualized CAC progression 11 Agatston Units Factors associated with CAC progression: Baseline CAC, high triglyceride levels, bisphosphonate therapy
Prognostic relevance of vascular calcification in KTR			
Roe <i>et al</i> <sup>[61]</sup> , 2010	112 asymptomatic incident KTR without history of CVD	6 yr	Median CAC at study inception 70 (33% of patients had no CAC) CAC was associated with increased risk of the composite endpoint of coronary artery bypass surgery, percutaneous intervention or myocardial infarction, cerebrovascular accident or peripheral arterial disease (revascularization or amputation), and all-cause mortality. Per 100 unit increase in CAC: HR = 1.05, 95%CI: 1.00-1.11; <i>P</i> = 0.045
Nguyen <i>et al</i> <sup>[62]</sup> , 2010	281 enrolled	2.3 yr	CAC independent predictor of the composite endpoint of cardiovascular death, myocardial infarction, stroke or transient ischemic attack and revascularization. For a 2.72 fold increase in CAC, HR = 1.40, 95%CI: 1.12-1.75, for a 2.72-fold increase in CAC, <i>P</i> < 0.003 <sup>1</sup>

<sup>1</sup>The hazards ratios is calculated for a 2.72 times increase in coronary artery calcification on a natural log scale. CAC: Coronary artery calcium score; AoC: Aorta calcium score; CVD: Cardiovascular disease; KTR: Kidney transplant recipient.

also have a negative impact on the cardiovascular health of transplant recipients. The available evidence is too limited to clearly establish and disentangle the relative influence of single factors on the bone-vascular axis.

A few studies tested the impact of renal function restoration *via* kidney transplantation on vascular calcification and yielded conflicting results (Table 1). The comparability and generalizability of these study results is hampered by the small sample size, the lack of a consensus on how to evaluate vascular calcification progression, the difference in follow-up time between studies, and the lack of control groups with comparable degrees of baseline renal dysfunction and calcification burden. Hence the results must be interpreted in the context of a considerable heterogeneity of data collection and interpretation. In a preliminary observation of 23 kidney transplant recipients and 17 chronic hemodialysis patients submitted to sequential chest computed tomography scans, Moe *et al*<sup>[54]</sup> reported an almost complete arrest of coronary artery calcium (CAC) progression in post-transplant patients and continued accrual of calcium in patients on dialysis, over a follow-up period of 15-20 mo. However, while no new calcium deposition was noted in individuals free of calcification at baseline, a trend toward an increase in aortic calcification was noted in transplant recipients

and controls. A few subsequent studies showed that cardiovascular calcification continues to progress after kidney transplantation (Table 1), although this may occur at a slower rate than in patients receiving dialysis. Mazzaferro *et al*<sup>[55]</sup> reported an annual CAC change among individuals with baseline CAC > 15 Agatston units of 8.8% and 31.0% in transplanted patients and controls, respectively. Deregulation of bone and mineral metabolism pathways probably contribute to the continued deposition of calcium in soft tissues even after transplantation. Mazzaferro *et al*<sup>[55]</sup> showed an independent association of serum PTH and CAC progression in a study that enrolled 41 transplant recipients and 31 dialysis patients, independent of the use of vitamin D. In a series of 197 patients, Maréchal *et al*<sup>[56]</sup> reported an independent association of CAC and aortic calcium score progression with history of prior cardiovascular disease, presence of calcification at study inception, use of statins, serum levels of vitamin D and serum phosphate levels (median annualized score progression: 11, interquartile range: 1-58 and 5, interquartile range: 0-62 mg respectively). Of interest, there was no evidence of vascular calcification regression after transplantation in any of these three studies.

Finally, Seyahi *et al*<sup>[57]</sup> described a CAC prevalence of 35.3% in 150 kidney transplant recipients (median

time from transplantation: 83 mo, interquartile range 31-269 mo) without prior history of cardiovascular disease. During an average follow-up of 2.8 years, CAC progression ranged from 28%-38% (median annual CAC progression: 11.1%, interquartile range: -51.5 to 185.5). Notably, 34 (35.0%) individuals with evidence of CAC at study conclusion were free from CAC at study inception (incidence rate 12.5%/year). Finally, CAC regression was documented in only 2 patients (1.3%). Independent predictors of progression were serum triglycerides levels (OR per mg/dL increase: 1.007, 95%CI: 1.002-1.012), presence of CAC at baseline (OR = 5.23, 95%CI: 1.93-14.19), and use of bisphosphonates (OR = 2.64, 95%CI: 1.04-6.68)<sup>[57]</sup>. In this case bisphosphonates use may have been a confounder by indication; that is, patients with the worst degree of bone disease - likely associated with parallel vascular disease - received bisphosphonates.

Other smaller studies<sup>[58-60]</sup> investigated vascular calcification prevalence and progression in kidney transplant recipients yielding conflicting results on the impact of kidney transplantation and renal function restoration on accumulation of vascular calcification and its progression.

As shown in the general population and maintenance dialysis patients, vascular calcification *per-se* has been associated with an unfavorable outcome in transplant recipients. In a cohort of 112 incident transplant recipients without history of cardiovascular disease, each 100 unit increase in CAC score was associated with a 5% (HR = 1.05, 95%CI: 1.00-1.11;  $P = 0.045$ ) increased risk of death or major cardiovascular events 6 years after surgery<sup>[61]</sup>. Similarly, in a larger cohort of 281 transplant recipients without history of cardiovascular disease, Nguyen *et al*<sup>[62]</sup> documented an independent association of baseline CAC score and the risk of a composite endpoint of cardiovascular death, myocardial infarction, coronary revascularization, stroke and transient ischemic attack ( $P < 0.003$ ). No data are available yet to associate the progression of cardiovascular calcification and outcome in recipients of a kidney transplant.

## FUNCTIONAL VASCULAR CHANGES

Increased arterial stiffness can be measured non-invasively by tonometry or ultrasound based methods. The etiopathogenesis is multifactorial and includes atherosclerosis, myocytes apoptosis and degradation of collagen fibers in the media as well as accumulation of calcium in the intima and media layers of the vessel wall. Hence, although vascular stiffness has been seen as a surrogate marker of vascular calcification it is not merely dependent on this pathological process. Current evidence supports the notion that a successful kidney transplantation is associated with an improvement in indices of compliance of large [*i.e.* pulse wave velocity (PWV)] and peripheral-muscular [*i.e.* augmentation index (AIx)] arteries<sup>[63,64]</sup>. While epidemiological studies

in the general population and CKD patients suggest a link between arterial stiffness and bone health, the relative contribution of renal function restoration and amelioration of bone mineral abnormalities to vascular stiffness improvement after kidney transplantation remains unclear. Indeed, PWV and AIx improve very quickly after surgery at a time when bone mineral metabolism abnormalities cannot have been reversed yet. Therefore, functional vascular parameters possibly improve as a consequence of the partial restoration of glomerular function following kidney transplantation<sup>[65]</sup>. As in CKD subjects<sup>[66,67]</sup>, it is unclear whether an increase in arterial stiffness is a promoter or a consequence of progressive renal function decline<sup>[68,69]</sup>. In a prospective cohort study of 101 subjects receiving a functional graft, glomerular filtration rate decline was associated with smoking and acute rejection episodes in the first year after surgery, while it was associated with donor age and aortic stiffness after the first year from transplantation<sup>[69]</sup>. Among 45 normotensive kidney donors the compensatory hyperfiltration response to renal mass loss was reduced in donors with increased aortic stiffness prior to organ explant<sup>[68]</sup>. These results suggest a vicious cycle in which chronic kidney disease may induce arterial wall changes and stiffening that in turn promote loss of renal function.

Although mostly based on studies of limited sample size, several factors have been linked with arterial dysfunction and stiffness in kidney transplant recipients. Traditional CV risk factors<sup>[70,71]</sup> as well as specific risk factors such as immunosuppressive regimens<sup>[72]</sup> or abnormalities of bone and mineral metabolism<sup>[73,74]</sup> have been linked with changes in arterial wall stiffness. In a series of 47 kidney transplant patients, increased bone turnover (assessed by serum levels of bone alkaline phosphatase, osteocalcin, beta-crosslaps) was associated with elevated PWV, during the first 24 mo after surgery<sup>[74]</sup>. In another cross-sectional study of 89 renal transplant patients PVW, but not Aix, was associated with elevated serum levels of 1,25 vitamin D and osteoprotegerin, further corroborating the notion of a bone-vascular cross-talk<sup>[73]</sup>. Although some authors have investigated changes in PWV and ankle brachial index before and after kidney transplantation as a surrogate for vascular calcification, these measures are only indirectly linked and may be responsible for adverse outcomes based on different mechanisms. In a prospective study of 253 transplanted patients, both aortic calcification (HR per 1 unit increase in the aortic calcification score: 1.09, 95%CI: 1.02-1.17) and PWV (HR per 1 m/s increase: 1.45, 95%CI: 1.16-1.80) independently predicted the occurrence of any cardiovascular events during a 36 mo follow-up<sup>[75]</sup>.

## CONCLUSION

Current evidence suggests that mineral and bone disorders persist in large degree after successful kidney transplantation. Alterations of mineral and bone metabolism most likely contribute to vascular

calcification progression. Although data are scarce and heterogeneous, renal function restoration does not seem to halt vascular calcification. Available data suggest that CAC progresses at similar or at best at a slightly attenuated rate in transplant patients compared to dialysis patients. As a marker of vasculopathy<sup>[76]</sup>, vascular calcification is associated with an increased risk of unfavorable events in kidney transplant recipients, as previously shown in the general population and CKD patients. These observations underline the importance of considering the post-transplant state as a state of persistent moderate kidney dysfunction with the attendant disorders of mineral metabolism and bone remodeling. In fact, the glomerular filtration rate after a single successful kidney transplantation typically averages about half that of a patient with normal renal function. This situation varies greatly according to the age of the recipient and donor, the condition of the graft at the time of anastomosis (fully functional vs marginal status graft) and the prior cardiovascular risk level and control of risk factors in the recipient. A selection bias should also be considered while analysing the data from the literature, as only patients with the best risk profile and the lowest amount of iliac calcification (and likely systemic calcification) are added to the transplant lists. Whether a careful management of bone and mineral metabolism with new therapeutic advances will improve the cardiovascular risk of transplant recipients remains to be verified in future studies.

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