DOES THE 25-OH-VITAMIN D LEVEL AFFECT THE INSULIN RESISTANCE IN THE PATIENTS WITH NON-DIABETIC CHRONIC KIDNEY DISEASE?

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Abstract

Introduction. The aim of this study was to investigate the effects of vitamin D deficiency on insulin resistance in patients with non-diabetic chronic kidney disease.

Materials and Method. A total of 104 patients with non-diabetic, stage 2 and 3 chronic kidney disease, who had presented to the outpatient clinic during 2 winters, were included in the study. HOMA-IR rate of > 2.6 was accepted as insulin resistance. Severe 25-OH-vitamin D deficiency was defined as < 10 ng/mL, and 10-30 ng/mL was defined as vitamin D insufficiency. The difference in insulin resistance between the patients determined as having severe vitamin D deficiency and vitamin D insufficiency was investigated.

Results. Severe vitamin D deficiency was observed to be higher among women (61.8% vs. 38.2%), whereas insufficiency was more common among men (63.3% vs. 26.7%, $p<0.05$). Insulin resistance was observed to be higher in the group with severe deficiency (11.5 vs. 7.82, $p<0.05$). Insulin resistance was observed in 60% and 36.7% of the groups with severe deficiency and insufficiency, respectively ($p<0.05$).

Conclusion. Severe vitamin D deficiency had resulted in insulin resistance at a greater rate compared to vitamin D insufficiency in patients with non-diabetic chronic kidney disease (stage 2-3).

Key words: vitamin D, insulin resistance, chronic kidney disease.

INTRODUCTION

Vitamin D has an important role in energy metabolism and glucose balance of the body. Studies have reported a correlation between vitamin D insufficiency and insulin resistance (1-3).

Calcium has important roles in different cellular functions. Vitamin D increases the calcium absorption through the intestines, and the calcium intake and consumption by the tissues and cells (4).

Calcium is effective in the functioning of beta cells of the pancreas where insulin secretion takes place (5,6). Therefore, vitamin D is the stimulator of insulin secretion. Additionally, it increases the insulin receptor formation by the cells susceptible to insulin (7).

Almost ten different compounds have been defined to demonstrate vitamin D efficacy. Among those, cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are the most important compounds biologically and chemically. Ergocalciferol and cholecalciferol are metabolized in the liver and turned into 25-OH-vitamin D. Subsequently, it is transformed into its active form 1,25-hydroxyvitamin D by the enzyme 1-alpha hydroxylase in the kidneys. Patients with chronic kidney disease have the risk of vitamin D deficiency due to 1-alpha hydroxylase insufficiency. This leads to impaired organ functions and metabolism. Treatment with active forms of vitamin D may correct the abnormalities in bone and mineral metabolism, immune disorders and cardiac functions (8, 9). In the light of these data, it may be concluded that vitamin D deficiency, which is observed as a result of chronic kidney disease, leads to insulin resistance. Chronic kidney disease is a risk factor for cardiovascular diseases, which is also similar for insulin resistance. Thus, treatment of vitamin D deficiency gains importance in patients with chronic kidney disease.

In this study, we aimed to investigate the effect of the level of vitamin D deficiency on the development of insulin resistance in patients with chronic kidney disease.

MATERIALS AND METHOD

The level of vitamin D may vary according to the seasons. Patients, who had presented to the internal medicine clinics of Tepecik Training and Research Hospital during 2 winters (December,

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January, February), were included in the study. A total of 270 patients, 100 with stage-2 and 170 with stage-3 chronic kidney disease, were retrospectively evaluated (December 2016, January-February 2017; December 2017, January-February 2018).

Fifty-two patients with previous diagnosis of diabetes, 34 patients with recent diagnosis of diabetes, 49 patients with previous vitamin D replacement therapy and 31 patients on replacement therapy were excluded from the study.

One hundred and four patients with accessible parameters to calculate the MDRD and HOMA-IR, with a glomerular filtration rate between 30-60 mL/min according to the MDRD and diagnosis of stage 2-3 chronic kidney disease, with no diagnosis of diabetes (fasting blood glucose <100 mg/dL) and not receiving vitamin D replacement, were included in the study.

Glomerular filtration rate (GFR) was calculated according to the formula: $\text{MDRD (GFR)} = 186 \times ([\text{Scr}]^{-1.154}) \times ([\text{Age}]^{-0.203}) \times (0.742 \text{ if female})$.

Insulin resistance was measured using the HOMA-IR method (fasting insulin level ($\mu\text{U/mL}$) $\times$ plasma glucose level (mg/dL)/405). Patients with a HOMA-IR value of ≥ 2.6 were classified as having insulin resistance.

Patients with a 25-OH-vitamin D level of <10 ng/mL were accepted to have severe vitamin D deficiency, and those between 10-30 ng/mL were accepted to have vitamin D insufficiency.

As descriptive statistics, the mean $\pm$ standard deviation (SD) was expressed for normally distributed numeric variables, and frequency (n) and percentage (%) were expressed for categorical variables. For the numerical variables, normality was checked using the Shapiro-Wilk test. Correlation between vitamin D group and HOMA and gender was analyzed using the Pearson Chi-Square test; the statistical significance of higher insulin resistance observed in vitamin D deficiency group compared to insufficiency group was analyzed using the one way two proportion z test. The difference between vitamin D groups with regard to numeric variables was analyzed using the Student's t test if the parametric test assumptions were provided, and using the Mann-Whitney U test if they were not provided. Type 1 error was accepted as 0.05 in all

Table 1. Vitamin D status according to gender

Vitamin D	Severe deficiency	Insufficiency	p
Gender			
Male, n (%)	21(38.2)	31(63.3)	<0.05
Female, n (%)	34 (61.8)	18 (36.7)	

analyses. Analyses were conducted using the IBM SPSS V22 and Minitab 18 Trial program packages.

RESULTS

Data obtained from patients with stage 2-3 non-diabetic chronic kidney disease were evaluated according to vitamin D levels, which were grouped as severe vitamin D deficiency (n= 55) and vitamin D insufficiency (n= 49).

In the severe vitamin D deficiency group, 34 patients were female (61.8%) and 21 were male (38.2%). In the vitamin D insufficiency group, 18 patients were female (36.7%) and 31 were male (63.3%) (Table 1).

A significant correlation was observed between the severe vitamin D deficiency and insufficiency groups and gender (p=0.011).

The mean age was 63.13 $\pm$ 18.10 in the severe vitamin D deficiency group and 62.3 $\pm$ 12.84 in the insufficiency group. Etiological diagnosis and rates of chronic kidney disease in both groups have been presented in Table 2.

The insulin level was observed to be significantly higher in the group with severe vitamin D deficiency (11.5 vs. 7.82, p<0.05). The blood glucose levels were similar between the groups (88.4 vs. 88.1, p=0.86), Table 3.

Insulin resistance was observed in 60% and 36.7% of the groups with severe deficiency and insufficiency, respectively. Insulin resistance was observed to be higher in the group with severe deficiency (p<0.05), Table 4. A statistically significant difference was observed between the groups with regard to insulin resistance.

DISCUSSION

In our study, severe vitamin D deficiency was observed to be higher among women, whereas insufficiency was more common among men with stage 2-3 non-diabetic chronic kidney disease, p<0.05.

Table 2. Etiological diagnosis of chronic kidney disease

Vitamin D	Severe deficiency	Insufficiency
Etiology, n (%)		
Hypertension	30 (54.5)	27 (55.1)
Atherosclerotic nephropathy	8 (14.5)	8 (16.3)
Nephrotic syndrome	2 (3.6)	4 (8.1)
Glomerulonephritis	6 (10.9)	5 (10.2)
Multiple myeloma	7 (12.7)	4 (8.1)
Others	2 (3.6)	1 (2.0)

Both insulin resistance and insulin levels were higher in the group with severe deficiency, $p < 0.05$.

Vitamin D is synthesized from 7-dehydrocholesterol in the skin in response to ultraviolet- B (UVB) light of 290-315 nm wavelength, and this production is the main endogenous source of vitamin D. UVB is essential for the production of vitamin D. Our country has a variable sunlight distribution. In order to prevent this difference, we included patients who had presented to the hospital in one city and during the winter.

The female population has a lower active role in life compared to the male population in our country. This determines a lower amount of sunlight due to the time they spend at home. We observed that severe vitamin D deficiency was higher among women than in men (61.8% vs. 38.2%), $p < 0.05$.

Insulin resistance alone is a risk factor for cardiovascular mortality. In patients with chronic kidney disease, the most common cause of mortality is cardiovascular disease. Furthermore, vitamin D deficiency is increased inversely proportionally to the glomerular filtration rate in patients with chronic kidney disease. In our study, severe vitamin D deficiency in the chronic kidney disease group was found to cause a higher level of insulin and a higher rate of insulin resistance compared to the vitamin D insufficiency group. In this patient population, the risk of cardiovascular disease may even increase and lead to higher mortality and morbidity.

In the Insulin Resistance Atherosclerosis Study (IRAS), a correlation between insulin resistance, atherosclerosis and cardiovascular event was demonstrated. Following this study, the relationship between insulin resistance and cardiovascular disease was also demonstrated in a cohort study including 2938 patients (10-12).

In the metaanalysis conducted in 2012 including 65 studies, insulin resistance determined by the HOMA method was suggested to be a good marker for cardiovascular disease (13).

Furthermore, hyperinsulinemia developing in animal models due to insulin resistance has been shown to have a critical role in atherosclerotic plaque formation (14).

In The Framingham Offspring study, 1739 patients without cardiovascular disease were followed-up for 5 years, and the incidence of cardiovascular disease was shown to be increased in those with vitamin D insufficiency compared to those without insufficiency (15).

Likewise, in the Health Professional Follow-up study, the risk of myocardial infarction was demonstrated to be increased in patients with a vitamin D level of below 15 ng/mL compared to those with a level above 30 ng/mL (16). In the cohort study of Dobnig *et al.*, patients undergoing coronary angiography were examined 8 years later and significantly increased cardiovascular mortality rates were observed among patients with severe vitamin D deficiency (< 8 ng/mL) (17). In a meta-analysis including 7 prospective studies conducted in 2017, high HOMA-IR level was related to higher cardiovascular risk and mortality at a rate of 34% (18).

In patients with non-diabetic chronic kidney disease, the effect of vitamin D deficiency level on insulin resistance has not been well documented. Deficiency and insufficiency of vitamin D negatively affect the beta cell functions of the pancreas via calcium ions, and result in impaired insulin secretion, stimulation of secretion and development of insulin resistance (5,6).

In patients with chronic kidney disease, vitamin D deficiency is common and this may lead to the development of insulin resistance. Chronic kidney disease alone is a risk factor for cardiovascular diseases. As shown in studies, both vitamin D deficiency and presence of insulin resistance have critical roles in the development of cardiovascular diseases.

In our study, it was observed that vitamin D deficiency in the group with chronic kidney disease led

Table 3. Insulin and glucose levels in the groups

Vitamin D	Severe deficiency(n=55)	Insufficiency (n=49)	P
Insulin (uIU/mL) Median (min-max)	11.5 (2-35.4)	7.82(3-28.6)	< 0.05
Glucose (mg/dL) Mean $\pm$ SD	88.4 $\pm$ 11.3	88.1 $\pm$ 9.1	0.86

Table 4. Distribution of HOMA-IR outcomes between the groups in patients with chronic kidney disease

Vitamin D		
Severe deficiency n (%)	Insufficiency n (%)	p
33 (60%)	18 (36.7%)	< 0.05
22 (40%)	31 (63.3%)	

to a higher rate of insulin resistance compared to the group with vitamin D insufficiency. In such a situation, the incidence of cardiovascular diseases already present in this patient population may even increase and lead to further mortality and morbidity.

In conclusion, it is important to conduct a close follow-up of this patient group by means of vitamin D deficiency, and to perform replacement therapies effectively. The strengths of this study are that the current dietary requirements of vitamin D need to be increased in the chronic kidney disease to have an effect on decreasing insulin resistance and cardiovascular disease.

The limitation of this study is retrospective and we believe that this study should be confirmed by further randomized prospective studies.

Conflict of interest

The authors declare that they have no conflict of interest.

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