



# Vitamin D Pleiotropy after Renal Transplantation



Jean J Filipov\*

Department of Nephrology and Transplantation, University Hospital "Alexandrovska", Bulgaria

\*Corresponding author: Jean J Filipov, Department of Nephrology and Transplantation, University Hospital "Alexandrovska", Sofia, Bulgaria Clinical Center of Nephrology, Medical University-Sofia, Bulgaria, Email: [jeanphillipov@yahoo.com](mailto:jeanphillipov@yahoo.com)

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**Abbreviations:** KT: Kidney Transplantation; KTRs: Kidney Transplant Recipients; CKD: Chronic Kidney Disease; UTI: Urinary Tract Infections; DM: Diabetes Mellitus; NODAT: New Onset DM After Transplantation; RCTs: Randomized Controlled Trials; CVD: Cardio Vascular Disease

## Introduction

Vitamin D (VD) insufficiency is widely spread worldwide. It is even more often detected after kidney transplantation (KT). Graft and patient survival are limited after KT due to neoplasia, cardiovascular mortality and infection. In addition, VD has increasing importance, spanning beyond calcium-phosphorus metabolism. It is associated with renal protection, anti-neoplastic properties, diabetes control, and immune modulation. Therefore, vitamin D is being evaluated as a treatment option for improvement patients' outcomes after KT.

## Prevalence and Causes for Vitamin D Insufficiency after Kidney Transplantation

It could be expected, that after successful KT a rapid improvement in VD status occurs. However, the suboptimal VD levels are highly prevalent in kidney transplant recipients (KTRs). Our studies demonstrate VD sufficiency rate below 20% in the summer-autumn period, dropping further to 2.59% in the winter fall [1,2]. Similar findings were detected in other centers [3]. Several factors explain these results. Firstly, there is a high prevalence of chronic kidney disease (CKD) stage 3 and over after KT-up to 70%. Secondly, transplant-specific factors play an important role: reduced sun exposure and use of sun-protecting cosmetics in order to reduce the risk for skin carcinomas; post-transplant proteinuria, diabetes and obesity (due to increased urine loss, reduced intestinal reabsorption and lower bioavailability). Immunosuppressive agents also have detrimental effect on VD status-e.g. steroids (increased VD catabolism) and calcineurin inhibitors (suppressed hepatic synthesis). Similar to the general population, 25-hydroxyvitamin D (25VD) is used to evaluate the vitamin D status after renal transplantation.

## Vitamin D, Proteinuria and Renal Function after Kidney Transplantation

Several post-transplant studies indicated, that lower 25VD levels are associated with poorer graft function, faster decline

of graft GFR, and worse kidney function in the long run [4,5]. Our findings also demonstrate that poorer VD status in KTRs is associated with higher proteinuria [6]. Possible explanations for the findings are RAAS suppression, nuclear factor  $\kappa$ B inactivation, Wnt/ $\beta$ -catenin pathway suppression, and up regulation of slit-diaphragm proteins. In addition, paricalcitol treatment ameliorated proteinuria after KT [7]. Contrary to these findings, cholecalciferol supplementation did not significantly affect proteinuria and tubular atrophy/interstitial fibrosis after KT. The single-center study VITA-D also failed to demonstrate significant renoprotection from cholecalciferol treatment [8,9].

## Vitamin D and Infection after Kidney Transplantation

KTRs are at increased risk for infection, especially during the early post-transplant period. However, infection is a leading cause for patient and graft loss after KT. Several studies showed lower infection risk in patients with higher VD levels in the general population [10]. There are conflicting reports considering the association between infection risk and post-transplant VD status. Lower VD was associated with higher incidence of opportunistic pulmonary infections in KTRs [11,12]. However, VD supplementation did not reduce infection rate after KT, according to the VITA-D study [9]. VD status had no influence on the prevalence of urinary tract infections (UTI) in our transplant center; However, Kwon et al. [13] demonstrated that VD is an independent risk factor for post-transplant UTI [12,13].

## Vitamin D and Diabetes Mellitus

Despite the studies in the general population, indicating inverse correlation between 25VD and diabetes mellitus (DM) incidence, the data in KTRs are scarce. After KT, the development of post-transplant diabetes mellitus is usually linked to steroid and calcineurin inhibitors use. Our experience did not demonstrate better VD status in KTRs with better-controlled DM [14]. In addition, currently there are no results from interventional studies in this

cohort of patients. However, an interventional trial is currently underway, evaluating the effect of cholecalciferol supplementation on the incidence of new onset DM after transplantation (NODAT) [15].

### Vitamin D and Rejection

The vitamin D receptor is detected in all immune cells. In vitro studies demonstrated that calcitriol suppressed T and B-lymphocyte proliferation, inhibited dendritic cells and macrophages, suppressed interleukin and immunoglobulin G production, and down regulated major histocompatibility complex class II expression. Unfortunately, the trials in KTRs have controversial findings. Bienaimé et al. [16] demonstrated lower acute rejection incidence in better VD status [16]. Yet, the initial results from the VITA-D study do not reveal any positive effects from cholecalciferol supplementation on rejection prevalence [9]. The present controversy indicates the need for more multicenter randomized controlled trials (RCTs), evaluating the association between rejection and VD status after KT.

### Vitamin D and Neoplasia after Renal Transplantation

Neoplasia is a major cause for patient and graft loss after KT. VD suppresses cellular proliferation and angiogenesis, stimulates cell differentiation and reduces the metastatic potential. Several human studies in the general population indicate lower cancer incidence (colorectal, breast and pancreatic cancer) in VD sufficient subjects [17]. The studies in KTRs are controversial. Poorer pre-transplant VD status was related to higher post-transplant cancer incidence [18]. In addition, supplementation with active VD also reduced the malignancy risk in KTRs for certain types of neoplasia-breast, colon and ovary [19]. Other studies do not demonstrate positive effect from calcitriol prevention in KTRs [20]. Therefore, the anti-neoplastic properties of VD after renal transplantation need further assessment.

### Vitamin D and Cardiovascular Disease (CVD) after Renal Transplantation

CVD is a major contributor to mortality after successful KT, due to the persistent CKD-associated vascular and cardiac abnormalities. Several reports associated low VD with increased vascular calcifications after KT, probably by influencing endothelial dysfunction or suppressing cardiomyocyte proliferation via the VD receptor [21,22]. However, Zitterman et al. [22] demonstrated that high post-transplant 25VD levels were also linked to increased calcification risk [22]. A more recent study also did not establish significant protective role of 25VD levels in CVD incidence in KTRs [19].

### Vitamin D and Mortality after Kidney Transplantation

Higher overall mortality in KTRs is observed, compared to the general population, due to CKD-related mineral bone disease, infection, CVD, and neoplasia. Several reports indicate better survival in subjects with higher 25VD, both in the general population and CKD cohorts. Similar findings were established after renal transplantation-poorer VD status was associated with poorer post-transplant patient survival [4]. Unfortunately, prospective interventional RCTs are still lacking.

### Conclusion

Despite the numerous results from in vivo and animal studies, or in the general population, the results for VD pleiotropy in KTRs are still controversial. This is due to the small, single center, usually observational trials. Currently, two large prospective, interventional RCTs (VITALE, CANDLE-KIT) are being performed, evaluating the effect of cholecalciferol supplementation on different end-points: post-transplant mineral bone disease, graft function, proteinuria, blood pressure, incidence of rejection, NODAT, cancer, CVD, and all-cause mortality. In addition, we can speculate, that a target 25VD level is needed for VD pleiotropy to occur, similarly to the effect of 25VD on calcium-phosphorus metabolism. Another issue to consider in the future is the type of supplementation to achieve the needed pleiotropic effect-native VD or calcitriol/VD-analogue.

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