

# Assessment of Circannual Rhythm in Plasma Level of Vitamin D Among Kidney Transplant Recipients in Mashhad

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We studied plasma vitamin D level in 96 kidney transplant recipients and its circannual rhythm. Blood samples were tested for 25-hydroxy vitamin D, parathyroid hormone, creatinine, phosphate, and calcium levels in winter and summer 2014. The mean age was 41 years, and the mean transplant age was 6.1 years. Plasma levels of 25-hydroxy vitamin D were  $18.0 \pm 15.0$  ng/mL in winter and  $18.3 \pm 14.7$  ng/mL in summer ( $P = .64$ ). Parathyroid hormone was inversely correlated with vitamin D level in both seasons ( $r = -0.044$ ,  $P < .001$ ). There was no relationship between vitamin D and other variables. Our study showed vitamin D deficiency is prevalent among kidney transplant recipients both in winter and summer. Also, vitamin D level did not rise from winter to summer. It is recommended to routinely check on kidney transplant recipients' vitamin D status.

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Vitamin D deficiency is a worldwide health problem.<sup>1</sup> Kidney transplant recipients are at greater risk for vitamin D deficiency, as some of their medications interfere with vitamin D metabolism.<sup>2,3</sup> Furthermore, kidney transplant recipients are advised to decrease sun exposure to reduce the risk of skin cancer,<sup>4</sup> while sunlight is the major trigger of vitamin D production in the skin.

Serum vitamin D level changes during the year, it peaks in late summer after abundant sun exposure and again decreases through late winter. This circannual rhythm is believed to play a role in musculoskeletal homeostasis.<sup>5</sup> It is not well known whether this rhythm is preserved in kidney transplant recipients or not. During only 6 years, between 2006 and 2012, more than 13000 kidney transplantations have been performed in Iran.<sup>6</sup> We are now faced with a big population of kidney transplant recipients in whom the prevalence of

vitamin D deficiency has not been studied. Further, Iran's latitude (and therefore sunlight intensity),<sup>7</sup> and clothing custom<sup>8</sup> differ from other countries where previous studies were performed. We aimed to assess the frequency of vitamin D deficiency and the rhythm of plasma vitamin D level changes during the year in kidney transplant recipients.

In this cross-sectional study, we included kidney transplant recipients who visited university hospital clinics during winter 2014. All the participants received a maintenance dose of prednisolone, 2.5 mg/d, during the study and were under cyclosporine and mycophenolat mofetil regimen. Exclusion criteria were vitamin D or calcium supplement consumption during the past 6 months, dramatic decrease in glomerular filtration rate (GFR) according to the Modification of Diet in Renal Disease (MDRD) formula, and the need for vitamin D and calcium deficiency treatment

(osteoporosis and hyperparathyroidism).

Demographic data of the participants were also gathered in the beginning and the participants were given instructions on how to protect themselves against sunlight: to stay inside during peak sunlight intensity (around noon) and to apply sunscreen with a sun protector factor of 50 before going out. Random blood samples were drawn during winter and summer 2014. Serum levels of creatinine, phosphate, calcium, 25-hydroxvitamin D (electrochemiluminescence, Cobas E411, Germany), and intact parathyroid hormone (PTH) were measured. Sample size was calculated according to the previously reported vitamin D deficiency frequency to be 90%.<sup>9</sup> Descriptive statistical values were presented as mean  $\pm$  standard deviation. For categorical data, the chi-square test and the Fisher exact test were used. Continuous variables were compared with the Wilcoxon rank-sum test. *P* values less than .05 were considered significant. The study protocol was approved by the research ethics committee in Mashhad University of Medical Sciences (thesis reference code: 7317), and informed consent was obtained from all of the participants.

A total number of 96 participants (45 men and 51 women) entered and remained in our study. Their mean age was  $41.0 \pm 12.8$  years and the mean time from transplantation was  $73.7 \pm 48.1$  months. Table 1 displays participants' laboratory data. None of the laboratory measures changed significantly from winter to summer. We encountered only a slight increase in 25-hydroxvitamin D from winter to summer ( $18.0 \pm 15.0$  ng/mL to  $18.3 \pm 14.7$  ng/mL, *P* = .64). During winter, 75 participants (78.1%)

had less than normal levels of 25-hydroxvitamin D ( $< 30$  ng/mL) and 39 (40.6%) were deficient ( $< 10$  ng/mL). These numbers did not change much in the summer (Table 2).

We did not find any correlation between 25-hydroxvitamin D level and age, sex, transplant age, glomerular filtration rate, calcium, or phosphate, neither in the summer nor in the winter. Although we encountered a difference in deficiency intensity between men and women, no significant correlation was found when we categorized 25-hydroxvitamin D deficiency. We found a negative correlation between the level of 25-hydroxvitamin D and intact PTH both during summer and winter ( $r = -0.044$ , *P* < .001).

Kidney transplant recipients suffer from a variety of skeletal complications (osteoporosis and osteomalasia). Their medication regimen plus calcium, PTH, and vitamin D metabolism dysfunction may be the risk factors for these complications.<sup>10,11</sup> Glucocorticoids lead to bone loss by promoting osteoclasts and suppressing osteoblasts.<sup>12</sup> In addition, they increase vitamin D catabolism which may explain how they reduce intestinal and renal calcium absorption.<sup>2,12</sup> Furthermore, cyclosporine and tacrolimus, which are routine medications prescribed for kidney transplant recipients, inhibit an enzyme with 25-hydroxylase activity in the liver. Theoretically, they can reduce vitamin D activation in these patients.<sup>3,13</sup>

In the only previous study on vitamin D in Iranian kidney transplant recipients, by Savaj colleagues, 45% of the participants were vitamin D deficient

**Table 1.** Demographic and Laboratory Data of the Participants

Parameter	Winter	Summer	<i>P</i>
Glomerular filtration rate, mL/min/1.73 m <sup>2</sup>	61.3 $\pm$ 20.7	60.4 $\pm$ 21.0	.19
25-hydroxyvitamin D, ng/mL	18.0 $\pm$ 15.0	18.3 $\pm$ 14.7	.64
Intact parathyroid hormone, pg/mL	40.3 $\pm$ 21.3	40.8 $\pm$ 21.2	.65
Serum calcium, mg/dL	9.3 $\pm$ 0.5	9.3 $\pm$ 0.4	.31
Serum phosphorus, mg/dL	4.0 $\pm$ 0.5	3.9 $\pm$ 0.5	.49

**Table 2.** Vitamin D Level Categories During Winter and Summer by Sex

25-hydroxyvitamin D, ng/mL	Winter		<i>P</i>	Summer		<i>P</i>
	Women (%)	Men (%)		Women (%)	Men (%)	
< 10	25 (49.0)	14 (31.1)	0.25	24 (47.1)	14 (31.1)	.21
10 to 20	12 (23.5)	15 (33.3)		11 (21.6)	18 (40.0)	
20 to 30	3 (5.9)	6 (13.3)		5 (9.8)	3 (6.7)	
> 30	11 (21.6)	10 (22.2)		11 (21.6)	10 (22.2)	

(< 20 ng/mL) and 49.5% had insufficiency (20 ng/mL to 30 ng/mL), while 68.8% of our participants had vitamin D levels below 20 ng/mL. Therefore, the overall frequency of vitamin D insufficiency was lower in our study although the intensity was higher. Savaj and colleagues did not find a correlation between vitamin D and calcium or phosphate levels either.<sup>9</sup>

Burkhalter and coworkers studied kidney transplant recipients and found 90% vitamin D insufficiency in winter and 60% in summer. The median of vitamin D level was 17.62 ng/mL (44 nmol/L) in summer and 12.41 ng/mL (31 nmol/L) in winter, although their participants carried out the sunlight protection instructions. While the median vitamin D in our study, both in summer and winter, was 12 ng/mL. Burkhalter and coworkers claimed 20 to 30 minutes of sunlight exposure daily around noon was adequate for more vitamin D production in the skin during summer.<sup>14</sup>

In a study on the general population of Isfahan, Iran (latitude 32.63' N), vitamin D level rose from 18 ng/mL in winter to 21 ng/mL in summer; a mere 16% increase,<sup>15</sup> while there was 42% increase in kidney transplant recipients in Basel.<sup>14</sup> This can also support our findings although healthy individuals are not recommended to seek shelter around noon. In another study on local and foreigner women living in United Arab Emirates, vitamin D level was measured 10.4 ng/mL and 25.2 ng/mL, respectively. The difference can be due to clothing and cultural habits but both groups still suffer vitamin D deficiency. Further, vitamin D came out to have a reversed circannual cycle decreasing from winter to summer. This was attributed to outdoors' daytime hot weather which prevents people from going out in summer.<sup>8</sup>

The city of Mashhad's latitude (36.30' N) is just between that of Dubai (24.95, N) and Basel (47.57, N), and its weather is more similar to Dubai's during summers and to Basel's during winters. Therefore people in Mashhad would have clothing similar to people in Basel during winter (which is covering against sunlight), while during summer due to hot weather they prefer to stay inside (like people in Dubai) and when they happen to go out they will not receive enough sunlight due to Islamic clothing costume (while people in Basel would go out with shorts and short sleeves). This hypothesis supports why we did not encounter change in vitamin D

level from winter to summer.

Unfortunately, we could not compare our findings with Mashhad's general population regarding prevalence of vitamin D deficiency. Further, we could not assess how much our study population followed sunlight protection instructions due to both our crowded clinics and incompliance of the participants in filling out the questionnaires. There is a possibility that our participants met the instructions more carelessly during winter, so that filled the gap in vitamin D level between winter and summer. Fortunately, we could gather a study sample double the size of Basel study although we had to exclude many participants due to their need to raise corticosteroid level, decrease in glomerular filtration rate, or need of vitamin D supplementation. For future studies, we recommend assessment of vitamin D deficiency in Mashhad general population. Also studies must be designed to compose guidelines on vitamin D supplementation in kidney transplant recipients.

In conclusion, vitamin D deficiency is very common among kidney transplant recipients in Iran although Iran has abundant sunlight. Circannual rhythm of vitamin D level has been dampened in these patients which may be due to hot weather and Islamic clothing costume during summers. According to high frequency of vitamin D deficiency among them, it is recommended to check their vitamin D status routinely.

#### CONFLICT OF INTEREST

None declared.

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