Novel predictive risk factor of erectile dysfunction: Serum 25-hydroxy vitamin D

Mustafa Ozan Horsanalı | Huseyin Eren | Eyup Dil | Alper Caglayan | Ozgur Erdogan | Fatih Ekren

1Urology Department, Cigli Region Training Hospital, Izmir, Turkey
2Faculty of Medicine, Urology Department, Recep Tayyip Erdogan University, Rize, Turkey

Abstract
The present study aimed to investigate the association between the severity of erectile dysfunction (ED) and serum 25-hydroxy vitamin D. It also sought to determine the cut-off level of serum 25-hydroxy vitamin D for ED. This study included 130 men who had ED between 2018 and 2019. Patients were divided into three groups according to their scores on the international index of erectile function-5 (IIEF-5) Turkish validated short form questionnaire. The serum 25-hydroxy vitamin D results were compared between the groups. The mean age of the patients was 49.28 ± 13.62 years. Groups 1, 2 and 3 included 44 (33.8%) patients with severe ED, 56 (43.1%) patients with moderate ED and 30 (23.1%) patients with mild ED, respectively. Statistical significance was observed between the groups and serum 25-hydroxy vitamin D levels. A positive correlation was detected between the IIEF-5 scores, serum testosterone and serum 25-hydroxy vitamin D levels. A cut-off level for serum 25-hydroxy vitamin D was calculated as 27.32 ng/ml. During multivariate analysis, we found that serum 25-hydroxy vitamin D levels were independent prognostic risk factors for decreased IIEF-5 scores. Decreased serum 25-hydroxy vitamin D levels were associated with decreased IIEF-5 scores. Therefore, vitamin D replacement therapy may improve symptoms.

KEYWORDS
25-hydroxy vitamin D, endothelial dysfunction, erectile dysfunction, hypogonadism, nitric oxide

1 | INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to maintain satisfactory erections during sexual intercourse and is one of the most common diseases among ageing men (Selvin, Burnett, & Platz, 2007). Multiple factors can cause ED in ageing men, such as metabolic syndrome, diabetes mellitus, hypertension and hyperlipidaemia (Banks et al., 2013). Vascular ED is the most common type of ED, and several studies have reported that ED is a marker of cardiovascular disease (Dong, Zhang, & Qin, 2011; Mustafa Ozan Horsanalı Shah et al., 2016; Thompson et al., 2005). The underlying pathophysiology of vascular ED is related to the reduction of endothelial function (Sullivan et al., 1999).

Vitamin D is a member of a steroid hormone family that is produced in human skin through sunlight stimulation (Feldman et al., 2000). Although 25-hydroxy vitamin D’s [25(OH)D] role in calcium homeostasis and bone metabolism is well known, it can also contribute to cell proliferation and differentiation and the regulation of the endocrine system. It also has anti-inflammatory, anti-apoptotic and anti-fibrotic effects and can regulate the function of the genitourinary, cardiovascular and immune systems (Krysiak, Szwajkosz, & Okopię, 2018; Shah et al., 2016). 25(OH)D also plays an important
role in endothelium, as it stimulates the production of nitric oxide from endothelial cells and has anti-oxidant effects (de Kreutzenberg et al., 2011; Polidoro et al., 2013). In addition, several studies have determined that low 25(OH)D levels are associated with decreased serum testosterone levels (Manson & Bassuk, 2015; Wang et al., 2015; Wehr, Pilz, Boehm, März, & Obermayer-Pietsch, 2010). While current descriptions of serum 25(OH)D insufficiency or deficiency have been made according to the 25(OH)D serum levels established for the treatment of osteoporosis, there is no consensus on the optimum cut-off level for serum 25(OH)D during the beginning of treatment for patients with ED. Performing a clinical determination of decreased serum 25(OH)D levels and initiating treatment may be important for patients with moderate or severe ED. This study aimed to investigate the cut-off level of 25(OH)D for the treatment of ED. It also sought to determine the association between serum 25(OH)D levels and the severity of ED.

2 | MATERIALS AND METHODS

We retrospectively analysed 130 patients between 18 and 80 years old who were admitted to the Cigli Region Training Hospital Urology Department and Recep Tayyip Erdogan University Urology Department between June 2017 and October 2018 for complaints of ED. Patients were included in the study, and data were recorded after approval was established with the 2020/07 local ethics committee (No. 16.01.2020). The international index of erectile function-5 (IIEF-5) Turkish validated short form questionnaire was administered to all the patients (Turunç, Deveci, Güvel, & Peşkircioğlu, 2007). Anthropometric variables, such as weight, height, waist circumference, body mass index and the presence of comorbid diseases, were recorded. After a detailed history and physical examination were performed on all the patients, the patients underwent overnight fasting. Between 08:00 and 10:00 a.m., blood samples from the antecubital vein were taken and serum glucose, lipid profile, follicular stimulating hormone (FSH), luteinising hormone (LH), total testosterone, prolactin, oestradiol and 25(OH)D levels were analysed. Serum 25(OH)D levels were analysed with a chemiluminescence assay (the ADVIA Centaur XP®. Siemens). The intra-assay coefficients of variation were 11.9% at a vitamin D concentration of 13.6 ng/ml; 9.9% at a vitamin D concentration of 17.2 ng/ml; 7.2% at a vitamin D concentration of 28.2 ng/ml; 6.1% at a vitamin D concentration of 46.1 ng/ml; 6.0% at a vitamin D concentration of 73.2 ng/ml; and 4.2% at a vitamin D concentration of 114.1 ng/ml. The test’s reference range was 4.2 to 150 ng/ml (10.5–375 nmol/L). The test’s accuracy was 0.99 (ID - LC/MS/MS) + 0.53 ng/ml (r = .96), and its detection limit was 3.20 ng/ml (8.0 nmol/L). The study’s exclusion criteria included the presence of uncontrolled diabetes mellitus, uncontrolled hypertension, uncontrolled lipid metabolism disorders, neurological diseases, haematological diseases, endocrine diseases, cardiac diseases, urinary tract infections, malignancies, chronic kidney failures, metabolic syndrome and psychiatric diseases; medical treatment, smoking and a history of pelvic surgery, cardiac surgery, or pelvic radiotherapy; or the receipt of any drug that interferes with vitamin D levels. After adjusting the IIEF-5 score to 8 points, an receiver operator characteristics curve (ROC) analysis was used to calculate the cut-off value of 25(OH)D. Patients were divided into three groups according to the IIEF-5 scores. Group 1 included patients with IIEF-5 scores lower than 8 (0–7 points, severely symptomatic patients); group 2 included patients with IIEF-5 scores higher than 7 points and lower than 20 points (8–19, moderately symptomatic patients); and group 3 included patients with IIEF-5 scores higher than 19 points (20–25 points, mildly symptomatic patients). All variables were statistically compared between the groups.

All statistical analyses were conducted using the SPSS Statistics 20.0 (IBM Inc., Chicago, USA) package program. Categorical variables were described by frequencies and percentages, and continuous variables were described by means and standard deviations. The Kolmogorov–Smirnov test was used to evaluate the normality of the distributions. A one-way analyses of variance (ANOVA) test was used to compare the groups. Pearson’s correlation analysis was applied to measure correlation. A multivariate analysis was performed after age, diabetes mellitus and waist circumference were adjusted. A p value of less than .05 was chosen as the criteria for statistical significance.

3 | RESULTS

We retrospectively analysed 130 patients with ED. The mean age of the patients was 49.28 ± 13.62 years. The demographic and laboratory characteristics of the patients and groups are summarised in Table 1. The cut-off values for 25(OH)D were calculated with ROC analysis, and 27.32 ng/ml level was accepted as the cut-off level. The area under a curve was 0.421, and the p value was 0.014 with a sensitivity of 64% and a specificity of 66% (Figure 1). While 52 (40%) patients had serum 25(OH)D levels lower than 27.32 ng/ml, 78 (60%) patients had serum 25(OH)D levels higher than 27.32 ng/ml. The means and standard deviations of the 25(OH)D, serum total testosterone, oestradiol, FSH, LH and prolactin levels were 24.64 ± 8.71 ng/ml, 4.64 ± 1.78 ng/ml; 39.91 ± 12.25 pg/ml, 6.54 ± 5.95 mL/mL, 6.33 ± 2.80 mL/mL and 13.15 ± 11.13 ng/ml, respectively. According to the IIEF-5 scores, 44 (33.8%) patients had severe ED, 56 (43.1%) patients had moderate ED and 30 (23.1%) patients had mild ED. The statistical differences between the groups’ demographic and laboratory parameters are summarised in Table 1. Although the post hoc test revealed statistically significant differences between group 1 and group 3 (p: .047) and group 2 and group 3 (p: .032), there were no statistically significant differences between group 1 and group 2. Pearson’s correlation analysis showed positive correlations between the serum testosterone levels and serum 25(OH)D levels (r: .185; p: .033), positive correlations between the serum 25(OH)D levels and C-Reactive Protein (CRP) (r: .219; p: .012) and positive correlations between the serum 25(OH)D levels and IIEF-5 scores (r: .193; p: .028). The results of the univariate and multivariate analyses are summarised in Table 2. According to
the multivariate analysis, 25(OH)D was observed as an independent prognostic risk factor for IIEF-5 scores in men with moderate and severe ED.

4 | DISCUSSION

The present study revealed that serum 25(OH)D levels were associated with the severity of ED. Patients with low serum 25(OH)D levels had decreased IIEF-5 scores. We aimed to calculate the cut-off values for 25(OH)D to separate patients with severe or moderate ED from mild ED, which can be treated through modifications to lifestyle. The relationship between the cut-off levels of 25(OH)D and 25(OH)D deficiency in cases of ED is debated in the literature to this day. While some studies have suggested 20 ng/ml as the appropriate cut-off level for 25(OH)D (Lutsey et al., 2015; Reis et al., 2009), others have recommended 30 ng/ml as the cut-off level most suited for the treatment of ED (Farag et al., 2016; Ginde, Liu, & Camargo, 2009). All cut-off levels that have been used to determine 25(OH)D deficiency have been assumed in research studying the role of 25(OH)D on bone metabolism. We considered that 25(OH)D cut-off levels may be different during the treatment of ED so that we could calculate the cut-off levels for 25(OH)D in patients with ED. Because of the retrospective design of this study, we were unable to investigate the effect of vitamin D replacement therapy on recovery from ED symptoms.

Although ED is related to multiple issues, most common pathophysiologic factors involve vascular disorders associated with impairment to endothelial function (Sullivan et al., 1999). Recent studies have revealed that the underlying pathophysiologic mechanisms of decreased serum 25(OH)D that is related to ED may be based on endothelial dysfunction. Barassi et al. identified an association between decreased 25(OH)D levels and reduced nitric oxide synthesis from the endothelium (Barassi, Pezzilli, Colpi, Corsi Romanelli, & Melzi d’Eril, 2014). A cell culture study on human umbilical vein endothelial cells indicated that serum 25(OH)D can increase nitric oxide (NO) production, resulting in vasodilatation of the cavernosal arteries via endothelial nitric oxide synthase activation (Andrukhova et al., 2014). According to recent literature, 25(OH)D deficiency may play a key role in modulating the function of endothelial cells and contribute to erectile function through different pathways. We found a positive correlation between serum 25(OH)D levels and testosterone levels. Therefore, we believe that reduced serum 25(OH)D and testosterone levels...
may cause vascular endothelial dysfunction due to decreased serum NO levels.

Endothelium secretes and expresses 25(OH)D and receptors. Low serum 25(OH)D levels can increase proinflammatory cytokines, such as tumour necrosis factor-alfa and interleukin-6 (Di Rosa et al., 2012; Sorenson & Grant, 2012; Tarcin et al., 2009). When compared to patients who do not have ED, patients with ED have increased plasma reactive oxygen metabolites and decreased total anti-oxidant status (Barassi et al., 2009). 25(OH)D deficiency may be related to the increased generation of superoxide anions and the activation of an oxidant cascade, which can result in ED (Hirata et al., 2012; Wong, Delansorne, Man, Svenningsen, & Vanhoutte, 2010). Several studies have observed that 25(OH)D progressively prevents proinflammatory cytokines and increases anti-inflammatory cytokines (Cannell, Grant, & Holick, 2014). In the current study, we found that serum 25(OH)D levels were associated with serum CRP levels. These findings may be related to decreased serum 25(OH)D levels, which could be triggered by inflammatory pathways.

In Culha et al.’s study of 90 patients with ED, they determined that when compared to patients with mild ED, patients with moderate and severe ED showed reduced levels of 25(OH)D. According to the authors, the cut-off level for serum 25(OH)D was 15 ng/ml with a sensitivity of 71.4% and a specificity of 73.2% (Culha et al., 2018). In the present study, the cut-off level for 25(OH)D was calculated to be 27.32 ng/ml with a sensitivity of 64% and a specificity of 68%. In addition, we determined similar results for the association between serum 25(OH)D levels and ED symptom scores (IIEF-5).

In Basat et al.’s research, which investigated the association between ED and 25(OH)D levels in 98 patients with type 2 diabetes mellitus, they observed low IIEF-5 scores in patients with decreased serum 25(OH)D levels. They also determined that low serum testosterone levels were associated with low serum 25(OH)D levels (Basat et al., 2018). In addition, Canguven et al. asserted that vitamin D replacement treatment improved erectile function in middle-aged men by increasing their serum testosterone levels (Canguven, Talib, El Ansari, Yassin, & Al Naimi, 2017). In another study that compared hypogonadal and normal gonadal function in patients with type 2 diabetes mellitus, serum 25(OH)D levels were lower in patients with hypogonadism than in patients with normal gonadal function, but they were not correlated with ED prevalence or severity in either group (Bellastella et al., 2014). Caretta et al. discovered possible associations between serum 25(OH)D levels and ED in their study of patients with type 2 diabetes mellitus. They also determined a connection between decreased IIEF-5 scores and lower concentrations of 25(OH)D (Caretta et al., 2016). The current study produced similar results. Although we observed decreased IIEF-5 scores and a positive correlation between serum

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Testosterone mean ± std dev, ng/ml</td>
<td>.001</td>
<td>1.19 (0.86–1.64)</td>
<td>.280</td>
</tr>
<tr>
<td>Estradiol mean ± std dev, pg/ml</td>
<td>.360</td>
<td>0.98 (0.93–1.03)</td>
<td>.491</td>
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<tr>
<td>FSH mean ± std dev, mUI/ml</td>
<td>.011</td>
<td>1.02 (0.91–1.15)</td>
<td>.682</td>
</tr>
<tr>
<td>LH mean ± std dev, mUI/ml</td>
<td>.106</td>
<td>0.89 (0.68–1.17)</td>
<td>.428</td>
</tr>
<tr>
<td>Prolactine mean ± std dev, ng/ml</td>
<td>.138</td>
<td>1.01 (0.93–1.09)</td>
<td>.741</td>
</tr>
<tr>
<td>Dehydroepiandrosterone mean ± std dev, ug/dl</td>
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<td>1.00 (0.99–1.00)</td>
<td>.975</td>
</tr>
<tr>
<td>25-Hydroxy Vitamin D mean ± std dev, ng/ml</td>
<td>.022</td>
<td>1.05 (0.99–1.12)</td>
<td>.031</td>
</tr>
</tbody>
</table>

Abbreviations: FSH, Follicle stimulating hormone; LH, luteinising hormone.

Bold values indicate statistical significance (p < .05).
25(OH)D and serum testosterone levels in patients with severe and moderate ED when serum 25(OH)D levels were lower than 27.32 ng/ml in the univariate analyses, there was no statistical significance between serum testosterone levels and serum 25(OH)D levels in the multivariate analyses. As a result, we determined that serum 25(OH)D levels are not predictive of decreased serum testosterone levels in men with ED.

This study contained some limitations. First, due to the study’s retrospective design, we were unable to evaluate patients’ vascular status using penile coloured Doppler ultrasonography. The study was also limited by the results of the 25(OH)D replacement therapy, as we were unable to treat patients with decreased serum 25(OH)D levels or to determine how these levels affected the severity of ED.

There is increasing evidence about the association between serum 25(OH)D levels and ED. This study determined that decreased 25(OH)D levels in the multivariate analyses. As a result, we determined that serum 25(OH)D levels are not predictive of decreased serum testosterone levels in patients with severe and moderate ED when serum 25(OH)D levels were lower than 27.32 ng/ml could indicate the need for medical therapy, higher levels may be associated with presence, severity and composition of carotid atherosclerosis in type 2 diabetes. Nutrition, Metabolism and Cardiovascular Diseases, 21(4), 286–293.

D and incident heart failure: The ARIC (Atherosclerosis Risk in Communities) study. JACC. Heart Failure, 3(5), 347–356.


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