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Research Article

Periods of Vitamin D Deficiency Predispose Kidney Transplant Patients to Increased Incidence of Infection – Retrospective Single-Centre Study in Hungary

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Abstract

Transplant recipient patients are susceptible to infections due to their immunosuppressive treatments and surgical intervention. Vitamin D has positive effects on the immune system and metabolism promoting healthier homeostasis and more efficient immune response, thus is an advisable complementary therapy in kidney transplant recipients (KTRs).
Poisson regressions were used to analyse associations between incidence of infections and vitamin D levels and deficiency. Group comparisons explored the connections between vitamin D levels and infections, calcium, and phosphate levels in relation to kidney function and parathyroid hormone (PTH) levels in deficiency/insufficiency/sufficiency periods of KTRs. KTRs had significantly lower level of 25(OH)D during infected compared to infection-free periods ($p<0.0001$). The incidence/number of infections was significantly higher during vitamin D deficiency compared to insufficiency or sufficiency ($p<0.0001$). Calcium level was significantly higher in the sufficient group compared to the insufficient or deficient groups ($p=0.0031$ and $p=0.0496$, respectively).
Periods of vitamin D deficiency in KTRs are associated with vulnerability to infections, therefore monitoring of vitamin D level and applying supplementation reaching the sufficient level (30ng/ml) is recommended if deficiency is detected. Primarily to reduce infections and avoid disturbances in immune activation, but also because it has negative impact on the quality of life of KTRs.

Keywords: Vitiligo, Guan Yin Citta Dharma Door, Killing Karma, Spiritual healing, Buddhist practice

Introduction

Kidney transplant recipients (KTRs) are much more susceptible to infections due to necessary immunosuppressive therapies, but also because of their surgical intervention [1-3]. Their most common infections affect the respiratory and urinary tracts [4,5], these are, similarly to other infections, also increasing the rate of graft rejection, thus it's important to explore the options to prevent infections [2,6]. Viral infections may alter the activity of immune cells contributing to acute rejection [7,8]. Cytomegalovirus (CMV), BK polioma virus (BKV), Epstein Barr virus (EBV), Varicella zoster virus (VZV) are the most common viral infection in transplanted patients [9-14]. In KTRs the most common and nosocomial bacteria

causing infections are E. coli, Klebsiella p. and Clostridioides difficile [1,15,16]. Transplanted patients require longer treatment periods for their infections compared to healthy people because of immunosuppression (ISU), which causes additional difficulties, and could be the cause of the recognised [17,18] degrading effect of infections on quality of life.

In order to reduce the occurrence of infections in KTRs it is advisable to apply complementary treatments such as vitamin or mineral supplementation and dietary support. Vitamin D3 can be applied as dietary supplement both for healthy people (more in winter time in the tempered zone and all year further north) and patients with specific diseases (osteoporosis, skin diseases, kidney and liver diseases, malabsorption etc) [19,20]. In KTRs vitamin D3 supplementation is advisable - even in countries with abundant sunlight as the circannual rhythm of vitamin D may dampened in them [21] -, since the prevalence of 25(OH)D insufficiency or deficiency in KTRs is higher not only during and after 1-year post-transplant but also in long-term [22].

Vitamin D has well-known role in calcium homeostasis but its non-osteometabolic effects have been intensively investigated in the last few years [23-26], including the regulation of the immune system [27,28]. It was discovered in the past decade that vitamin D receptor (VDR) and key vitamin D metabolizing enzymes are expressed in different immune cell types [29]. Vitamin D is potent regulator both the innate and adaptive immunity including antimicrobial actions through induced production of antimicrobial agents [30] as well as modulating the balance of Th1/Th2 and inhibiting IL-17, a regulatory cytokine production of regulatory Th17 cells [31,32]. This beneficial effect of vitamin D was well recognized in the COVID-19 pandemic [33], which drew attention to that long-known scientific knowledge the principal cells in the lung, i.e. airway epithelial, alveolar macrophages and dendritic cells constitutively express CYP27B1, thus can synthesize active vitamin D locally [34].

The risk of infections and consequent transplant rejections are more common among those who have low serum level of 25(OH)D before transplantation [35], as well as with suboptimal function of the graft [36-38]. Accordingly, optimal level of vitamin D is expected to protect transplant recipients from infections [35,39-42]. Vitamin D plays a central regulatory role in cellular metabolism, thus a well-balanced metabolic state may also be an important player in these processes through sufficient energy levels for optimal cellular function, communication, signaling and repair [26]. Additionally, low serum 25(OH)D level was connected with increased risks of several diseases such as cardiovascular disease, diabetes and cancers, and also to all-cause mortality [37,43-46]. There are multiple approaches to classify serum 25(OH)D levels into deficient, insufficient and sufficient categories [20]. Most societies and agencies define deficiency as < 20 ng/ml, some of them use the term “inadequacy risk” instead of deficiency. The biggest difference is seen in the 20-30 ng/ml range, where all classifications can be found, i.e. "deficiency risk”, “insufficiency” and “sufficiency" [20]. Consensus is mostly observed at 30-50 ng/ml, what most organizations consider to be sufficient levels [20].

The active form of vitamin D as an endocrine hormone, calcitriol (1,25(OH)2D), which is produced from 25(OH)D by 1α-hydroxylation mainly through kidney function [47-49]. However, a well-functioning transplanted kidney is also capable of producing a certain level of active form of vitamin D [50]. Nonetheless, most KTRs require 25(OH)D supplementation. The scientific meaning of this is that even though the activity of 25(OH)D is 1/500 of that of 1,25(OH)2D on the calcitriol receptor (VDR), but since the serum level of 25(OH)D is 1000 times higher than 1,25(OH)2D, the inactive 25(OH)D can contribute to the total vitamin D activity, particularly in renal failure [50]. However, peripheral tissues can also produce 1,25(OH)2D, and able to take over this role in case of intermittent and reduced renal function up to a certain level [51], moreover this is a continuous process during the intracrine mode of action of vitamin D balancing immune system and possibly, similarly the metabolism [52].

Vitamin D and the parathyroid glands regulate the calcium homeostasis, in the latter, parathyroid hormone (PTH) is produced, when the calcium level drops [47,49]. PTH is increasing the reabsorption rate of calcium, the 1α-hydroxylation of 25(OH)D in the kidney to support increased absorption of calcium - in parallel with magnesium - in the intestine, and the serum level of 25(OH)D, as well as bone reabsorption in the skeleton to increase plasma calcium level [48]. PTH also regulates phosphate level, but in an opposite way than calcium, namely increasing its excretion in the proximal tubules [53,54]. In the kidney the α-hydroxylation of 25(OH)D, the excretion of phosphate and production of nephrogenous cyclic adenosine monophosphate (NcAMP) are also regulated by the fibroblast growth factor 23 (FGF23) in response to elevated phosphate or vitamin D levels or CKD [55,56].

The complexity of this area can be clearly perceived from the above. Therefore, in our study we wanted to examine only a small part of this, for which a retrospective study is also suitable. We aimed to study the incidence of infections during vitamin D deficient periods using measurements of vitamin D levels and infection counts within a ± 3 months’ time frames after 1year post-transplantation period of KTRs. We applied the classification of the European Society of Endocrinology, where deficiency is defined when 25(OH)D < 20 ng/ml, insufficiency between 20-30 ng/ml and sufficiency as higher than 30 ng/ml [20]. Moreover, as the regulatory circuit between 25(OH)D, calcitriol, calcium, phosphate and PTH is disrupted in KTRs compared to healthy individuals [57], we aimed to investigate the associations between serum 25(OH)D, calcium, phosphate levels in relation to kidney function (chronic kidney disease stages - CKD stages) and parathyroid hormone (PTH) level in KTRs in a retrospective single-centre study.

Materials and Methods

Study design

Our study is a retrospective analysis of electronic health records (EHRs) of adult kidneytransplanted patients under the outpatient care of a single-centre (Department of Surgery, Transplantation and Gastroenterology, Semmelweis University of Budapest, Hungary, Faculty of Medicine). Attendances until the 3rd July 2023 (study end date) were selected in the study filtering the eMedsol EHR system, resulting in 343 eligible transplanted patients. Every physician treated the patients under the same protocol based on the guidelines [58] as all patients belong to the same department, where guideline updates always incorporated and agreed with the treating physicians. A subsample of 170 from the 343 of patients were randomly selected due to resource constraints. Inclusion and exclusion criteria were applied to select study patients (Supplementary Figure 1). Inclusion criteria were kidney-transplanted, adult patient, and the exclusion criteria were multi-organ transplant (also liver, pancreas, heart etc), lack of 25(OH)D measurement, having insufficiently detailed electronic records (e.g. missing infection dates), patient with unrelated diseases with therapies that may affect the 25(OH)D level or infection rate (i.e. inflammatory bowel diseases, osteoporosis).

Data collection

The exposure of primary interest was the 25(OH)D level measured in ng/mL (LIAISON 25 OH Vitamin D TOTAL Assay No#310600, DiaSorin Inc, Stillwater, NM, USA) by the central clinical laboratory (Department of Laboratory Medicine, Semmelweis University, Hungary). The 25(OH)D measurements were performed when the treating physician deemed them to be clinically indicated during standard care. Data of 25(OH)D levels were selected for statistical analysis after stable graft function (no sign of rejection and stable parameters of kidney function) and with a minimum of 1 year after transplantation. The following clinical variables were also extracted: date of birth, gender, date and type of transplantation, type of donor (living, cadaver), type of immunosuppression, diagnosed chronic diseases, dates and types of infections (cystitis, upper airway infection and pneumonia, as identified by increased C-reactive protein (CRP) level, documented symptoms and antibiotic therapy), CRP, calcium, phosphate and PTH levels as well as CKD stages. CKD stages were classified based on the glomerular filtration rate from G1 to G5 using the UK Kidney Association guideline [58]. The incidence and count of infections were considered if diagnosed within a ±3 month's interval before or after a vitamin D measurement [39]. The other clinical data detailed above were matched to the date of the 25(OH)D measurements, however not all the 25(OH)D measurements has matched pairs of CRP, CKD, PTH, calcium and phosphate. All the colleagues who worked on the selection of patients used the same inclusion and exclusion criteria as were described in the relevant sections and in the flow chart.

Clinical data collected from the records of the patients were irreversibly pseudonymized prior to analysis. Our study was approved by the Regional and Institutional Committee of Science and Research Ethics of Semmelweis University (RKEB 268/2022).

Data processing and data series for statistics

Inclusion and exclusion criteria were applied to the 170 randomly selected patients. When preparing the data sets, we first excluded all vitamin D measurements for 1 year after transplantation in all patients (Supplementary Figure 1), leaving 130 study patients whose clinical data were used for statistical analysis. All the 130 patients have a consecutive measurement series of vitamin D, CRP, PTH, calcium and phosphate levels and eGFR as well as consecutive medical records of infections. For patients who did not have a measurement for about a year, we took into account the first recorded vitamin D measurements older than 1 year.

After creating a series of a vitamin D measurements for each of the patients, we extracted the dates and types of infections from all available records within the ±3 month's interval before or after a vitamin D measurement. Then, vitamin D levels and corresponding incidence (0: no infection, 1: infection was recorded) and count (0-1-2-3-4-etc., as many as recorded) of infections were paired - without incomplete pairs. After that, all clinical parameters (CRP, CKD, PTH, calcium and phosphate) were added to the data pairs described above. It should be noted that these clinical data were sometimes missing at the time of vitamin D measurements. Thus, series of cases (case: clinical data of patients for a specific vitamin D measurement) were compiled for each of the 130 patients, which were then used for the statistics.

Vitamin D was used as both a continuous and categorical variable in the hierarchical analysis. We categorized the levels of 25(OH)D into the 3 ESE groups as described above (deficient is < 20 ng/ml, insufficient is between 20-30 ng/ml and sufficient as greater than 30 ng/ml) [20].

Statistical analysis

Mixed effect generalised linear models, specifically Poisson regressions with logarithmic link function were used to evaluate the association between 25(OH)D levels and the incidence and count of infections as well as the incidence and count of infection in diabetic and in non-diabetic patients. Age, gender, type of immunosuppression (ISU), and 25(OH)D level or additionally CKD stages and PTH levels were the fixed effects in the models, the other model predictors were patients as random effects. Mixed effect linear regression were applied to evaluate the associations of calcium, phosphate, CRP, PTH levels and CKD stages across the vitamin

D deficient, insufficiency and sufficiency groups of cases. The significance levels were presented as follows: ****: $p < 0.0001$; **: $0.001 < p < 0.01$; *: $0.01 < p < 0.05$. IBM SPSS Statistics for Windows Version 28.0.1.0 (IBM Corporation, Armonk, NY, USA) was used for hierarchical analyses.

Results

Study population

343 transplanted patients were eligible for the study and from them a subsample of 170 were randomly selected. Applying the inclusion and exclusion criteria clinical data series of 130 patients were included in the statistical analyses. Vitamin D measurements ranged from 29/Nov/2007 until 10/March/2023 with the matchable dates of infections and dates of clear documentation of infection-free periods. The number of the values of vitamin D ranged from 1 to 18 per patient (median (Q25 and Q75): 4 (3 and 8); mean±SD: 5.76 ± 4.47). Diabetes (n=23) and hypertension (n=68) were the most common chronic diseases among the included 130 KTRs, less common diseases in KTRs represented by 1-4 patients (i.e. heart diseases, asthma, gout, epilepsy, arthritis/osteoarthritis, chronic obstructive pulmonary diseases, etc.), except obesity with 8 patients (Supplementary Table 1). The characteristics of 130 patients are summarized in Table 1.

The mean ± SD of 25(OH)D levels in KTRs was 29.8±10.6 ng/ml, the median was 28.5 ng/ml with quartiles (Q25 and Q75): 23.3 ng/ml and 34.6 ng/ml (Table 1). Significantly lower levels of 25(OH)D were detected in infected as compared to infection-free periods ($p<0.0001$) (Figure 1A).

The number of infected events were around the third of the infection-free events (23.3% vs 71.7%), while the two groups of immunosuppression represented with a similar weight in our study (53.8% vs 46.2%) (Table 1).

Analysis of the incidence and count of infections and laboratory parameters in relation to vitamin D levels

Applying the hierarchical model we found significant association between vitamin D deficiency and the incidence and count of infections ($p < 0.0001$ in both cases), moreover vitamin D level showed significant negative association with the incidence and count of infections ($p < 0.0001$ in both cases). A 10 ng/ml increase in the 25(OH)D level was associated with 37% and 25.6% decrease in the incidence and count of infections, respectively. Immunosuppression neither with nor without steroids did not show significant association with infections. Additionally, the incidence and the count of infections were significantly higher in vitamin D deficient group of cases compared to the insufficient or sufficient vitamin D level cases ($p < 0.0001$ in all cases) as presented in Figure 1B and C. The CRP level did not significantly differ across the three groups of vitamin D levels (Figure 1D). The incidence and count of infections did not differ significantly between diabetic and non-diabetic KTRs (Figure 1E and 1F).

When CKD stages and PTH levels were incorporated into the Poisson regression the included number of cases decreased to 20% of the original number of cases because the relatively small number of clinically indicated PTH measurements. Nonetheless, the association of vitamin D deficiency with the incidence and count of infections remained significant ($p =0.004$ and 0.047, respectively). CKD stages and PTH levels were not significantly associated with the incidence and count of infections (CKD $p = 0.593$ and 0.448, respectively; PTH $p = 0.547$ and 0.408, respectively).

Characteristics of patients

Patients	**N**	**%**
all patients	130	100
male	69	53
female	61	47
Age (years)	**mean**	**± SD**
all patients	57.5	13.9
male	56.9	14.1
female	58.0	13.9
Type of donor	**N**	**%**
all patients	130	100
living	16	12.3
cadaver	114	87.7
Type of immunosupression (ISU)	**N**	**%**
all patients	130	100.0
ISU without steroid	70	53.8

ISU including steroid	60		46.2	
Presence of infection	**N**		**%**	
all 25(OH)D measurements	749		100	
no infection	537		71.7	
with infection (within ±3months)	212		28.3	
25(OH)D level (ng/ml)	**mean (± SD)**		**median (Q25/75)**	
all 25(OH)D measurements	29.8 (10.6)		28.5 (23.3/34.6)	
without infection	31.4 (9.9)		29.5 (25.4/35.8)	
with infection (within ±3months)	25.6 (11.2)		24.8 (18.1/31.1)	
Groups of cases based on 25(OH)D levels	**All (%)**	**Deficiency (%)**	**Insufficiency (%)**	**Sufficiency (%)**
All 25(OH)D measurements	749 **(100%)**	109 **(14.5) (**100%)	330 **(44.1)** (100%)	310 **(41.4)** (100%)
without infection	537 (71.7)	39 (35.8)	245 (74.2)	253 (81.6)
with infection (within ±3months)	212 (28.3)	70 (64.2)	85 (25.7)	57 (18.4)
Ca	714 (95.3)	104 (95.4)	318 (96.4)	292 (94.2)
P	155 (20.7)	14 (12.8)	49 (14.8)	92 (29.7)
PTH	162 (21.6)	29 (26.6)	89 (26.9)	44 (14.2)
CKD stages (all)	574 (76.6)	91 (83.5)	277 (83.9)	206 (66.4)
CKD 1	25 (3.3)	9 (8.3)	5 (1.5)	11 (3.5)
CKD 2	198 (26.4)	26 (23.9)	89 (27.0)	83 (26.8)
CKD 3a	127 (16.9)	18 (16.5)	62 (18.8)	47 (15.2)
CKD 3b	115 (15.3)	17 (15.6)	64 (19.4)	34 (11.0)
CKD 4	83 (11.1)	15 (13.8)	44 (13.3)	24 (7.7)
CKD 5	26 (3.6)	6 (5.5)	13 (3.9)	7 (2.3)
in diabetic patients	121 (16.2)	33 (30.3)	57 (17.3)	31 (10)
in non-diabetic patients	628 (83.8)	76 (69.7)	273 (82.7)	279 (90)

Table 1: Patient characteristics.

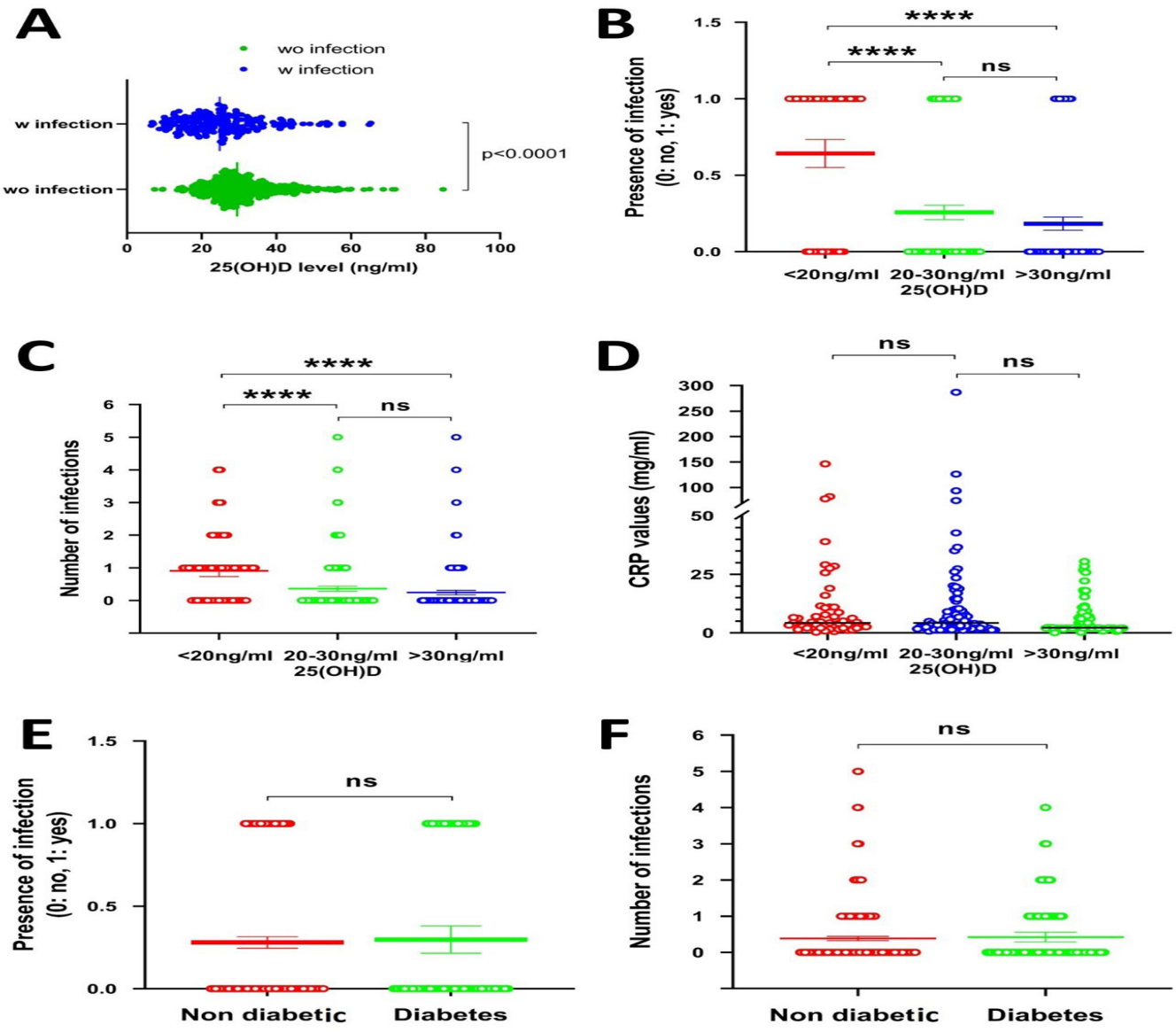


Figure 1: Level of 25(OH)D in cases with and without infections. A. Comparison of 25(OH)D levels in infection-free and infected periods of KTRs. Comparisons of the incidence/count of infections as well as CRP levels in KTRs based on 25(OH)D levels. B. Incidence of infection was significantly higher in vitamin D deficient periods compared to insufficient and sufficient level ones. C. Counts of infections were significantly higher in vitamin D deficient periods compared to to insufficient and sufficient level ones. D. CRP levels did not differ between the three groups of cases. Comparisons of the incidence/count of infections in diabetic and non-diabetic KTRs. E. Incidence of infection was not significantly different between diabetic and non-diabetic patients. F. Counts of infections were not significantly different between diabetic and non-diabetic patients. The points on the figures correspond to 6month time periods of patients, the multiple time periods per patients have been considered in the random effect models, but not highlighted in the figures. w: with, wo: without, lines in B-C, E-F: mean, error bars in B-C, E-F: 95%CI, lines in D: median, ****: $p < 0.0001$, ns: not significant.

Additionally, similar distribution of CKD stages and PTH levels were found in vitamin D deficient, insufficient and sufficient level group of cases (Figure 2 A, B). Only calcium levels were significantly higher in cases with sufficient vitamin D levels compared to insufficient and deficient ones ($p = 0.0031$ and $p = 0.0496$, respectively) (Figure 2C). Phosphate level did not differ significantly between the 3 groups (Figure 2D).

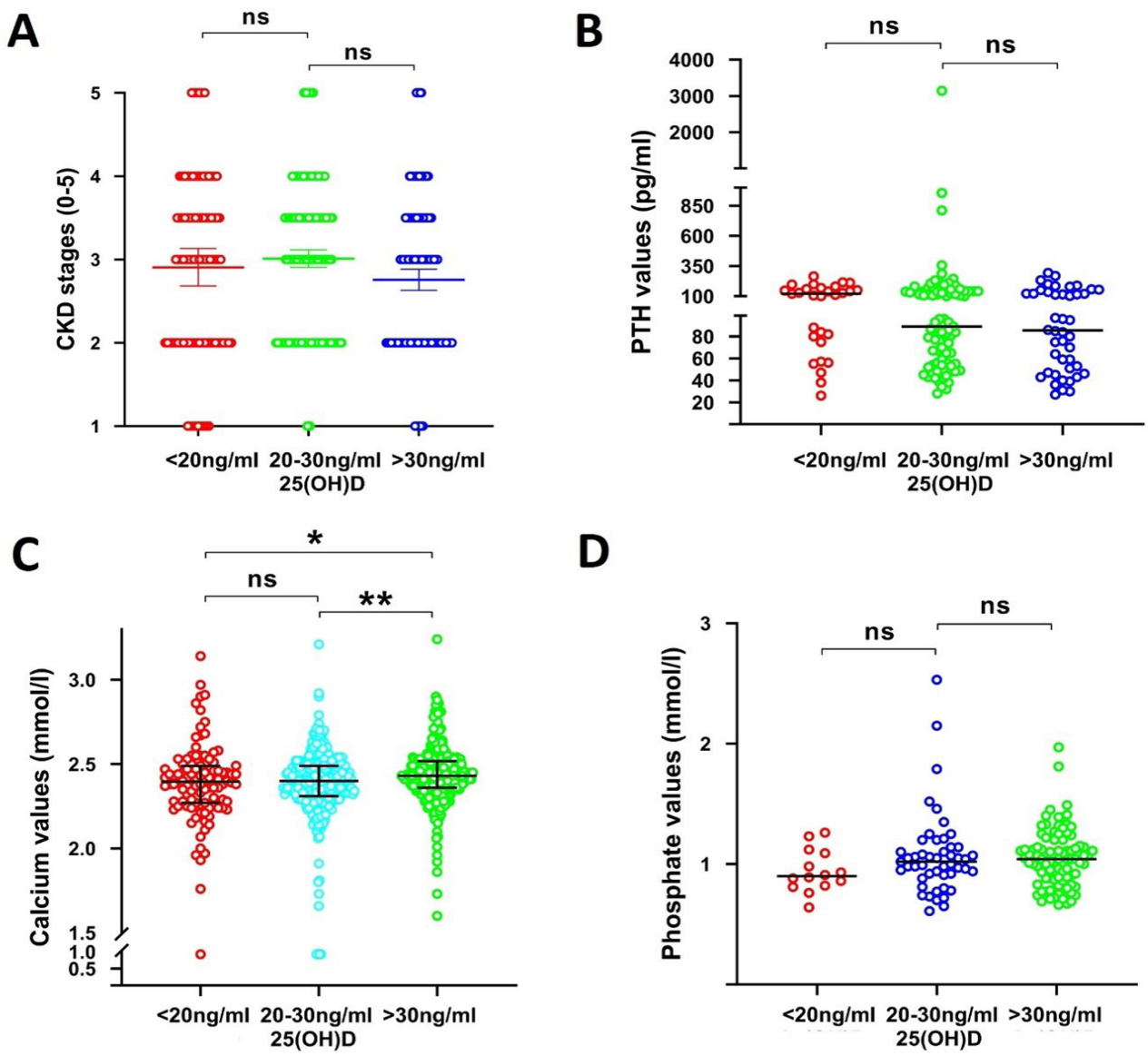


Figure 2: Comparisons of CKD stages and PTH, calcium and phosphate levels in the 3 groups of cases created based on 25(OH)D levels in KTRs. A. The distribution of different CKD stages did not differ in the 3 case groups based on 25(OH)D levels. B. PTH levels were similar in all the three groups of cases based on 25(OH)D levels. C. Calcium levels were significantly higher in cases with sufficient vitamin D levels compared to deficient and insufficient ones. D. Phosphate levels were similar in the 3 groups of cases based on 25(OH)D levels. The points on the figures correspond to 6month time periods of patients, the multiple time periods per patients have been considered in the random effect models, but not highlighted in the figures. Lines in A: mean, error bars in A: 95%CI, lines in B-D: median, error bars in C: interquartile ranges, *: p = 0.0496; **: p = 0.0031, ns: not significant

Gender showed significant association with the incidence and count of infections ($p < 0.001$ in both cases). In men 24.2% lower incidence and 29.8% lower count of infections were estimated as compared to women.

Discussion

Complementary therapies are important parts of disease prevention, they may reduce the side effects and increase the effectiveness of conventional treatments [59]. Several studies reported that higher levels of 25(OH)D are associated with lower rates of all-cause mortality or cardiovascular disease (CVD) [60], and also its deficiency (25(OH)D level < 20 ng/ml) is associated with the incidence of several other diseases [23,24,61-68]. Proper function of the liver and kidney is necessary for the production of a sufficient level of the active form of vitamin D, which has several important roles in healthy metabolism and immune regulation, enabling its positive effects on diseases mentioned above [24,26]. We aimed in our study to investigate the incidence and count of infections during vitamin D deficient periods of KTRs and also we were interested in the association between vitamin D levels and CKD stages as well as PTH, calcium, phosphate and CRP levels in these patients with specific kidney function.

We found that KTRs had significantly lower level of 25(OH) D during infections compared to infection-free periods after 1year post-transplantation and in later time periods, which consistent with other studies reported inverse association with 25(OH)D level and infections in KTRs [39,41,42]. Additionally, in our study significantly higher incidence and count of infections were detected in vitamin D deficient group of cases in KTRs (following the European Society of Endocrinology criteria, where deficiency defined as lower than 20 ng/ml), as compared to the insufficient and sufficient ones. Our results complement the findings of other studies in this field. Fernández-Rueiz et al only investigated the association of infection and vitamin D level at the post-transplant months 1, 3, 6 and 12, and they defined vitamin D deficiency following the criteria of Institute of Medicine (i.e. lower than 12 ng/ml) and indicated that vitamin D status influences the risk of infection in early post-transplant period [41]. In our study, the incidence of infections were assessed in the same time frames of ± 90 days of vitamin D levels, as theirs. However, we defined the deficiency in on a more refined scale (i.e < 20 ng/ml, 20-30 ng/ml and >30 ng/ml) based on the ESE guideline [20], and we found significantly higher incidence and count of infection in our vitamin D deficient group (< 20 ng/ml). They concluded that vitamin D sufficiency at any time post-transplantation was significantly associated with 66% lower odds (OR) and 43% lower rate of infection (IRR) within ± 90 days of vitamin D levels. Although our data collection periods overlap, they analyzed vitamin D levels at any time after transplantation, and they did not separate the clinically distinct early post-transplantation period with an increased risk of infection, as we did. Similarly to the previous study, Kalluri et al, found that vitamin D sufficiency was also significantly associated with a 65% lower incidence for infection (IRR: 0.44) within the firstyear post-transplantation [39]. Concordant with our results, this study also found that none of their investigated groups of immunosuppression were significantly associated with the incidence of infection. However, steroid use was a significant predictor of multiple infections in their results. In the study of Schreiber et al, vitamin D levels were measured at the time of liver transplantation and 6 month later [42]. They defined vitamin D deficiency as < 20 ng/ml and infections were categorized as viral and bacterial infections. They found that vitamin D deficiency was common at time of transplantation and 6 months later as well without a significantchanges in median 25(OH)D levels. In univariable analysis only, they found that vitamin D deficiency was a risk factor for the incidence of infections in the first 6 months of post-transplant period (IRR: 1.52), and even more, for bacterial infections after 6 up to 30 months post-transplant (IRR: 2.29) [42]. Comparing our set-up with these studies, we excluded the periods of transplantation before 1year post-transplantation, as well as transplant rejections in order to avoid the effect of surgical intervention and instable graft function related infections to specifically investigate the connection between vitamin D levels and infections.

We assume that higher levels of 25(OH)D are the causes of lower frequencies of infections. However, we can't exclude the possibility that infections may contribute to decreases in 25(OH)D levels as well [14]. It is supported those studies, which found that immune cells are locally produce calcitriol by their 1α-hydroxylase enzymes from 25(OH)D, and thus this active hormone through VDRs can modulate immune response against viral or bacterial infections [33]. Therefore, serum 25(OH)D is used by the mitochondrial CYP27B1 of monocyte/macrophage to promote transcriptional upregulation of cathelicidin and β-defensin 4 which both are antimicrobial proteins, facilitating autophagosome generation and promote bacterial killing in autolysosomes [52]. This intracrin process is distinct from the endocrine action of vitamin D, where 1,25(OH)2D is regulated not only by its precursor, but also by PTH and FGF23 [69]. In contrary, the role of vitamin D in immune response – and possibly in its other non-osteometabolic effects -, is regulated primarily by the availability of the 25(OH)D [33]. That is why a 1000 times higher amount of 25(OH)D, compared to the active form, can impact on a healthier homeostasis and immune regulation and not only in KTRs – as we described in the introduction [50]. Although it has much less affinity to VDR, but in intracrine processes probably the locally produced 1,25(OH)2D may take over its role or they may function in parallel.

Empirically and based on clinical studies, infections have a higher incidence in diabetic patients than in non-diabetic ones [70]. Thus, we investigated, whether diabetes in KTRs similarly follows a higher incidence of infection. We found that there was no significant difference between the incidence and count of infections in diabetic and non-diabetic KTRs in our study, which presumably means that diabetes

may not represent an additional risk of infection in KTRs.
Investigating the connections of vitamin D level to calcium and phosphate we found that calcium levels were significantly higher in the vitamin D sufficient group as compared to insufficient and deficient ones. Active vitamin D, independently from PTH, increases the absorption of calcium from gut, calcium efflux from bone and reabsorption from distal convoluted tubules [71]. Our results presumably means that although in KTRs where the active vitamin D production thought to be decreased because of their reduced kidney function, a sufficient level (around 30ng/ml) of 25(OH)D able to increase calcium level even in KTRs. Additionally, it may be explained by the recommendations suggesting to maintain a slightly elevated PTH levels in KTRs with CKD stages 3b-4 (upper normal level or slightly above the upper normal level), which enable a more adequate production of active vitamin D levels with optimal bone metabolism and also overcome PTH reaction deficiency [72].
We did not find differences in the distribution of phosphate among the 3 groups. However, calcitriol increases the absorption of phosphate from intestine, renal tubules and bone [73]. These findings may explained by the low number of pairs in our data of vitamin D and phosphate cases, as well as the previously mentioned slightly elevated levels of PTH, which recommended, to allow the necessary phosphaturic effect of PTH [72]. Vitamin D level (25(OH)D) should be maintained within the safe and physiologically optimal range in KTRs, monitoring the calcium, phosphate and PTH levels in relation to CKD stages, based on individual assessment to avoid calcification [71,72].
The two groups of immunosuppression, ISU including or without steroids, were represented in a similar weight in our study. However, compared to other studies we did not find significant correlation between them and vitamin D level in general [74,75]. The first study found invers association only between calcineurin inhibitors (CNIs) and vitamin D level, while the other immunosuppressive agents unaffected the level of vitamin D [75]. The other study found association with more ISU medication [74]. However, these differences are not challenging our results, namely that KTRs in vitamin D deficiency states are more exposed to infections. Our result suggests, and thereby helps everyday practice, that vitamin D supplementation is necessary in those KTRs where a temporary vitamin deficiency detected in order to avoid chance of increased infections and related rejections.
A strength of our study is the single-centre design, which ensures the same treatment and laboratory protocol. Additionally, we defined vitamin D levels in more detail than others, reaching more refined results. Moreover, our data suggest that patients were treated following the recommendations cited above, thus, it can be considered a representative population of KTRs.
Limitations of our study are the different number (in phosphate levels even too low) of paired clinical data used in some of the analyses, which possibly result from the retrospective nature of the study, which include only data, that were necessary for daily care as requested by the physicians. Additionally, the retrospective nature of the study did not allow study specific sample collection as well. Moreover, we could not investigate the number of immune cells in relation to infection and vitamin D levels as KTRs are treated by ISU.

Conclusions

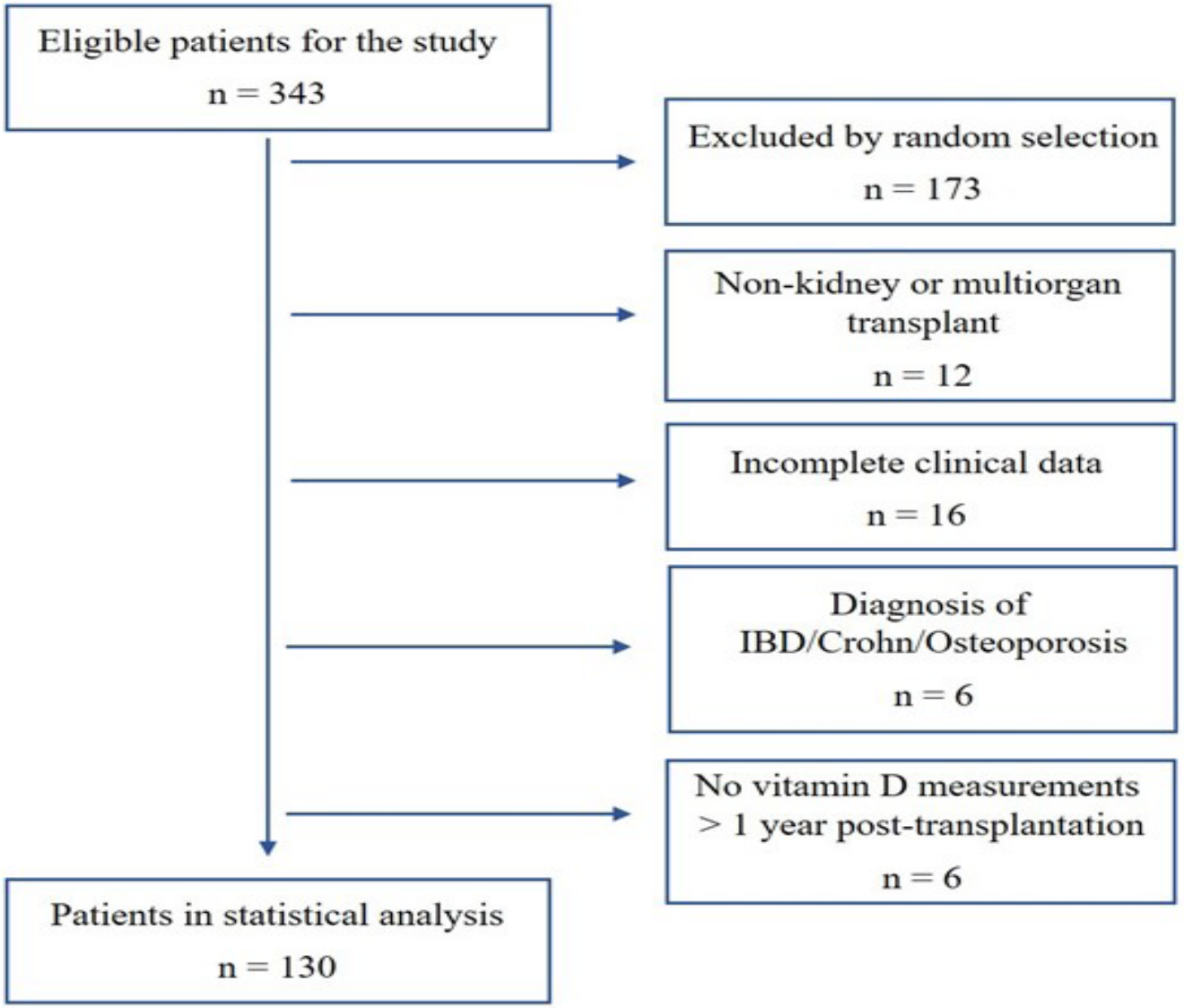
We found that KTRs have significantly lower levels of 25(OH)D during infections compared to infection-free periods. Moreover, vitamin D deficient periods were associated with significantly increased infections. Additionally, the sufficient (> 30 ng/ml) vitamin D level may improve the reduced kidney function in relation to calcium metabolism, as well as the regulation of immune system, possibly at least partly through the improved homeostasis generally, including glucose, lipid and energy homeostasis, which are similarly important in immune system regulation. However, because of the risk of vascular calcification since imbalanced regulatory mechanism exists in KTRs, vitamin D levels should be maintained in the safe, biologically optimal range to avoid infections related to vitamin D deficiency, but still allow an optimal metabolism, included calcium homeostasis. Our result suggests, and thereby helps everyday practice, that vitamin D supplementation is necessary in those KTRs where a temporary vitamin deficiency detected in order to avoid the chance of increased infections and related rejections.

Supplementary files

Chronic disease	N	%	Chronic disease	N	%
All patients	**130**	**100**	**All patients**	**130**	**100**
Alport syndrome	2	1.5	Hypertension	68	52.3
Acute myocardial infarction	3	2.3	Hyperthyroidism	1	0.8
Angina pectoris/Instable angina	3	2.3	Hypothyroidism	1	0.8
Osteoarthritis/ Arthrosis	1	0.8	Hypertriglyceridaemia	1	0.8
Asthma	2	1.5	Ischemic heart disease	4	3.1

Autoimmune kidney disease	1	0.8	Multiple myeloma	1	0.8
COPD	1	0.8	NODAT	5	3.8
Diabetes	18	13.8	Obesity/severe obesity	8	6.2
Epilepsy	1	0.8	OSAS	1	0.8
Glomerulonephritis	1	0.8	PCKD	7	5.4
Goodpasture syndrome	1	0.8	PCLD	1	0.8
Gout	1	0.8	Psoriasis	1	0.8
Hyperlipidaemia	3	2.3	Saldino-Mainzer syndrome	1	0.8
Hyperparathyreodism	1	0.8	SLE	1	0.8

Supplementary Table 1: Chronic diseases in the 130 included patients.



Supplementary Figure 1:

Abbreviations

BKV - BK polioma virus
CKD - chronic kidney disease
CMV - Cytomegalovirus
CNIs - calcineurin inhibitors
COPD - chronic obstructive pulmonary disease
CRP - C-reactive protein
CVD - cardiovascular disease
CYP27B1 - cytochrome P450 family 27 subfamily B member 1
EBV - Epstein Barr virus
EHRs - electronic health records
FGF23 - fibroblast growth factor 23
IL-17 - interleukin 17
IRR - incidence rate ratio
ISU - immunosuppression
KTRs - kidney transplant recipients
NcAMP - nephrogenous cyclic adenosine monophosphate
NODAT - new onset diabetes
OR - odds ratio
OSAS - obstructive sleep apnea syndrome
PCKD -polycystic kidney disease
PCLD -polycystic liver disease
PTH- parathyroid hormone
SLE - systemic lupus erythematosus
Th1/Th2/Th17 - T helper 1,2 and 17 cells
VDR - vitamin D receptor
VZV - Varicella zoster virus

Author Contributions

A.P.: access to cohort patients, idea, data processing, literature search, paper review; G.B: data processing, mixed model Poisson regression, literature search, paper review, G.S.: data retrieval, paper review, A. S.: paper review, Z.N.: conception, design, data processing, statistical analysis, visualization, literature search, paper writing, and final approval. All authors have read and agreed to the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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