25-Hydroxyvitamin D Deficiency in Kidney Transplant Recipients

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Introduction. After kidney transplantation, patients appear to have vitamin D deficiency due to the use of immunosuppressive treatment and prevention of sunlight. This study was designed to determine vitamin D serum levels in kidney transplant patients in comparison with healthy individuals.

Materials and Methods. Forty-six kidney transplant patients with a creatinine clearance greater than 60 mL/min and 46 healthy individuals with normal kidney function were tested for serum levels of calcium, phosphorus, 25-hydroxyvitamin D, and parathyroid hormone at the end of the summer.

Results. Thirty-one participants were men and 15 were women in each group. The mean age was 41.0 ± 14.2 years in kidney transplant recipients and 41.4 ± 13.7 years in the control group. Inadequate serum 25-hydroxyvitamin D was seen in 93.5% of the transplant patients and in 89.1% of the controls. There was a 58.7% vitamin D insufficiency (20 ng/mL to 30 ng/mL) and a 34.8% deficiency (lower than 20 ng/mL) in the patients, and these rates were 58.7% and 26.0% in the control group, respectively. There was no significant difference between the two groups.

Conclusions. Vitamin D deficiency is prevalent in kidney transplant patients. Lack of a significant difference between our two groups may be attributable to the high prevalence of vitamin D deficiency in general population and the use of vitamin D supplementation in transplant patients. Indeed, adequate doses of vitamin D in these patients are undetermined. They may need higher doses for normalization of serum vitamin D and metabolic requirements.

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INTRODUCTION

Numerous studies on different age and racial groups have shown the incidence of hypovitaminosis D in different societies in the world is high, even in developed societies, especially in regions with low sunlight.[1-5] Vitamin D deficiency is associated with the production of parathyroid hormone (PTH), increased bone reabsorption, and risk of bone fracture. Severe vitamin D deficiency causes osteomalacia in adults and rickets in children, and the treatment of vitamin D deficiency removes all above impairments.[6-13]

In addition to the kidneys, other tissues also have 1-hydroxylase activity. In fact, these tissues locally convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which has paracrine effects on cell growth regulation and immunomodulatory effects. The role of vitamin D deficiency is known in hypertension, diabetes mellitus, cardiovascular disease, autoimmune diseases, and malignant diseases.[14-22]

Transplantation is an established therapy for end-stage diseases of the kidney and improves most of the metabolic disorders that cause renal osteodystrophy; however, these disorders remain in the most of the kidney transplant recipients.[23-28] Quick reduction of bone density is observed in 12 months after transplantation and mostly 6 months after it. In the first months after kidney transplantation that prednisolone dose is high, bone loss is more obvious.[29-32]

Factors like the high level of PTH and cyclosporine and vitamin D deficiency affect bone loss intensification after transplantation. Steroids and immunosuppressive drugs, which must be taken by transplant patients, are influential on vitamin D catabolism and intensify the lack of this vitamin in these patients.[17] Because immunosuppressive treatments that are applied in transplant patients are associated with a high risk of skin carcinoma, kidney transplant patients are recommended to use sunscreen products and prevent direct contact sun light. Correct and regular use of an effective sunscreen cream reduces vitamin D skin absorption up to 95%.[15,17] Also, the PTH level will be reduced in the first year after transplantation. As a result, 1,25-dihydroxyvitamin D level after transplantation is variable and has been reported to be high, low, or in normal level.[33]

For evaluation of bone diseases, 1,25-dihydroxyvitamin D blood level is measured after transplantation. However, despite its normal level, 25-hydroxyvitamin D is reported low in these patients. In fact, the level of blood 25-hydroxyvitamin D depends on vitamin resources in the body and external intake and sun light, and it should be used for measuring vitamin D in persons that may be afflicted by vitamin D deficiency.[17,33,34] The consumption of extra doses of 25-hydroxyvitamin D (in spite of normal blood level) reduces chronic hyperparathyroidism after kidney transplantation, the development of calcium intestinal absorption, and osteoblasts activation.[35]

In spite of the importance of vitamin D deficiency in kidney transplant patients, the studies on the 25-hydroxyvitamin D level in these patients are few.[5,6,17,29,36] In one study, the level of 25-hydroxyvitamin D in these patients was reported very low in comparison to a control group,[17] and in another study, it was high, about 27% to 50%.[29] Some of the disadvantages of this survey were the lack of control group in some of them, the lack of accurate matching, and using persons with severe kidney function disorders.[17,37,38]

Different factors are effective on the recovery of bone metabolism in kidney allograft recipients. Vitamin D deficiency is one of these important factors.[39,40] Because of the lack of research about 25-hydroxyvitamin D deficiency in kidney transplant patients and serious side effects of this deficiency, this study was designed to determine vitamin D serum levels in kidney transplant patients in comparison with healthy individuals.

MATERIALS AND METHODS

This study was performed on 46 kidney transplant patients and 46 age- and sex-matched controls. The case group was consisted of kidney transplant recipients aged 10 to 70 years old who were operated at least 6 months earlier and had a normal kidney function (creatinine clearance ≥ 60 mL/min). The calculation method of creatinine clearance was based on Cockroft-Gault equation. The exclusion criteria were administration of anticonvulsants and heparin, advanced liver disease (acute and chronic hepatitis and cirrhosis), history of malignancies, and concurrent transplantation of other organs. Informed consent was obtained from the participants and voluntarily participation in the research and assuring its safety for participations were complied with. After the determination of eligible participants, data were collected on age, sex, the time of kidney transplantation, the cause of kidney insufficiency, the type of immunosuppressive treatment and doses, the use sunscreen products, and consumption of vitamin D and calcium supplements.

The control group was selected from healthy persons aged 10 to 70 years old among of the kidney transplant recipients' relatives with a similar life style for reduction in the effect of intervening variables on blood 25-hydroxyvitamin D. Individuals with the following conditions were excluded from the study: kidney dysfunction or any kind of kidney diseases; advanced liver disease; history of malignancies; hyperthyroidism or hypothyroidism; diabetes mellitus; anticonvulsant, steroid, or heparin administration; daily vitamin D or multivitamin consumption in the past 3 months and parenteral intake of vitamin D3 within the past year; pregnancy; and lactation.

Data on the use of vitamin supplements and sunscreen were collected using a questionnaire. In both groups, daily use of sunscreen products every 3 hours during the day was considered positive. The administration of at least 1 calcium pill per day and vitamin D supplement were registered positive. Also, all of the participants were referred to a laboratory for the collection of fasting blood samples. Vitamin D metabolites are not sensitive to light and are consistent in ambient temperature (40°C). If the tests are done immediately after sampling, there is no need to special laboratory measures, but if the test will be performed some time later, the samples should be preserved in a cool place. The 10-mL blood samples were centrifuged and separated serums were collected in 2 separate microtubes. In this study, biochemical markers including creatinine, calcium, phosphorus, albumin, and PTH were measured at the same day in the samples. Measurement of 25-hydroxyvitamin D was performed concurrently after the end of sampling on one day by one person, in order to reduce test errors due to conducting test in different times. Microtubes were preserved in freezer at -20°C (maximum 1 week after sampling).

The level of serum 25-hydroxyvitamin D were measured by enzyme-linked immunosorbent assay method (IDS, UK) with a sensitivity of 0.5 ng/mL. Intact PTH was evaluated by immunoradiometricassay (Biomerica, USA) with a sensitivity of 1 pg/mL. The serum level of 25-hydroxyvitamin D was evaluated as follows: sufficient, higher than 30 ng/mL; insufficient, between 20ng/mL and 30 ng/mL; deficient, lower than 20 ng/mL.[41]

After the collection of data and entering them in an SPSS software database (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA), the *t* test was used for comparing quantitative variables including calcium, phosphorus, creatinine, and albumin. The qualitative variables were analyzed by the chi-square test, and quantitative variables without normal distribution were analyzed by the Wilcoxon rank sum test. *P* values less than .05 were considered significant.

RESULTS

Forty-six kidney transplant patients, 31 men (67.4%) and 15 women (32.6%), were compared with 46 sex-matched individuals in the control group. The mean age was 41.0 ± 14.2 years and 41.4 ± 13.7 years in the kidney transplant and control groups, respectively (P = .90). Demographic data of the kidney transplant patients are shown in the Table.

Eleven participants (23.9%) in the kidney transplant group and 19 (41.3%) in the control group had been using sunscreen products regularly since 6 months before sampling (P < .001). In the kidney transplant patients, 30 patients (62.5%) were using vitamin D supplement, but in the control group no one was using this supplement (P < .001). There were no associations of using vitamin D supplement, serum calcium level, and sunscreen in each group with serum 25-hydroxyvitamin D level. The mean level of serum calcium and PTH in the kidney transplant patient was higher than that in the controls, but these differences were not significant (Figure 1).

The range of serum PTH in the kidney transplant patients was 2.1 pg/mL to 198 pg/mL. Multiple linear regression showed no relationship between blood vitamin D and PTH level. The mean blood 25-hydroxyvitamin D was 15.4 ± 9.2 ng/mL in the kidney transplant group and 15.6 ± 9.7 ng/mL in

Baseline Data of Kidney Transplant Patients

Characteristic	Value
Mean age, y	41.0 ± 14.2
Sex	
Male	31
Female	15
Cause of kidney failure	
Diabetes mellitus	8
Hypertension	6
Unknown	23
Posttransplant time, mo	37.1 ± 28.39
Medications, %	
Prednisolone	100
Cyclosporine	97.8
Mychophenolate mofetil	84.8
Azathioprine	8.7
Vitamin D supplement	65.0
Calcium supplement	65.0

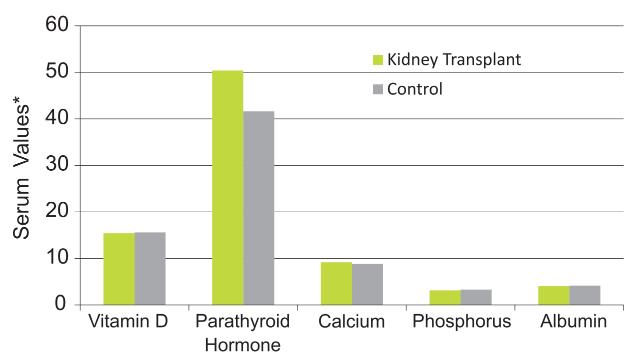

Figure 1. The mean of serum variables in kidney transplant patients and the control group.
*Scale for vitamin D level is ng/mL; for parathyroid hormone, pg/mL; and for calcium, phosphorus, and albumin, mg/dL.

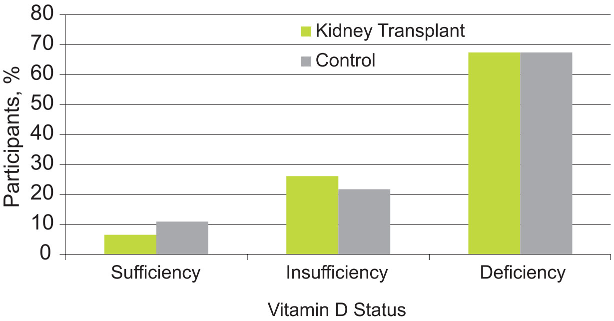

Figure 2. The frequency distribution of serum 25-hydroxyvitamin D status in kidney transplant patients and the control group.

the control group (*P* = .94).

Thirty-one participants (67.4%) in the kidney transplant group and 31 in the control group (67.4%) had vitamin D deficiency (lower than 20 ng/mL) (Figure 2). The frequency of vitamin D deficiency and insufficiency were not significantly different between the three groups of kidney transplant patients with less than 1 year, 1 to 5 years, and more than 5 years of posttransplant (*P* = .37).

DISCUSSION

In this study, only 6.5% of the transplanted patients had enough blood level of vitamin D and 93.5% had low serum vitamin D levels (21.7% insufficiency and 67.4% deficiency). Considering these findings, the high incidence of vitamin D deficiency in transplanted patients is clear. There was a high incidence of vitamin D deficiency in the control group, too. In Gonzalez and coworkers' study, 97% of dialysis patients in comparison with 86% of transplant patients had 25-hydroxyvitamin D deficiencies.[5] In Boudville and Hodsman's study, 27.3% of kidney transplant recipients had deficiency and 75.5% had insufficiency.[29] In this study, a vitamin D level lower than 30 ng/mL was considered insufficient and lower than 16 ng/mL was considered deficient.[29] Reinhardt and colleagues reported that of 129 transplanted patients, 63 had intensive vitamin D shortage at the time of transplant; however, blood vitamin D level increased during the time after graft, but remained lower than normal range.[36] This problem shows that transplant patients had low levels of 25-hydroxyvitamin D with a normal kidney function. In Fleseriue and Licata's study, the mean rate of 25-hydroxyvitamin D levels in blood among transplant group was 19.5 ± 9.9 ng/mL.[39]

These studies show the high incidence of vitamin D deficiency in kidney transplant population. There was no control group in the abovementioned studies. In Iran, there is no study on the incidence of vitamin D deficiency in kidney transplant patients. However, studies on general population in Iran showed a high prevalence of this shortage, reported in 81% of Tehrani citizens aged 20 to 64 years old,[42] and 88.9% in Mazandaran.[43] Our sampling of the study population was done at the end of the summer. One of the reasons of no statistical difference in the mean levels of blood 25-hydroxyvitamin D between our two groups was the high incidence of hypovitaminosis D in our general population. In our study, the control group was selected from the members of patient's families because of food, living place, and the rate of sun light similarities.

Ouerings and associates[17] conducted a case-control study (31 participants in each group) on patients who had kidney transplantation 6 months before, were not recovered by vitamin D supplements, and all of them had been using sunscreen. The control group was selected from patient referred to dermatology clinic that had not used sunscreen for 6 months. The blood level of vitamin D was measured at the end of the winter. The mean blood level of vitamin D in transplant people was 15.9 ng/mL and 20 ng/mL in the control group (*P* = .007). Creatinine level after transplantation was lower than 4 mg/dL and PTH was between 37 pg/mL and 1058 pg/mL.

Most of our patients had not been using sunscreen according to our recommendations, and some of them had used it irregularly. Surprisingly, the rate of consumption of these supplements in the control group was higher. Despite the lack of statistical relationship between using sunscreen cream in each group with the level of vitamin D, not using sunscreen in transplantation group and common use of it in the control group must have affected the level of vitamin D in blood of the two groups. No question were asked about whether the sunscreens were standard or not or about their using directions. Lack of knowledge among the kidney transplant population and also the high cost of sunscreen preparations can be the reasons of inadequate use of these supplements. On the other hand, our patients were treating with calcium and vitamin D, and because of ethical considerations, this study was done without discontinuing using these supplements. Using vitamin D supplements (calcium D) could be effective in increasing blood levels of vitamin D in transplant patients.

Calcium level was high in our study group, which could be related to calcium supplement consumption in this group. However, the difference between the two groups was not significant. Intact PTH levels in our subject group were slightly higher than that in the control group. These findings accord the previous studies of hyperparathyroidism after transplantation. In Abdallah and coworkers' study, the PTH level was a little higher during transplantation and in many patients it reached to normal level at the end of the third month.[44] This finding can be justified in this way that in spite of the improvement of the transplant kidney function and calcium and vitamin D consumption, some degrees of secondary hyperparathyroidism will be remained in these patients. This finding suggests higher level of serum vitamin D for adequate PTH suppression in transplant patients.

The level of albumin in our kidney transplant group was significantly lower than that in the control group, which can be attributed to undesirable nutrition in these patients and albumin catabolism intensification by immunosuppressive drugs. Finally, in this study, 4 transplant patients were receiving 2 immunosuppressive drug and 42 were receiving 3 drugs. Whether the immunosuppression diet differs and doses are effective in vitamin D level of patients warrant further studies.

CONCLUSIONS

We could not find any differences between transplant patients and healthy individuals in blood levels of vitamin D in Sari city, Iran. We recommend, however, this study be done in a higher number of patients, with taking into consideration of the high incidence of vitamin D deficiency our general population. What was interesting in this study was the high frequency of vitamin D deficiency in spite of using vitamin D supplement and the low level of using sunscreen in transplant patients. We can speculate that training of transplant patients and higher rate of sunscreen use increases the prevalence of 25-hydroxyvitamin D deficiency, and the present dose of vitamin D will not be sufficient. In addition, this study shows some degrees of secondary hyperparathyroidism in transplant patients compared with the general population, while serum vitamin D is similar, and this suggests higher levels of serum vitamin D for adequate PTH suppression in these patients. Thus, it seems that it is essential to conduct studies for reaching a desirable dose of 25-hydroxyvitamin D supplements in transplant patients for correction of metabolic disorders in these patients. Also, the high prevalence of vitamin D deficiency in general population should be surveyed and needs the correction of diet and life style.

CONFLICT OF INTEREST

None declared.

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