INTRODUCTION

Nutritional vitamin D deficiency is an increasingly recognised condition in the general population worldwide, even in developed societies, and especially in high latitude regions (MacLaughlin and Holick, 1985; Holick, 2004; Chapuy et al., 1997; Hanley and Davison, 2005). Vitamin D deficiency is also prevalent in the general population in Latvia (Meija et al., 2010). Vitamin D deficiency is associated with more intense secretion of parathyroid hormone (PTH) and increased bone resorption, leading toward high bone fracture risk (Lips, 2001). Recent data also support an indirect effect of vitamin D deficiency on fracture incidence through increased muscle weakness and falls (Bishoff-Ferrari et al., 1997; Hanley and Davison, 2005). Severe vitamin D deficiency causes osteomalacia in adults and rickets in children (Dawson-Huges et al., 2005).

Serum concentration of 25-hydroxyvitamin D (25(OH)D) is considered a composite measure of overall vitamin D adequacy because it reflects both an individual’s intake and the cutaneous production of vitamin D (Hollis, 1996).

Hypovitaminosis D has also been demonstrated in chronic kidney disease (CKD) patients (Cunningham and Makin, 1997; Gonzalez et al., 2004; Taskapın et al., 2006; Ningwekar et al., 2012). In CKD patients, low serum 25(OH)D levels may aggravate secondary hyperparathyroidism and very low levels are associated with the osteomalacia of renal failure (National Kidney Foundation/KDOQI clinical practice guidelines, 2003). In the CKD patient population vitamin D deficiency is associated with worse survival (Pilz et al., 2011), especially due to increased cardiovascular mortality (Drechsler et al., 2011).

Kidney transplantation is the most effective (clinically and financially) treatment for patients with end-stage renal disease. Successful kidney transplantation restores renal function and 1α-hydroxylation in proximal tubules of the grafted kidney, thus reestablishing normal production of active vitamin D. Unfortunately, it does not correct nutritional vitamin D deficiency, which mostly depends on sunlight exposure and external intake. Insufficient vitamin D stores might be attributed to several different mechanisms. Steroids and other immunosuppressive medications taken by transplanted patients can increase vitamin D catabolism and intensify the lack of this vitamin in these patients (Querings et al., 2006). Because kidney grafted patients have higher risk of skin carcinoma, they are recommended to use...
sunscreen and avoid direct sunlight. At the same time, it is well established that regular use of sunscreen reduces vitamin D skin absorption up to 95% (Matsuoka et al., 1987; Querings et al., 2006). Thus, vitamin D deficiency in this population could be very widespread even in summer (when in the general population 25(OH)D reaches its peak level), and it could be an important problem affecting effective recovery of bone metabolism in kidney allograft recipients (Fleseriu and Licata, 2007; Kokado, 2006).

It should be also noted that vitamin D receptor is found not only in organs involved with calcium and phosphorous regulation (kidney, gut, parathyroid gland, bone), but it is also expressed in other tissues, suggesting that vitamin D might play other important roles in our bodies. Recently recognised negative non-skeletal effects of vitamin D deficiency include worsening insulin resistance, diabetes mellitus, hypertension, and malignancy (Holick, 2007). Moreover, evidence exists that vitamin D might play a role in the regulation of immune cell proliferation, differentiation, and responsiveness, suggesting that vitamin D deficiency may be of particular consequence in the transplant population (Lemire, 1995).

Despite the importance of vitamin D deficiency in the kidney transplantation population, few studies have evaluated vitamin D status in transplant recipients (Lomonte et al., 2005; Ewers et al., 2008; Stavroulopoulos et al., 2007). Mostly, compared to the general population, adult post-renal transplant patients have an increased prevalence of 25(OH)D deficiency and elevated parathyroid hormone (PTH) levels (Marcen et al., 2009a; 2009b).

In Latvia, the exact prevalence of nutritional vitamin D deficiency in the population of kidney graft recipients is unknown. Therefore, the main purpose of the present study was to estimate the prevalence of hypovitaminosis D in the cohort of patients after kidney transplantation in a single kidney transplantation centre in Latvia. It was aimed to determine relationships between vitamin D level and kidney graft function, time since transplantation, gender, use of particular immunosuppressive medications, and biochemical parameters such as parathormone, calcium, phosphorus and alkaline phosphatase.

MATERIALS AND METHODS

This cross-sectional study was performed on 165 randomly selected kidney transplant patients who were followed in the outpatient nephrology clinic at Pauls Stradiņš Clinical University Hospital, Riga, Latvia, at a latitude 57 °N, between 1 June 2012 and 1 September 2012, i.e. a period when serum level of 25(OH)D is expected to be at its annual maximum. The patients were eligible if they were 10 to 80 years old, were transplanted at least six months earlier and had given informed consent. Exclusion criteria were acute illness, life-threatening comorbidity, mental disorders, administration of anticonvulsants and heparin, malabsorption syndrome, chronic diarrhea, advanced liver disease, history of malignancies, patients with prior parathyroidectomy or who had received any vitamin D compounds (ergocalciferol, colecalciferol, alphacalcidol and calcitriol) after transplantation, and need for dialysis. The Study was approved by the Institutional Ethics Committee.

Data were collected on age, sex, time since kidney transplantation, cause of kidney failure and type of immunosuppressive medication.

Vitamin D status was classified as per „Guidelines for the diagnosis, prevention and treatment of osteoporosis in Latvia” (Rasa et al., 2011):

1. Sufficient: 25(OH)D level more than 30 ng/mL;
2. Insufficient: 25(OH)D level 20–30 ng/mL;
3. Mild to moderate deficiency: 25(OH)D level 10–20 ng/mL;
4. Severe deficiency: 25(OH)D level less than 10 ng/mL.

Nonfasting blood samples were drawn between 09.00 and 13.00. Serum intact parathyroid hormone (iPTH), 25(OH)D, creatinine, urea, albumin, calcium, phosphate, and alkaline phosphatase were measured. The serum concentrations of creatinine (reference interval: 60–120 µmol/L), urea (reference interval: 1.8–7.1 mmol/L), albumin (reference interval: 35–55 g/L), phosphate (reference interval: 0.8–1.5 mmol/L), total alkaline phosphatase (reference interval: 40–150 IU/L), and serum calcium (reference interval: 2.15–2.55 mmol/L) were measured according to standard procedures in the biochemical laboratory at Pauls Stradiņš Clinical University Hospital. Serum calcium levels were adjusted according to serum albumin level. Serum 25(OH)D levels were measured using the ARCHITECT 25-OH Vitamin D chemiluminescent microparticle assay (Abbot Laboratories, Abbot Park, IL, USA). Intact PTH levels (reference interval: 12–72 pg/mL) were measured using ARCHITECT Intact PTH chemiluminescent microparticle assay (Abbot Laboratories, Abbot Park, IL, USA). The calculation of kidney graft function, i.e. estimated glomerular filtration rate (eGFR) was based on the Cockcroft-Gault equation.

Data were expressed as mean ±SD or median and range for variables that were not normally distributed. The unpaired t-test was used for comparison of means of continuous variables. Mann-Whitney test for comparison of discrete data, analysis of variance (ANOVA) with Bonferroni post-hoc test for multiple comparisons between groups and the chi-square test for comparison of proportions between variables. Relationships between variables were examined using Pearson’s product moment correlation analysis. Probability values of 0.05 were considered to be significant. Data analysis was performed using SPSS 17.0 for Windows.

RESULTS

Characteristics of the study population are described in Table 1. In 165 transplant patients who had received kidney graft and were eligible to participate in this study, the me-
The mean 25(OH)D was 22.71 ± 7.06 ng/mL, and only 30/165 (18%) patients were vitamin D sufficient. 71/165 (43%) patients showed an insufficient 25(OH)D level, 62/165 (38%) patients were mildly vitamin D deficient, and 2/165 (1%) were severely vitamin D deficient, even in summer, but without additional vitamin D supplement (Fig. 1). No significant correlation was found between vitamin D status and age, time since kidney transplantation nor use of different immunosuppressive medications. A marginally significant difference was observed in the 25(OH)D level between men and women (mean 25(OH)D level in men was 23.63 ± 6.91 ng/mL; mean 25(OH)D level in women was 21.60 ± 6.34 ng/mL, P = 0.05). Only 20% of men and 15% of women had an optimal 25(OH)D level, 49% of men and 37% of women had vitamin D insufficiency, and 31% of men and 48% of women had vitamin D deficiency (mild to severe) (Fig. 2). There was no significant difference between premenopausal women (mean age 36.9 ± 10.6 years) and menopausal women (mean age 64.6 ± 4.8 years) in terms of the 25(OH)D level — 21.18±6.53 ng/mL and 22.25±6.42 ng/mL, respectively (P = NS). The mean serum creatinine level in whole study population was 0.16 ± 0.08 mmol/L and mean eGFR was 48.6 ± 17.1 ml/min/1.73 m². In our study we did find a significant correlation between vitamin D and kidney graft function: the serum creatinine level was negatively correlated with the 25(OH)D serum level (r = –0.21; P < 0.01) (Fig. 3). The mean iPTH was
110.9 ± 87.5 pg/mL and 94/165 patients (57%) had iPTH levels above the upper limit of the recommended range for their stage of CKD, according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, i.e. persisting secondary hyperparathyroidism (Anonymous, 2009). We observed high correlation between the 25(OH) D level and iPTH (Pearson’s r = −0.35, P < 0.0001) (Fig. 4). iPTH was dependent on graft function, as it was correlated positively with the serum creatinine level (Pearson’s r = −0.36, P < 0.0001). We also found a negative correlation between total alkaline phosphatase and the 25(OH) D level (Pearson’s r = −0.20, P < 0.01). No other significant correlation was found between the 25(OH)D level and serum biochemical variables.

**DISCUSSION**

25-hydroxyvitamin D (25(OH)D) is the storage form of vitamin D in the human body and represents both cutaneous synthesis and ingested sources of vitamin D (diet and medications). It is also the main circulating form of vitamin D in blood. Therefore, the serum 25(OH)D level is considered to be the best measure of native vitamin D status. The general consensus of a recent review was that serum 25(OH)D concentration should be more than 30 ng/mL to ensure vitamin D repletion in the general population and for patients with CKD and patients after successful kidney transplantation (Dawson-Huges et al., 2005; Anonymous, 2009). Levels > 40 ng/mL may be also justified, as at this level maximum function of 25-hydroxylase appears to be achieved (Hollis et al., 2007). In addition, in a study of dialysis patients no patient with 25(OH)D > 40 ng/mL had radiological evidence of subperiosteal resorption (Ghazali et al., 1999). However the cut-off values for vitamin D deficiency and insufficiency are not universally agreed in the literature. We used the cut-off values recommended by the Guidelines for the diagnosis, prevention and treatment of osteoporosis in Latvia (Rasa et al., 2011), which are in agreement with many other European osteoporosis guidelines as well as with the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (Anonymous, 2009).

Our study showed that only 18% of the studied patients, who had not received additional supplementation with native vitamin D, presented with a sufficient 25(OH)D level (25(OH)D > 30 ng/mL) during summer season when expected cutaneous vitamin D production reaches its peak. The rest of the study population was vitamin D insufficient (43%) or vitamin D deficient (38%), while 1% of patients showed severe vitamin D deficiency. This is in agreement with many other publications showing high prevalence of vitamin D insufficiency or deficiency in a wide range of populations (healthy postmenopausal women, critically ill hospitalized patients, CKD patients not yet on dialysis, patients with ESRD on dialysis, etc.) (Lips et al., 2006; Lee et al., 2009; LaClair et al., 2005; Jean et al., 2008; Lips, 2007). There were also publications revealing suboptimal vitamin D status of patients after successful kidney transplantation. Stavroulopoulos A. et al. demonstrated vitamin D insufficiency in 29% of the recent transplant recipients and in 43% of long-term transplant recipients, but vitamin D deficiency was observed in 56% of the recent transplant recipients and 46% of long-term transplant recipients, while severe deficiency — in 12% and 5% of patients, respectively (Stavroulopoulos et al., 2007). Ewers et al. showed similar findings in the population of adult Danish kidney transplant patients, which was a group fairly similar to kidney transplant recipients in Latvia (same age, time since op-
ulation, ethnic origin, latitude, dietary habits and way of usual daily activities). In this Nordic country 51% of the patients with kidney graft had vitamin D insufficiency (25(OH)D 16–30 ng/mL), and an additional 29% had moderate-to-severe vitamin D deficiency (25(OH)D < 16 ng/mL) (Ewers et al., 2008).

Although this study was not designed to evaluate all possible reasons for inadequate vitamin D status (e.g. vitamin D dietary intake, sun exposure, use of sunscreen, etc.), we did found some correlates which may explain high prevalence of vitamin D insufficiency and deficiency in our kidney grafted patients. In our study population women were less vitamin D sufficient than men ($P = 0.05$). This is consistent with previous studies conducted in both the general population (Yetley, 2008) and in patients with chronic kidney disease (LaClair et al., 2005). It is well established that elderly postmenopausal women are at particular risk for vitamin D inadequacy (Hirani et al., 2010). This might be explanation of highly prevalent vitamin D insufficiency in our study population as well, because in our cohort we found significantly older women than men ($P < 0.05$) and more than two-thirds of female population in this study were postmenopausal.

In our study, we found an inverse correlation between 25(OH)D and PTH serum levels in transplant recipients. This is consistent with previous studies (Reinhardt et al., 1998; Boudeville and Hodsman, 2006). Secondary hyperparathyroidism remains an ongoing problem in patients even after successful renal transplantation. KDIGO and National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) guidelines recommend measurement of 25(OH)D and treatment in cases of insufficiency in patients with elevated PTH levels, based on the association between vitamin D insufficiency and hyperparathyroidism found in the general population and CKD patients (Cunningham and Markin, 1997). Apart from the well-known effect of circulating calcitriol on hyperparathyroidism, local production may also play a role. The enzyme 1-alpha hydroxylase is expressed in normal parathyroid tissue and over expressed in primary and secondary hyperparathyroidism (Segersten et al., 2002). This may explain the inverse correlation found between serum 25(OH)D and parathyroid adenoma size in cases of primary hyperparathyroidism and may also account for the inverse correlation found between serum 25(OH)D and PTH levels in dialysis patients (Ghazali et al., 1999) and in the post-transplant population.

We also found significant correlation between kidney graft function and the 25(OH)D level in our study cohort. Patients with higher serum creatinine concentration and lower eGFR rate had more pronounced vitamin D insufficiency and deficiency ($P < 0.01$). This is in agreement with published evidence on exceptionally high rates of vitamin D deficiency in patients with impaired renal function (patients with CKD 3–4, not yet on dialysis). They show even more severe vitamin D deficiency than that observed in the general population (Mehrotra et al., 2009). The reason for this marked 25(OH) D deficiency even in early CKD is multifactorial: partly due to nutritional deficiency (Heaney, 2008), due to reduced skin synthesis, and partly due to increased renal loss of vitamin D binding protein, which occurs as a result of proteinuria, a common finding in patients with impaired renal function and in patients with kidney graft (Jones, 2007; Cheng and Coyne, 2007).

The importance of parent vitamin D repletion for prevention of various pathological conditions is extensively explored recently (Heaney, 2008). Vitamin D is obtained through the diet or synthesised in the skin. It is subsequently activated by 25-hydroxylation in liver and then by 1-hydroxylation in kidney. Until recently, this was thought to be almost the only way to produce the active 1,25 vitamin D or calcitriol (Al-Badr and Martin, 2008; Heaney, 2008). The traditional viewpoint was that the calcitriol was responsible for all of the effects of active vitamin D in the body and that these effects were limited to regulation of bone and mineral metabolism (Jones, 2007; Heaney, 2008). A more expanded role for 25(OH)D was recently suggested because of the wide presentation of vitamin D receptor and 1-alpha hydroxylase in non-renal tissues such as the skin, vascular smooth muscle cells, pancreas, kidney, heart, immune system, intestine and sarcoid tissue (Holick, 2007; Mehrotra et al., 2009; Ai-Badr and Martin, 2008; Heaney, 2008). In addition to the classical pathway for activation of 25(OH) vitamin D to 1,25-(OH)$_2$ vitamin D, a peripheral autocrine pathway was confirmed, which results in calcitriol synthesis in a variety of peripheral (non-renal) tissues (Jones, 2007; Heaney, 2008). Given the potential importance of these autocrine functions and their effects on the comorbidities, such as cardiovascular disease found in association with CKD, it is very important to provide adequate amounts of native vitamin D to ensure the production of autocrine-derived calcitriol (Jones, 2007).

Because sunlight is the major source of vitamin D for most humans, renal transplant patients, who are advised to avoid the sun or wear sun protection, are deprived of the most important source of vitamin D. Effective dietary vitamin D sources are very few and practically nonexistent. Therefore, patients are at risk of developing vitamin D deficiency. Vitamin D deficiency is not only associated with increased risk for metabolic bone disease, but is associated with other severe health problems including cardiovascular disease and various types of internal malignancies (e.g. colon, prostate, and breast cancer) (Grant, 2002a; 2002b). Therefore, vitamin D supplementation seems to be the only feasible means of improving and correcting vitamin D status in kidney transplant patients. According to Ewers, et al. the average kidney transplant patient who avoids the sun needs a daily supplement of 880 IU vitamin D to reach the desired 25(OH)D concentration of 30 ng/mL (Ewers et al., 2008). To ensure 25(OH)D concentrations ≥ 30 ng/mL in all kidney transplant patients, even higher doses of vitamin D might be prescribed. Our study findings also confirm that routine screening for vitamin D deficiency in renal transplant patients is warranted (Querings et al., 2004).
In conclusion, our study in kidney transplant recipients in Latvia found that the prevalence of 25(OH)D insufficiency and deficiency is extremely high after renal transplantation, affecting more than 80% of our patients, particularly women. This may contribute, along with the reduced GFR, to the ongoing secondary hyperparathyroidism found in some patients. Thus, it is of the utmost importance to ensure that treatment of calcium and phosphorous disturbances and bone disorders after kidney transplantation include vitamin D supplementation in doses that bring vitamin D to the normal level in all patients. Until recently, many guidelines (Anonymous, 2009; Rasa, 2011) state that in the general population and in the transplanted patient population the level should be at least 800–1000 IU of vitamin D daily. Further prospective, interventional studies are needed to establish whether this dose is sufficient in kidney grafted patients and if this treatment has beneficial effects on hyperparathyroidism and other non-classical consequences of low vitamin D status.

REFERENCES


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D VITAMĪNA DEFICĪTS PACIENTIEM PĒC NIERES TRANSPLANTĀCIJAS LATVIJĀ

D vitamīna defīcītu bieži konstatē gan hroniskas nieru slīmības pacientiem, gan pacientiem pēc nieres transplantācijas. Šī pētījuma mērķis bija noteikt D vitamīna nepieciešamības ipatsvaru pacientiem ar transplantētu nieri Latvijā, kā arī atklāt nieres transplantātā funkcijas, pacientu dzimuma, lietoto imûnsupresijas preparātu, bioķīmisko analīzi un citu faktoru saistību ar D vitamīna līmeni šiem pacientiem. 25(OH)D līmeni serumā noteica 165 pacientiem pēc 165 pacientiem pēc nieres transplantācijas, kuru vidējais vecums bija 49.7 gadi. Vidējais 25(OH)D līmenis pētījuma populācijā bija 22.71 ± 7.06 ng/mL. Tikai 18% pacientu D vitamīna līmenis bija normāls, 43% pacientu novēroja D vitamīna nepieciešamību, 38% pacientu bija mērens, bet 1% pacientu — izteikts D vitamīna defīcīts. Tika konstatēta negatīva korelācija starp D vitamīna līmeni un transplantātā funkciju, kā arī paratireoidā hyperunkā un sārmainās fosfatāzes līmeni serumā. D vitamīna noteikšanai un D vitamīna defīcīta korekcijai ir būtiska loma pēctransplantācijas pacientu aprūpē.