Original Article

Determination of Effect of Oral Vitamin D to Improve Ventilatory Threshold in Healthy Young Adults with Vitamin D Deficiency

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Abstract

Background: Many studies have shown a high prevalence of vitamin D deficiency in different communities. Due to multiple roles of vitamin D in the body, this study was aimed to determine the effect of oral vitamin D3 on ventilatory threshold-1 in a condition of vitamin D deficiency.

Materials and Methods: Recent study performed on 25 healthy young adults with the serum levels of 25 Hydroxyvitamin D3 lower than 20 ng/ml, had referred to the sports medicine clinic of Taleghani Hospital of Tehran, in a one-year period (2016-2017). After primary evaluation, baseline ventilatory threshold-1 were determined by cardiopulmonary exercise testing (CPET). Then persons were treated with 50,000 IU/week of oral vitamin D3 for 8 weeks, and one week after the completion of treatment, ventilator threshold-1 was measured again, similar to the beginning conditions of the study, and its changes were studied.

Results: The mean baseline ventilatory threshold-1 of participants before any intervention was 22.46 ± 6.45 (ml/kg/min), and after 8 weeks of treatment by 50000 IU/week of oral vitamin D3, increased to 26.79 ± 5.33 (ml/kg/min) at the end of study, which there was a statistically significant increase in ventilatory threshold-1 ($p<0.001$).

Conclusion: Recent study showed that proper treatment of the vitamin D deficiency, improves ventilatory threshold-1 in healthy young adults.

Keywords: 25 Hydroxyvitamin D3, Anaerobic Threshold, Vitamin D deficiency

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Introduction

Vitamin D: Vitamin D is a public health interest because its deficiency is common and is associated with musculoskeletal diseases, as well as extra-musculoskeletal diseases, such as cardiovascular diseases[1-3]. In 2018, a study conducted by Chakhtoura et al. in relation to the status of vitamin D in the Middle East and North Africa (MENA), a high prevalence of vitamin D deficiency in these areas was reported[4]. In addition, a high prevalence of vitamin D deficiency in Athletes has been reported. A study by Sikora-Klak et al. on athletes, showed a high prevalence of vitamin D deficiency among them[5].

New scientific references mention vitamin D and its metabolites are hormones and hormone precursors rather than vitamins, since in the proper biologic setting, they can be synthesized endogenously[6]. 25 Hydroxyvitamin D3 (25-OH vitamin D3), is the dominant form of circulatory vitamin D, and has a half-life of about 2 - 3 weeks and is the best scale of vitamin measurement. Serum levels of 30 ng/mL and more of 25-OH vitamin D3, indicates adequate body vitamin D status and serum levels less than 20 ng/ml indicates vitamin D deficiency. Serum levels between 20-30 ng/ml means vitamin D insufficiency[6-8].

Among the many functions of vitamin D in the body, one of the most important is a role in bone health and muscle function. Other vitamin D functions include roles in gene regulation, participation in immunologic reactions, cardiorespiratory health, public health, survival and fertility[6,7,9,10]. Presence of the vitamin D receptors (VDR) in cardiac muscle, vascular tissue and skeletal muscle support a hypothesis that mentioned, vitamin D may impact the cardiovascular system's ability to transport oxygenated blood and the skeletal muscles' ability to use oxygen[10]. On the other hand, low levels of serum vitamin D3 and low cardiorespiratory fitness are both accompanied by increased cardiovascular and all causes mortality, which can indicates the effect of vitamin D on cardiorespiratory health[2,6,11,12].

Ventilatory Threshold: Maximal exercise capacity is applied to the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to extract oxygen from the blood. Ventilatory threshold (VT, also called ventilatory anaerobic threshold or VAT), referred to as the anaerobic threshold is an index used to estimate exercise capacity. Several different methods exist for measuring ventilation and respiratory gas parameters during exercise, however maximal aerobic capacity (VO2max) is usually obtained during a graded exercise test with the systems rely on breath-by-breath analysis techniques, which is called cardiopulmonary exercise testing (CPET). During the initial (aerobic) phase of CPET, which lasts until 50–60% of VO2max is reached, expired ventilation (VE) increases linearly with VO2 and reflects aerobically produced CO2 in the muscles. Blood lactate levels do not change during this phase because of minimal muscle lactic acid production. However, during the latter half of exercise anaerobic metabolism occurs because oxygen supply cannot keep up with the increasing metabolic requirements of exercising muscles. At this time, there is a significant increase in lactic acid production in the muscles and in the blood lactate concentration. Oxygen consumption (VO2) at the onset of blood lactate accumulation is called the lactate threshold (LT) or anaerobic threshold in which ventilation increases linearly more rapidly the ventilatory threshold (VT)[11,13,14] (Figure 1).

The VT1 is called the first VT. It is a marker of intensity that can be observed in a person's breathing at a point where lactate begins to accumulate in the blood, the point where the breathing rate begins to increase. A person who is at VT1 can no longer talk comfortably while exercising, but can still string together a few words. Second VT (VT2) is a higher marker of intensity than VT1, that lactate has quickly accumulated in the blood and the person needs to breathe heavily. At this rapid rate of breathing, the exerciser can no longer speak. Actually, VT2 can also be called the anaerobic threshold or lactate threshold[11,13-16].

Ventilatory threshold typically corresponds to a percentage of the VO2max in individuals and it normally occurs at a higher percentage of the VO2max in physically trained subjects. In other words, more VT1 means more aerobic phase of exercise and the more exercise capacity. Although different protocols are used during treadmill walking CPET, Bruce protocol is the most well-known and popular protocol used for test[13].

Potential association between Vitamin D and VT1: According to the undeniable effect of vitamin D in the health and the potential roles of vitamin D, serum levels of vitamin D are associated with the VT1. In the other words, the time a person can continue in aerobic phase metabolism during incremental exercise[11,13,14,16]. A significant positive associations between 25-OH vitamin D and parameters of CPET were detected in two large cohorts of healthy adults by Kaul et al. in 2016, they showed that subjects with high 25-OH vitamin D levels had an increase more than 25% in their exercise capacity compared with subjects with low 25-OH vitamin D levels[11]. However, until the study there was no comprehensive study examining the effect of vitamin D on ventilatory threshold in individuals with vitamin D deficiency. This provided a good opportunity to examine, therfore recent study was aimed to determine the effect of oral vitamin D3 on VT1, in a condition of vitamin D deficiency.

Methods

Recent study was conducted over a period of one year from December 2016 to December 2017. Participants included healthy young adults, aged 17 - 35 years old, who had referred to the Sports Medicine Clinic of Taleghani Hospital of Tehran, to assess physical fitness, to receive exercise program or to change life style, and in blood tests had serum levels of 25–OH vitamin D3 less than 20 ng/ml. Other inclusion criteria in the study included absence of any: definite acute or chronic disease; oral supplement intake containing vitamin D, in the last three months; oral drug or diet, tends to interfere with vitamin D intestinal absorption, in the last three months; gastrointestinal surgery, disrupts vitamin D absorption at any time; having physical activity of moderate intensity (≥ 3 days/weeks, 30 min in every session), in the last three months. In addition, exclusion criteria contained consumption of: prescribed medication from another drug manufacturing firm, prescribed medication against defined rules, any supplement containing vitamin D or a particular diet that is associated with vitamin D serum levels, any medication that affects VO2max values, occurrence of any disease that its treatment is more importance and regular exercise of moderate intensity (≥3 days/weeks, 30 min in every session).
In the first stage of the study, regardless of gender, 25 persons were selected from those who were qualified (serum levels of 25-OH vitamin D3 less than 20 ng/ml, accompany other inclusion criteria). Serum levels of 25-OH vitamin D3 of all people was measured in a given laboratory center in a fasting conditions (fasting for 10 hours), and with a same lab ELISA kit (Pishtaz®) based on the protocol. After initial evaluations and anthropometric measurements, body composition test was performed, and then individual experienced a CPET to determine the VT1. Finally, results were recorded in related forms.
In this study, body composition test aimed to determine the percentage of body fat (PBF) by the bioelectrical impedance analysis (BIA) method, of Javon Plus® system, in a similar condition (at morning and fasting for 4 hours) PBF was determined by a percentage of body composition. Aimed to determine VT1, a CPET rely on breath-by-breath analysis technique during a graded exercise test by CORTEX® system, with treadmill walking modality and the Bruce protocol, was performed in a similar condition (at morning and fasting for 4 hours). In this study, and based on previous studies, attainment of maximal exertion capacity was affirmed when subjects met 3 of 4 criteria: 1) Plateau of oxygen uptake (defined as < 50 mL/min increase with a 1% increase in treadmill grade), 2) Attainment ± 10 bpm (Beat per Minute) of age-predicted maximal heart rate, 3) Volitional exhaustion (defined as a rating of perceived exertion ≥ 18) and 4) Calculated respiratory exchange ratio (RER) >1.10 [11, 14, 17, 18]. In the study, the VT1 values was obtained based on the report of CPET, and was expressed with the unit of ml/kg /min.
In the next stage, all participants have been treated with 50,000 IU (International Unit) of vitamin D3 (produced by DANA® pharmacy co., named D-Vigel®) for 8 weeks. They were asked to use medication after lunch and on a certain day of the week. In addition, they asked to keep drug in a temperature of 15 to 30ºC, to prevent its deterioration. Finally, a week after completing treatment, they were asked to perform a serum 25-OH vitamin D3 test, same as the beginning conditions of the study and at the same laboratory center. Then they experienced the CPET again, same as the beginning conditions of the study, at the same center.
In the recent study, all participants completed the study, and we had not any sample loss. At the end of the study after data collection, SPSS (Statistical package for social science) software version 16.0 was used for data analysis and a significant level of statistical tests were considered 0.05. Because of the study conditions, we were not able to blinding, and only statistical analyst was unaware of intervention type. Figure (2) shows stages of the study in a flowchart.
The study subject was approved by the Ethics Committee of the School of Medicine of SBMU with the Code of Ethics IR.SBMU.MSP.REC.1395.389.

Results

In this study, 25 individuals with the serum levels of 25-OH vitamin D3 less than 20 ng/ml, which had inclusion criteria, were selected and then studied. Of

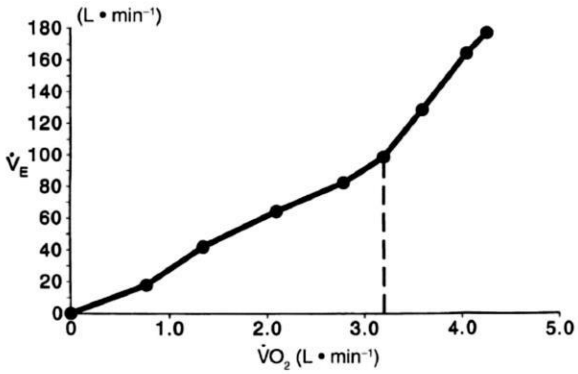

Figure 1. Relationship between intensity of exercise (VO2) and simultaneous, abrupt nonlinear increase in minute ventilation, signifying the ventilatory threshold[1].

this population, 20 persons (80%) were male, and the other five persons (20%) were female. In addition, the mean age of participants in the study was 26.88 ± 4.47 years old. The youngest individual had 17 and the oldest had 35 years old. Table 1 shows demographic properties of study individuals and Table 2 presents the summary of the data obtained from the study.

There was no significant linear correlation between PBF and the serum levels of 25-OH vitamin D3 (r = - 0.141; p = 0.501). In addition, there was no significant linear correlation between BMI and the serum levels of 25-OH vitamin D3 (r = - 0.183; p = 0.380).

The mean baseline serum levels of 25-OH vitamin D3 was 12.04 ± 3.96 at the beginning of the study, and increased to 40.32 ± 12.36 at the end of study, which there was a statistically significant increase (p<0.001).

In recent study, oral treatment by 50,000 IU vitamin D3 for 8 weeks significantly increased the mean VT1 values; an increase from the mean of 22.46 ± 6.45 ml/kg/min at the beginning of the study, to the mean of 26.79 ± 5.33 ml/kg/min at the end of the study (p < 0.001). This finding was the main of our study. Table 3 shows changes of VT1, before and after our intervention.

Discussion

Since a high prevalence of low serum levels of vitamin D has been reported in some areas that sunlight is abundant[19], examination of the response to oral treatment of vitamin D as an effective remedy

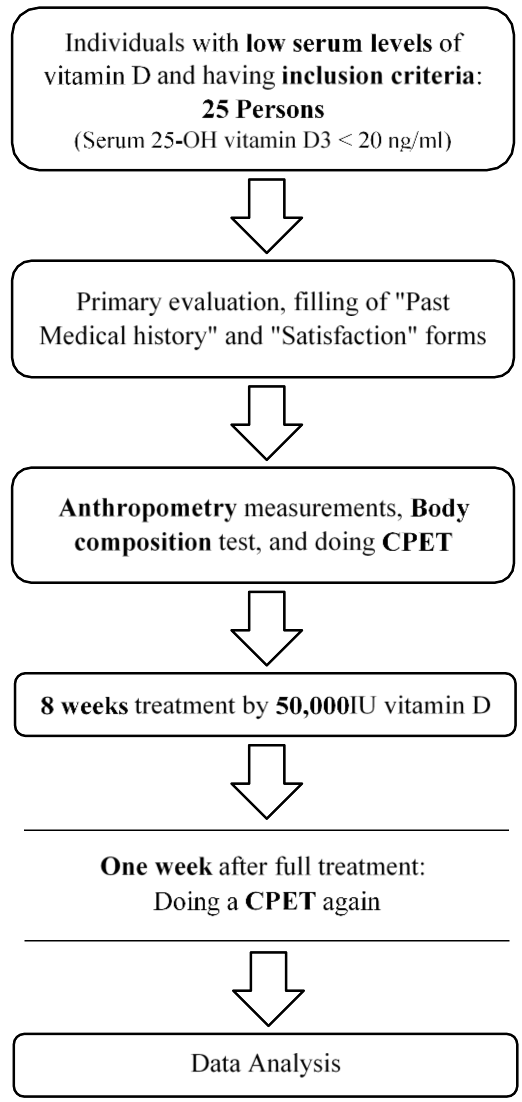

Figure 2. Flowchart of the study.

Table 1: Demographic properties of participants.

Detail		Property
Male	**Female**	**Sex**
20 persons	5 persons	
25 persons		**Total**
26.88 ± 4.47 years old		**Age**
27.65 ± 3.50 kg/m²		**BMI**
26.16 ± 4.86 percent		**PBF**
5 persons		***Smoking**

* Smoking during 6 months ago

Table 2: Summary of the study data.

Vitamin.D-2	Vitamin.D-1	VT1-2	VT1-1	PBF	BMI	Sex	Age	Samples
33	19/2	26/53	22/13	30/5	30/92	M	17	1
38	6/7	25/17	17/5	28/1	32/19	M	20	2
54	10/7	31/5	27/83	23/2	20/31	F	20	3
29	11/7	24/28	22/13	24/6	26/27	M	20	4
32	5/7	17/19	10/75	28/3	22/49	F	21	5
43	6/8	31/53	28/87	21/8	26/41	M	26	6
30	12/63	18/55	11/42	33/4	34/51	F	26	7
38	17/4	26/83	26/53	22/2	31/89	M	26	8
44	18/5	36/58	30/65	20	27/26	M	26	9
32	10/8	23/92	23	24	25/27	M	27	10
54	12/7	27/83	22/13	24/8	29/65	M	27	11
25	12/8	26/9	23/43	30/4	28/50	F	27	12
36	7/17	20/67	15/6	31/6	33/86	M	28	13
37	10/3	20/16	11/1	34/6	27/92	F	28	14
36	11/8	28/5	25/17	23/2	26/31	M	28	15
74	12/8	27/83	22	20	30/48	M	28	16
51	12/9	36/6	32/2	37/8	28/57	M	28	17
19	6/61	25/13	23/43	27/4	26/46	M	29	18
26	6/88	25/17	24/2	21/6	22/91	M	29	19
48	11/9	33/6	24/67	26/5	25/47	M	29	20
44	13/1	30/24	25/6	26/1	25/47	M	29	21
67	13/6	33/55	31/36	17/8	25/28	M	30	22
41	15/1	27/82	28/82	25/9	27/63	M	34	23
38	19/3	25/17	20/4	24	24/98	M	34	24
39	13/8	18/55	10/7	26/2	30/29	M	35	25

VT1-1: VT1 before intervention, VT1-2: VT1 after intervention, Vitamin.D-1: Vitamin D before intervention, Vitamin.D-2: Vitamin D after intervention, M: Male, F: Female, BMI: Body Mass Index, PBF: Percentage of Body Fat. *(By: Safarzadeh.A.MD. 2017)*

for the correction of the low serum levels of vitamin D3 and realizing study aims, seemed necessary. In addition to the potential effect of vitamin D on cardiovascular and musculoskeletal system also patients, who receive vitamin D have significantly larger improvements in inspiratory muscle strength[20]. Therefore, it is expected, correction of abnormal serum levels of 25-OH vitamin D3, leads to improve components of aerobic capacity and in the other words improves aerobic metabolism. Karefylakis et al. in the study in 2018, concluded that changes in vitamin D over a 6-month period were not associated with changes in aerobic fitness and Aerobic fitness is not impacted by temporal variations in 25-OH vitamin D3, But there was no therapeutic intervention in that study similar to our study, and they only computed tertiles for 25-OH vitamin D3 change, over 6 months in healthy individuals[10].

Unlike previous studies and documents[21-24], in this study, there was not significant revers linear correlation between the PBF and the levels of vitamin D3 (P = 0.501), as well as between the BMI and it (P = 0.380). Although it may require more detailed studies to achieve more accurate results, the difference in the recent study indicates that various mechanisms could potentially contribute to the robust association of vitamin with adiposity, a point which in the Baradaran's Study (2012) was also mentioned[25].

Table 3: Changes of VT, before and after intervention.

Min-Max	Mean ± SD	
10.7 – 32.2	22.46 ± 6.45	**VT1-1**
17.19 – 36.6	26.79 ± 5.33	**VT1-2**
	< 0.001	**P value**

* VT1-1: VT1 before intervention, VT1-2: VT1 after intervention

However, since the mean BMI of the all participants was in the range of overweight (27.65 ± 3.50 kg/m²), it seems to be a higher risk of low serum levels of vitamin D by increasing body weight, if individuals do not receive a proper supply of vitamin D.

The main objective of the recent study was to investigate changes that took place on the VT1 following prescription of vitamin D in people with vitamin D deficiency (levels less than of 20 ng/ml). In this study, following weekly oral treatment with 50,000 IU vitamin D3, the results were proceeded according to predictions and significant changes occurred in the VT1 followed intervention ($p<0.001$). The more individual cardiorespiratory fitness (CRF), the more VO2max (Maximum Cardiac Output x Arteriovenous Oxygen content difference) and VT1 will achieved [13, 14]. Since according to the Fick equation, VO2max is equal to the product of maximal cardiac output in difference of arteriovenous O2 content, and as previously discussed, it is expected that vitamin D affects variables of this equation. From another perspective, increase In VT1 means: 1) achieving greater intracellular oxygen supply, and 2) increase in mitochondrial capacity.

The cause of the VT is likely multifactorial, involving central neural drive, peripheral neural feedback, hormonal responses, increasing body temperature, and decreasing blood pH. Theoretically, when oxygen is not available in the mitochondria to accept hydrogen released during glycolysis, pyruvate must accept hydrogen to form lactate as an end product so that glycolysis can proceed. In fact, when glycolytic hydrogen production exceeds the mitochondrial transport capability, pyruvate must again accept the hydrogens to form lactate so glycolysis can continue[13, 14].

Therefore, it can be thought that vitamin D either has increased oxygen supply to intracellular aerobic metabolism, and or the mitochondrial capacity. Thus, it is possible that the effect of vitamin D on the VT1 exceeds its effects on the aerobic capacity components and intracellular oxygen supply, and it seems a need to study other effects of vitamin D in this regard and of course its effects at the substrate level.

After therapeutic intervention and data analysis, the mean serum levels of 25-OH vitamin D3, was significantly increased ($p<0.001$). Therefore, we concluded current drug regimen is suitable for treating vitamin D deficiency condition, and this concern will satisfied that with proper drug consumption, we would be probably no longer witnessing vitamin D deficiency.

Conclusion

Based on our study, we concluded that proper treatment with oral vitamin D, dosage of 50,000 IU/week, in the conditions of vitamin D deficiency could improve VT1 in healthy young adults.

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