Original Article

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Comparison of Different Vitamin D Replacement Modalities in Vitamin D-Deficient Patients

D Vitamini Replasman Tedavisinde Uygulanan Modalitelerin Karşılaştırılması

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Abstract

Purpose: There is no globally accepted treatment protocol for vitamin D deficiency. Here, we aimed to compare the efficacy of 3 different replacement modalities in vitamin D-deficient patients. Cross-sectional retrospective study.
Material and Method: The study was conducted in the endocrine outpatient clinic at Dr. Lütfi Kırdar Training and Research Hospital between March 2013 and July 2013. A total of 223 vitamin D-deficient patients aged 18-80 years were given replacement therapy. One hundred twenty five patients who met the inclusion criteria were included in the study. The patients were divided into three groups according to the modality of the treatment they received. The subjects of group 1 were given 300.000 IU vitamin D once orally, those of group 2 50.000 IU per week for six weeks and the patients in group 3 received 50.000 IU per week for eight weeks. Biochemical tests were performed before and after replacement therapy in all subjects and the results were recorded.
Results: The success of replacement therapy was defined as achieving a level of 25(OH)D of more than 20 ng/mL. The rate of treatment success was 97% in group 1, 95.3% in group 2, and 83% in group 3. There was no statistically significant difference in treatment success between the groups (p>0.05).
Discussion: Replacing vitamin D with a total of 300.000 IU at once or weekly split doses of 50.000 IU for 8 weeks, as recommended in the guidelines, has the same treatment success. Treatment with 300.000 IU vitamin D at once can be an alternative replacement modality in patients with poor compliance.
Keywords: Vitamin D, deficiency, replacement, protocol

Öz

Amaç: Vitamin D yapı olarak hormonlara benzer ve deride üretilir. İskelet sistemi sağlığı için gereklidir ve eksikliği birçok hastalıkla ilişkilendirilmiştir. Serum 25(OH)D düzeyi vücut D vitamini durumunu gösterir ve 20 ng/ml'nin altındaki değerler eksiklik olarak kabul edilir. Ülkemizde, 300.000 IU ve 50.000 IU D vitamini içeren 2 farklı preparat bulunur. Kılavuzlar replasman tedavisinde genellikle haftada 50.000 IU D vitamininin 8 haftalık kullanımını önerse de replasman tedavisinde kabul edilen genel bir tedavi yoktur ve uygulanan tedavilerin etkinliği farklıdır. Replasman günlük, haftalık ya da aylık verilebilir. Çalışmamızda, vitamin D eksikliği olan hastalara 3 farklı replasman tedavisi verdik ve etkinliklerini karşılaştırdık.
Gereç ve Yöntem: Çalışmamıza Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi, Tiroid hastalıkları polikliniğine Mart 2013 ile Temmuz 2013 tarihleri arasında gelen ve vitamin D eksikliği saptanan hastalar alındı. Bu prospektif çalışmada, yaşları 18-80 arasındaki toplam 223 hastaya replasman tedavisi verildi fakat 125 hasta çalışmaya dahil edildi. Hastalar 3 gruba ayrıldı ve her grup farklı replasman tedavisi aldı. Grup 1 300.000 IU D vitaminini bir kez oral aldı, grup 2 haftalık 50.000 IU D vitaminini 6 hafta süreyle oral aldı ve grup 3 haftalık 50.000 IU D vitaminini 8 hafta oral olarak kullandı. Replasman öncesi ve sonrası biyokimya testleri yapıldı ve sonuçlar kaydedildi. İstatistiksel analiz için SPSS 17 programı kullanıldı.
Bulgular: Serum 25(OH)D düzeyinin 20 ng/ml nin üzerinde olması yeterli sayıldığından replasman sonrası bu düzeyi geçenlerde tedavi başarılı sayıldı. Buna göre, grup 1'de başarı oranı %97, grup 2'de %95.3 ve grup 3'te %83 olarak saptandı. Gruplar arasında tedavi başarısı açısından istatistiksel olarak anlamlı bir fark yoktu (p>0,05). Her 3 replasman tedavisi de 25(OH)D düzeyini anlamlı olarak artırdı (p<0,05).
Tartışma: Replasman tedavisinde kılavuzların önerdiği haftalık 50.000 IU D vitamininin 8 haftalık kullanımı ile tek seferde 300.000 IU D vitamininin kullanımı aynı etkiye sahiptir. Tedaviye uyumun düşük olduğu hastalarda 300.000 IU D vitamininin bir kez verilmesi alternatif bir replasman tedavisi olabilir ve bu tedavi 3 aylık dönemlerle tekrarlanabilir.
Anahtar kelimeler: Vitamin D, eksiklik, replasman, protokol

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Introduction

Besides the usual description of vitamins, vitamin D has an exceptional place because of its similarity to several hormones. This secosteroid vitamin can be produced in the skin with the help of sunlight (1). An adequate level of vitamin D is essential for maintaining skeletal health and calcium-phosphorus metabolism (2). There have been several studies showing the relationship of decreased vitamin D levels with increased risk of developing cancer, cardiovascular diseases, diabetes, hypertension, autoimmune diseases, metabolic disorders, infections due to decreased immunity, and some neuropsychiatric diseases (3).

Serum concentration of 25-hydroxy-vitamin D [25(OH)D] is the best indicator of vitamin D status (4). A 25(OH)D level of greater than than 30 ng/ml is defined as sufficiency whereas, values of 20-30 ng/ml, <20 ng/ml and <10 ng/ml are considered insufficiency, deficiency and severe deficiency, respectively (5,6). Both D2 and D3 preparations can be used for the treatment of deficiency, however, vitamin D3 is the preferred treatment. There is 1 ng/ml increment in serum 25(OH)D level for every 100 IU vitamin D taken. There are various treatment modalities for vitamin D deficiency, however, there has been no consensus on treatment regimens. 2.000 IU/day or 50.000 IU/week vitamin D for 6 weeks is recommended for patients from birth to 18 years of age. 6.000 IU/day or 50.000 IU/week vitamin D for 8 weeks should be given to patients older than 18 years of age for vitamin D replacement. Two or three times of this dose is recommended for obese patients, patients with malabsorption syndromes and patients taking any treatment that interferes with vitamin D metabolism (6). While target value of serum 25(OH)D is between 30-50 ng/ml, levels between 50-100 ng/ml are considered overdose and levels more than 100 ng/ml are considered toxic (7). There are many studies stating that replacement treatment can be given daily, weekly or monthly. Different replacement modalities can be given considering patient's compliance, easy application of the drug and risk of overdose (5,6,7). In this study, we aimed to compare the efficacy of 3 different replacement modalities given to vitamin D-deficient patients.

Materials and Methods

The study was conducted in the endocrine and metabolism disorders outpatient clinic at Dr. Lütfi Kırdar Kartal Training and Research Hospital between March 2013 and July 2013. Patients' health records were scanned retrospectively from hospital computers and a total of 223 patients aged 18-80 years were found to be vitamin D deficient and were given different vitamin D replacement modalities. Patients with a history of gastrointestinal surgery or any chronic digestive system disease, taking any kind of vitamin D treatment or any drug interfering with vitamin D metabolism were not included in the study. Patients who did not come to control visit at the end of treatment or did not use the prescribed vitamin D preparation were also excluded. After evaluation, 125 patients were found to be eligible for the study. Data on age, sex, weight, height, duration of daily sun exposure, daily intake of dietary calcium, and vitamin D replacement modality were gathered from the hospital records. The patients included in the study were divided into 3 groups according to their treatment modalities named as group 1, 2 and 3. The patients in group 1 received 300.000 IU vitamin D at once, per oral. Patients in group 2 received 50.000 IU vitamin D preparation, once weekly for six weeks, per oral. In this group a total of 300.000 IU vitamin D was given in six-week period. The patients in group 3 received 50.000 IU vitamin D preparation, once weekly for eight weeks, per oral, as recommended in the guidelines. The study protocol was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki.

Biochemical Analysis

Patients' hospital records were searched in order to get laboratory results of 25(OH)D, calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) and parathormone (PTH) measurements before and after treatment (8. week).

Vitamin D was studied in the central biochemistry laboratory using high-pressure liquid chromatography (HPLC) in the system of Immuchrom technologies. Serum or plasma part of blood samples were taken into non-gel containing EDTA tubes and studied using HPLC. Ca levels were studied in the central biochemistry laboratory. Blood samples taken into dry biochemistry tube were studied using Beckman Coulter AU2700 clinical chemistry system and photometric color method. The reference range was 8.8-10.6 mg/dL for calcium. P levels were measured in the central biochemistry laboratory with Beckman Coulter system. Blood samples in dry biochemistry tubes were studied in AU2700 series with UV spectrophotometric method and the reference values were 2.5-4.5 mg/dL. ALP levels were also studied using Beckman Coulter system AU2700 series in the central biochemistry laboratory using kinetic color method and the reference range was 30-120 U/L. In order to determine serum parathormone levels, blood samples were taken into potassium-EDTA-containing biochemistry tubes and transported to the central biochemistry laboratory hormone division on ice. P levels were studied via in vitro chemiluminescent microparticle immunoassay (CMIA) method using the Architect i2000 SR immunoassay analyzer (Abbott technologies). The reference range was 4-2500 pg/mL for STAT protocol and 3-3000 pg/mL for routine protocol. The estimated normal values were 15-68.3 pg/mL.

Statistical Analysis

Statistical analysis was performed via SPSS 17 for Windows. Student's t-test was used for the comparison of the two gs and the one-way analysis of variance (ANOVA) was used in order to compare more than two groups. The mean and SD values were given as well as percentages. Pearson's correlation coefficient was used to determine the association between different variables. A confidence interval of 95% and a p value of less than 0.05 were considered statistically significant.

Results

General features of the patients are shown in Table 1. In group 1, 30 of 35 patients were female (86%) and 5 were male (14%). The mean age of the patients was 44.2±13.7 years. The mean daily intake of dietary calcium was 511.7±127.9 mg and the mean body

mass index was 27.7±5.3 kg/m^2. In group 2, 42 of 43 patients were female (98%) and 1 was male (2%). The mean age was 47.3±12.7 years. The mean daily intake of dietary Ca level was 533.7±123.6 mg and the mean body mass index was 29±12.7 kg/m^2. In group 3, 43 of 47 patients were female (92%), 4 patients were male (8%) and the mean age of the patients was 43±11.3 years. The mean daily intake of dietary calcium was 541.1±150.4 mg and the mean body mass index was 27±4.4 kg/m^2. Daily sun exposure time was found to be less than 4 hours in all patients. Daily sun exposure time was lower especially in patients who were being employed. Pre- and post-treatment laboratory results in the groups are shown in Table 2. Serum 25(OH)D levels of lower than 10 ng/ml were considered severe vitamin D deficiency. Ten of 35 patients (28.6%) in group 1, 20 of 43 patients (46.5%) in group 2, and 22 of 47 patients (46.8%) in group 3 had severe vitamin D deficiency before treatment. Although vitamin D replacement lowered serum PTH levels in all the three groups, it was not statistically significant in any group. Since a serum level of 25(OH) D more than 20 ng/ml is considered as sufficient, success was defined as achieving a 25(OH)D level of more than 20 ng/ml after replacement therapy. Accordingly, the rate of treatment success was 97% in group 1, 95.3% in group 2, and 83% in group 3. There was no statistically significant difference in treatment success between the groups (p>0.05). All the three replacement modalities provided significantly increased serum 25(OH)D levels (p<0.05). After replacement treatment, 2 of 43 patients (4.7%) in group 2 and 2 of 47 patients (4.3%) in group 3 had serum 25(OH)D levels of more than 100 ng/ml which is toxic. However, no patient in group 1, who had taken 300.000 IU vitamin D at once, had such a result. There was no statistically significant relationship between replacement modality and toxic vitamin D levels. The laboratory analysis at the end of treatment revealed that no patient in any of three groups had hypercalcemia.

Discussion

Although vitamin D deficiency is one the most frequent medical problems, there is not a widely accepted and used replacement protocol among physicians. According to the 2011 Clinical Practice Guideline of the Endocrine Society, 50.000 IU/week for 8 weeks is recommended for the treatment of vitamin D deficiency in adults (6). Besides this, physicians usually prescribe 300.000 IU vitamin D once monthly for two or three months. Despite the fact that different replacement options are used, efficacy and safety of these treatment modalities are not well known. There are just a few studies comparing different vitamin D replacement treatments in the literature (5,7,8,9). In our study, we compared the treatment regimen including 50.000 IU/week for 8 weeks with 300.000 IU once and 50.000 IU/week for 6 weeks. There is no study in the literature comparing single dose of 300.000 IU and weekly 50.000 IU of vitamin D. In their study, Ish-Shalom et al. (10) investigated whether the same cumulative dose of vitamin D3 given daily, weekly and monthly produces different effects. They randomized elderly patients with hip fracture to vitamin D3 supplementation protocols of 1500 IU/day, 10.500 IU/week and 45.000/month, and at the end of second month, there were no significant difference in serum 25(OH)D concentrations between the groups. Carnes et al. (11) have searched the efficacy of intermittently given high-dose vitamin D in adolescents. Patients received either 300.000 IU or 150.000 IU vitamin D once for a 6-month period for one year and the effects were compared to placebo. It was concluded that 300.000 IU vitamin D once for 6 months was safe and could be used in the treatment of vitamin D deficiency. In a review by Kearns et al. (12) in 2013, patient's adherence to treatment with daily and weekly administration of vitamin D was poor and 300.000 IU vitamin D once orally for a 3-month period was effective and safe both in increasing vitamin D levels and decreasing PTH levels. In our study, there was no significant difference in treatment success

Table 1. General features of the patients

	Group 1 (n=35)	Group 2 (n=42)	Group 3 (n=47)	p
Age (years)	44.2±13.7	47.3±12.7	43.04±11.3	NS
Sex (F/M, %)	86/14	98/2	92/8	NS
Weight (kg)	74±13.6	73.9±11.4	71.3±9.6	NS
BMI (kg/m^2)	27.7±5.3	29.04±12.7	27.01±4.4	NS
Daily Ca intake (mg)	511.7±127.9	533.7±123.6	541.1±150.4	NS

NS: Non-significant, BMI: Body mass index

Table 2. Laboratory results before and after treatment

	Before treatment			After treatment			p		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	p1	p2	p3
25(OH)D (ng/ml)	13.1±3.8	10.2±4.6	10.4±4.3	34.3±10.6	39.0±22.8	36.9±27.7	0.04	0.00	0.00
Ca (mg/dl)	9.2±0.4	9.1±0.4	9.1±0.4	9.3±0.4	9.2±0.3	9.2±0.4	0.47	0.15	0.34
P (mg/dl)	3.1±0.3	3.2±0.4	3.0±0.4	3.2±0.4	3.2±0.4	3.2±0.5	0.72	0.62	0.50
ALP (U/L)	79.6±24.7	78.3±41.2	82.7±25.7	72.3±22.6	75.6±39.5	76.2±25.6	0.74	0.42	0.95
PTH (pg/ml)	80.7±35.5	74.9±27.9	79.7±34.5	62.5±24.6	55.4±24.1	60.6±24.9	0.58	0.21	0.25

p1: Comparison of group 1 before and after treatment, p2: Comparison of group 2 before and after treatment, p3: Comparison of group 3 before and after treatment, Ca: Calcium, P: Phosphorus, ALP: Alkaline Phosphatase, PTH: Parathormone

rates. The most important risk of high-dose replacement at once is vitamin D toxicity. In our study, at the end of treatment, no patient in group 1, who received 300.000 IU vitamin D at once, had any toxic level. However, 2 patients in group 2 (4.7%) and 2 patients in group 3 (4.3%) had serum 25(OH)D levels higher than 100 ng/ml. This shows the safety of taking 300.000 IU vitamin D at once.

Mastaglia et al. (13) have claimed that total cumulative dose may be more important than dosage intervals in replacement treatment. In their study, the patients received either 5000 IU/day, 10.000 IU/day vitamin D or placebo and the results were screened at the end of the third month. Vitamin D levels were higher than 34 ng/ml in 75% of patients, who received 10.000 IU/day, whereas this rate was 50% in patients receiving 5000 IU/day. On the other hand, beside the importance of total cumulative dose, Chel et al. (14) have suggested that dosing interval may have significant effects. In their study, the patients received 600 IU/day, 4200 IU/week or 18.000 IU/month for 4 months. Even though the total cumulative doses were the same in each group, serum 25(OH)D levels showed most increment in daily treatment group and least increment in monthly treatment group.

Although Turkey is a country lacking vitamin D-containing or vitamin D-fortified foods, the main reason for vitamin D deficiency is inadequate sun exposure. Personal clothing habits play an important role in inadequate sun exposure. In our study, we also evaluated patients' clothing habits and observed that daily periods of sun exposure was shorter than 4 hours in all patients, and there was no significant difference between the groups. In a study by Bassil et al. (15) it was emphasized that even in sunny regions like Middle East and North Africa, rickets and osteomalacia were not rarely seen. This is probably because of clothing habits of people in these regions and also in Turkey which shows the importance of replacement treatment in vitamin D deficient people. The main limitations of the study include its retrospective cross-sectional design. Additionally, we evaluated the effects of high-dose replacement treatment on second month test results, but we did not assess possible acute effects. In order to get more accurate information about the safety of this replacement modality, it would have been better to analyze the metabolic effects in the first or second weeks of treatment.

Vitamin D deficiency replacement with 300.000 IU vitamin D at once or a total of 300.000 IU divided to 6 weeks has the same treatment success as described in the recommendation of the guidelines (50.000 IU/week for 8 weeks). Treatment with 300.000 IU vitamin D at once can be an alternative replacement modality in patients with poor compliance.

Ethics

Ethics Committee Approval: The study was approved by the Dr. Lütfi Kırdar Kartal Training and Research Hospital Ethics Committee, Informed Consent: All participants filled the informed consent form, Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Gülgün Arslan, Şule Temizkan, Mehmet Sargın, Design: Gülgün Arslan, Şule Temizkan, Mehmet Sargın, Data Collection or Processing: Mehmet Sayıner, Gülgün Arslan, Tülay Karabayraktar, Şule Temizkan, Analysis or Interpretation: Tülay Karabayraktar, Literature Search: Mehmet Sayıner, Tülay Karabayraktar, Writing: Mehmet Sayıner, Tülay Karabayraktar, Conflict of Interest: The authors have no conflict of interest, Financial Disclosure: This study was internally funded, the authors have nothing to disclose.

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