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Vitamin D Status has no Influence on the Incidence of Recurrent Urinary Tract Infections after Kidney Transplantation

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Abstract

Introduction. Recurrent urinary tract infections (rUTIs) after kidney transplantation (KT) are associated with significant decrease in graft survival. There is a growing body of evidence for the pleiotropic effects of vitamin D (VD), including immunomodulatory and antibacterial effect. The number of studies on VD's pleiotropic effects in kidney transplant recipients (KTRs) however is low. The aim of our study was to assess the influence of VD on the incidence of recurrent UTIs after KT.
Methods. The KTRs were tested for 25-hydroxyvitamin D (25VD) between 1.05.2012 and 30.11.2012. Patients within 12 months of transplantation, performed parathyroidectomy, concomitant intake of calcineurin inhibitors and mTOR inhibitors, advanced liver disease and VD supplementation were excluded from the study. Recurrent UTIs were defined as more than 3 episodes of active UTI within the last 12 months of testing for 25VD. Statistical analysis was carried out with SPSS version 22.0 and included descriptive statistics, Mann-Whitney U test. Determination of total 25VD was performed by a validated LC-MS/MS method.
Results. A total of 275 patients met the above-mentioned criteria (males 182, females 93). The mean 25VD in patients with rUTIs (n=14) was 51.41±25.17 nmol/L, whereas in the group without rUTIs (n=261) the level was 60.35±23.29 nmol/L. After matching the two groups for seasonal factors (sampling for 25VD in July, August, September) and gender 169 patients were selected, and 11 were with rUTIs. No significant difference was detected in the 25VD level in the two groups (53.30±18.37 vs 49.08±21.04 nmol/L), p=0.342.
Conclusions. Despite the higher 25VD in the KTRs without rUTIs, the difference between the two groups remained insignificant.

Key words: 25-hydroxyvitamin D, pleiotropic effects, recurrent urinary tract infections, renal transplantation

Introduction

Urinary tract infections (UTIs) are one of the most common complications after kidney transplantation (KT), with prevalence peaking up to 80% [1]. UTIs, including recurrent UTIs, are associated with graft failure, risk for rejection episode and decreased patient survival [2,3]. On the other hand, vitamin D is getting more and more popular for its pleiotropic effects-renoprotection, control of diabetes mellitus and hypertension, immunomodulation. One of these non-skeletal effects is stimulating protective immunity [4-6]. Low VD level predicts higher incidence of recurrent UTIs (rUTIs) in premenopausal women [7]. A recent study by Lowery *et al.* has revealed that poor VD status is linked to higher infection rate after lung transplantation [8]. However, there is still no data proving the protective role of VD in reducing the risk for infection, including UTI after KT. Therefore, the aim of our study was to assess the association between rUTIs and VD status after KT, measured by the serum level of 25-hydroxyvitamin D [25(OH)VD], as generally accepted [9].

Material and methods

Subjects

Three hundred ninety five kidney transplant recipients (KTRs) in our transplant center were tested for 25(OH)D between 01.05.2012 and 30.11.2012. The following selection criteria were applied: KTRs less than 36 months after kidney transplantation were excluded, patients with performed parathyroidectomy and unstable kidney function were also excluded from the study; subjects with advanced liver disease (Child-Pugh score B and over) and with vitamin D supplementation were not taken into consideration, as well as outliers for BMI and 25(OH)D (absolute value for Z-score greater than 3.29). Our study was approved by the Institutional Ethics Committee, and was in accordance to the Helsinki Declaration of 1975 (as revised in 2000). All participants gave their informed consent prior to inclusion in the study. Recurrent UTIs were defined as more than 3 episodes of UTI

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within 12 months before testing for 25(OH)D. In order to assess the link between VD status and rUTIs the patients in both groups (with and without rUTI) were matched for gender and months of sampling for VD, due to the influence of these factors on 25(OH)D [10-12].

Methods

Analysis of 25(OH)D

Determination of 25(OH)D was performed by a validated LC-MS/MS method developed in-house, utilizing extraction with hexane, d325(OH)D3 as internal standard, isocratic elution on C18 analytical column, positive-ion electrospray ionization, and selected reaction monitorring for the respective m/z transitions: 401→383 for 25(OH)D3, 413→395 for 25(OH)D2, and 404→386 for d325(OH)D3. This method was calibrated with the use of commercial, NIST (National Institute of Standards and Technology, USA) 972 traceable reference materials and was validated according to FDA guidance requirements, with documented selectivity and matrix effect, accuracy and precision within 7.5%; extraction recoveries averaging 57-73%; linearity range 3.0-300.0 nmol/L, R2>0.99, freeze-thaw stability for three cycles of 24 h, post-preparative stability for 96 h at 10°C, short-term stability at ambient temperature for 24 h in the dark and for 2 h at daylight; stock solution stability and long-term stability in plasma for 5 days at 4-8°C, and for 99 days at -20°C. It participated in DEQAS (UK Vitamin D External Proficiency Testing Scheme) external proficiency testing scheme with achieved certification for 2012.

Microbiological analysis

Conventional biochemical methods were used to identify different strains of uropathogens-automatic and semi-automatic biochemical identification systems-miniApi (bioMerieux, France) and BBL Crystal (BD). The antibiotic sensitivity was determined via disc-diffusion method, according to the accepted CLSI standard in Bulgaria.

Statistical analysis

Descriptive statistics, Fisher`s exact test and Mann-Whitney U test were used to investigate the association between 25VD and recurrent UTIs. Level of significance was set at P<0.05, SPSS 22.0 Software (SPSS Inc, Chicago, IL, USA) was used. In order to avoid distortions of parameter and statistic estimates, we screened the data for BMI and 25(OH)D level for outliers using the Z-score method, with cut-off values lower than /-3.29/ and higher than /+3.29/.

Results

Two hundred and twenty two patients were shortlisted after the selection criteria were applied. Males outnumbered the females (145 vs 77). The baseline characteristics of the group are depicted in Table 1.

Table 1. Basic characteristics of the study subjects, n=222

	Males n=145	**Females n=77**
Age (years)	43.67±13.08	43.51±11.42
Time after TR * (months)	112.49±54.83	121.25±53.73
eGFR † (ml/min/1,73m^2)	62.59±22.02	62.73±26.54
Vit.D concentration‡ (nmol/L)	65.77±24.12	52.58±21.57

*TR-transplantation, †eGFR-estimated glomerular filtration rate-CKD-EPI formula, ‡ total 25(OH)D

In almost 80% of the subjects suboptimal 25(OH)D levels were established (Figure 1). Out of 222 patients 8 were detected with recurrent UTIs. Two out of 47 VD sufficient kidney transplant recipients (KTRs) were detected with rUTIs (4.3%), compared to 6 KTRs with rUTI out of 175 patients with suboptimal VD status (3.4%). The difference was found to be insignificant, p=0.678 (Fisher's exact test, Figure 2).

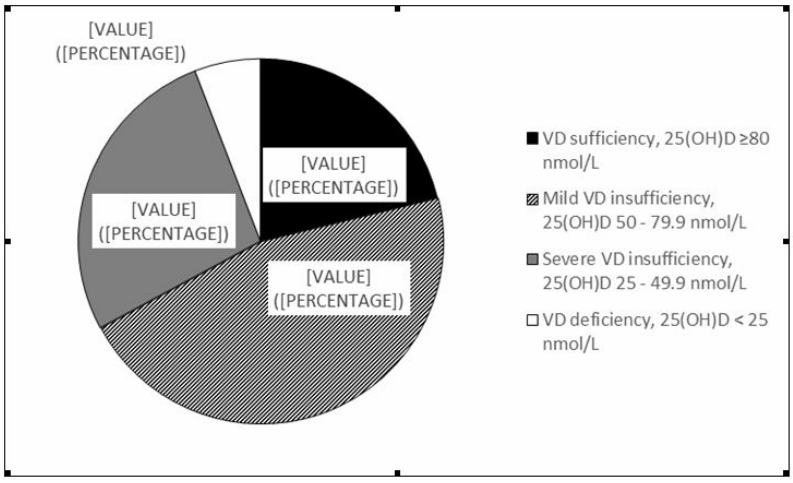

Fig. 1. VD status of the assessed KTRs, n=222; VD-vitamin D

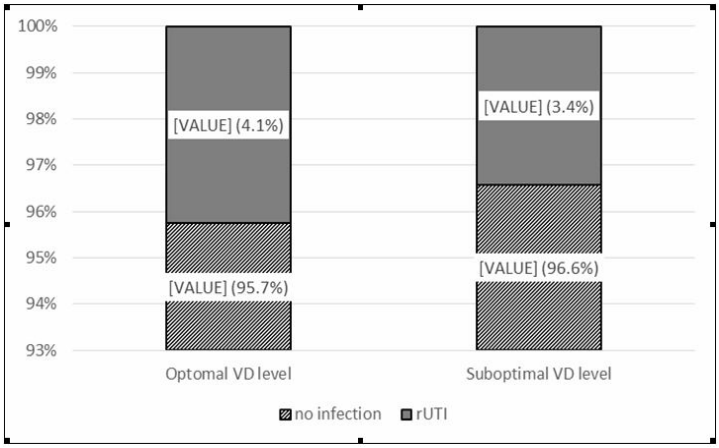

Fig. 2. rUTI incidence rate KTRs with optimal VD (n=47) vs KTRs with suboptimal VD level (n=175) VD-vitamin D, rUTI-recurrent urinary tract infection

In addition, VD status between patients with and without rUTIs was compared. The mean 25(OH)D for patients with rUTIs was 52.64±30.59 nmol/L, whereas in the group without infection-61.51±23.81nmol/L (Figure 3). The difference was insignificant, p=0.490 (Mann-Whitney U test).

In order to assess the link between VD level and rUTI incidence rate more accurately, the patients were matched according to gender and month of sampling. Patients

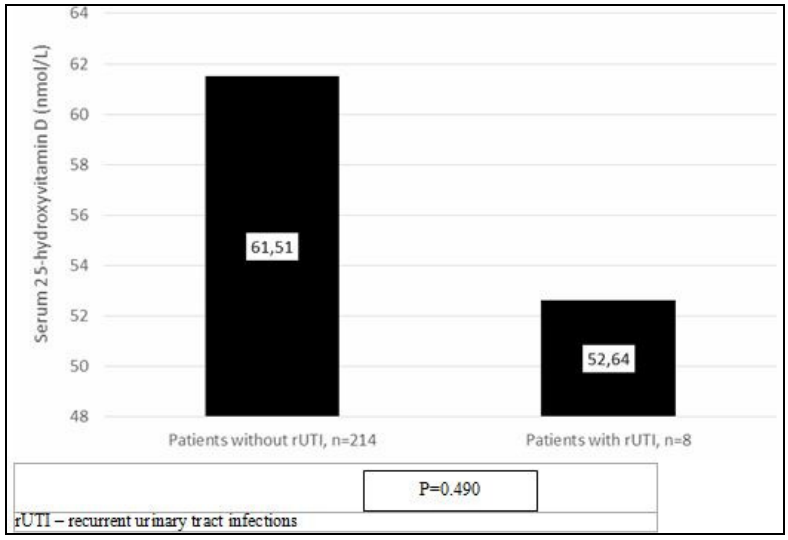

Fig. 3. Mean 25-hydroxyvitamin D levels in patients with rUTI and without rUTI

tested for 25VD in July, August, September were excluded due to the significant influence of summer testing on VD status. After the second selection was performed 56 patients were shortlisted. Five [5] out of 56 were with rUTIs. The mean 25(OH)D level for patients without infection was 48.25±18.19 nmol/L vs 48.24±26.26nmol/L. The difference was statistically insignificant (Mann-Whitney U test, p=0.978). The result is summarized in Figure 4.

Discussion

Considering the relationship between rUTIs and VD status we should bear in mind two basic considerations. UTIs are a frequent and important complication after KT, with various clinical presentations. The major risk factors for development of rUTIs are female gender, immunosuppression, in-dwelling catheters, anatomical abnormalities of the native kidneys or the graft, diabetes mellitus, urologic procedures, elderly patients, antibiotic resistance of the bacterial strains [2,13]. The influence of these factors gradually decreases with the increase of time interval after KT. In order to exclude most of the above-mentioned predictors for UTI incidence we deliberately selected patients with longer period of time after KT. In our study no significant association was established between VD status and rUTI incidence. It is possible that our results reflect the persistent influence of the well-known predictors in the course of time after KT, thus being the more important cause for higher rUTIs incidence rather than 25(OH)D level.

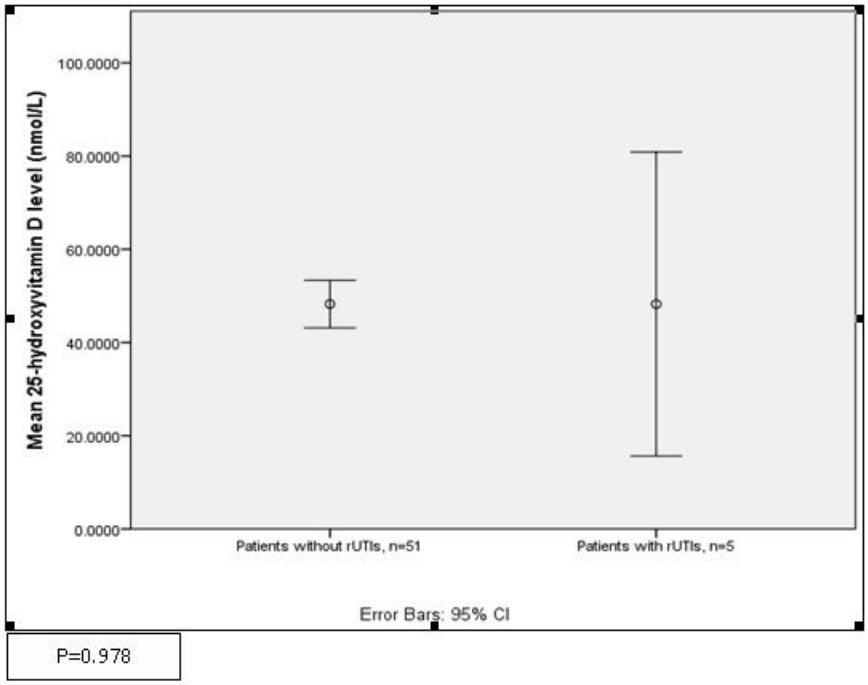

Fig. 4. Mean 25-hydroxyvitamin D, gender and season matched group, n=56
rUTI-recurrent urinary tract infections

Furthermore, the impact of 25(OH)D on infection rate after kidney transplantation is still unclear [14]. Indeed, several in vitro studies proved that calcitriol leads to an increased synthesis of cathelicidin, an antimicrobial peptide, by macrophages [15]. Calcitriol was also associated with increased production of interleukin 1 and monocyte proliferation [16,17]. Vitamin D3 supplementation reduced influence infection rate in humans and improved antiviral response in hepatitis C infected patients [18,19]. A retrospective study however failed to detect beneficial effect of regular VD supplementation on infectious mortality rate in patients on hemodialysis [20]. In addition, the number of reports linking VD status and infection rate after solid organ transplantation is small and insufficient. Therefore we can conclude that further data must be gathered in order to evaluate any potential relationship between 25(OH)D level and rUTIs after KT.
The major drawback of our study is its retrospective model and the relatively small number of patients with rUTIs. However, the studies assessing the pleiotropic effects after KT are mainly observational, except for 2 small studies reporting of the immunomodulatory effect of 25(OH)D in kidney transplant recipients [14,21,22)]. Evidently, larger prospective multicenter controlled studies with adequate VD supplementation are needed to evaluate the link between VD status and urinary tract infection rate in kidney transplant recipients.

Conflict of interest statement. None declared.

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