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Original article

Metabolic effects of vitamin D supplementation in vitamin D deficient patients (a double-blind clinical trial)

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ABSTRACT

Background: Vitamin D has recently been given a lot of attention for its role in controlling insulin secretion. Many studies have spoken of its role in weight management, blood sugar control and many other metabolic variables.
Patient and methods: In a randomized double-blind clinical trial, 210 people with vitamin D deficiency were randomly allocated into two groups receiving vitamin D (50,000 units per week) or placebo for 8 weeks.
Results: Vitamin D levels were significantly increased in the group receiving vitamin D supplementation (13.7 ± 5.2 unit increase versus 0.8 ± 2.8). The increased levels of vitamin D lead to significant changes in fasting insulin levels (6.8 ± 8.1 unit reduction versus 2.3 ± 3.7), a 2-h insulin (31.1 ± 34.9 unit reduction versus 4.5 ± 24.6) and Homeostasis Model Assessment (HOMA) indices.
Conclusion: Correction of vitamin D deficiency leads to increased insulin sensitivity that was significantly able to maintain glucose in the normal range with lower levels of insulin.

1. Introduction

According to the International Diabetes Federation (IDF) in 2015, about 7.2% to 11.4% of the global population have diabetes, with the highest growing trend in the Middle East and North Africa regions in 2040 (from 35.4 million in 2015 to 72.1 million in 2040) [1]. In addition, more than 80% of these people are overweight or obese (BMI ≥25 kg/m^2) [2]. There is widespread consensus on the significant correlation of overweight with insulin-resistance and diabetes [3].

Vitamin D has recently been given a lot of attention for its role in controlling insulin secretion. It directly activates the transcription of insulin receptor gene [4] and peroxisome proliferator-activated receptor delta (PPAR-δ) [5], and enhances insulin-mediated glucose transport in vitro by stimulating the expression of insulin receptors [6]. In vitro studies have shown that vitamin D may have functional role in maintaining glucose tolerance through increasing insulin secretion and sensitivity. Animal studies have suggested that vitamin D deficiency disturbs insulin-secretion, which can be corrected through vitamin D supplementation [7]. Mice with vitamin D receptors (VDR) mutations had impaired insulin secretion and lower glucose tolerance than those with active receptors [7]. Yet, results from studies into the relationship of vitamin D level with glucose or insulin homeostasis are uncertain. Many studies have failed in showing a significant correlation between these two factors.

Some animal [8–11] and human [12,13] studies suggest that vitamin D can play a role in secretion and impaired function of insulin, and increase insulin-tolerance through different mechanisms [14–17]. It also can be effective in the pathogenesis of type 2 diabetes [18]. Vitamin D deficiency is common among women with type 2 diabetes [19]. In addition, the administration of sugar for older men with vitamin D deficiency will result in higher insulin secretion [20]. Low levels of vitamin D are often observed in people at higher risk of having diabetes [21].

Several studies have recently been conducted into this area, including a 10-year research that revealed an inverse correlation between vitamin D serum and the risk of insulin-resistance [22]. Also, some studies into the effect of vitamin D supplements on people with diabetes and high sugar level have reported an improvement in insulin secretion [12–14,23]. A study into 5677 patients with impaired glucose-tolerance showed that the administration of 25-dihydroxyvitamin D increased insulin sensitivity by 54%. A 20-year follow-up study into 4843 diabetics

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suggested that daily intake of vitamin D was associated with lower incidence of type 2 diabetes.

Regarding the high prevalence of impaired glucose-tolerance and diabetes, as well as vitamin D deficiency in the region, this study aimed at investigating the effect of vitamin D supplementation on glucose and insulin metabolisms in non-diabetic people with vitamin D deficiency.

2. Methodology

2.1. Subjects

The fasting blood samples of 210 healthy overweight people (aged 38 ± 13 years) with vitamin D deficiency (vitamin D = 13.8 ± 3.9) were collected in the morning in a period from April to September. These people were randomly assigned to two groups (intervention and control) in a double-blind controlled trial. Vitamin D pearls of 50,000 IU were given to the intervention group in a weekly routine. The administered placebo was similar pearls containing sunflower oil. All blood samples were collected in the laboratory of the research center. All included subjects were healthy people with no history of infectious and inflammatory diseases, thyroid glands disorder, gastrointestinal diseases especially ulcer and inflammatory bowel diseases, pregnancy, frequent use of medications (such as bisphosphonates, calcitonin, thiazides, glucocorticoids, nonsteroidal anti-inflammatory drugs, thyroxine, warfarin or D3 supplements) that affect bone or calcium metabolism, 1 year prior to the study. All subjects were informed about their rights and signed the informed consent form. All research stages were approved by the Ethics Committee of Shahid Beheshti University of Medical Science (1175/1000). This trial was registered in the Iranian Clinical Trials Registry (Registration ID: IRCT201401122660N2).

2.2. Assays

All blood samples were immediately centrifuged and their serums were separated, aliquoted, and frozen at −20 °C. Vitamin D serum was measured with ELISA (enzo lifesciences, Farmingdale, New York). The fasting and 2-h blood sugar and insulin levels were measured using colorimetric and ELISA, respectively. Anthropometric indices such as weight, height, and waist size were measured by a trained and experienced specialist. The Food Frequency Questionnaire (FFQ) was administered to all subjects at the beginning and the end of study by a dietitian. Homeostasis Model Assessment (HOMA)-insulin-resistance (IR) was used to determine insulin-resistance, HOMA-S was used to determine insulin sensitivity and was expressed as percentage and HOMA-B was used to determine the function of the beta cell and was expressed as percentage. They were calculated by HOMA-2 calculator (www.dtu.ox.ac.uk/homacalculator/).

2.3. Statistical analysis

The data are expressed as the mean ± sd, with a 95% confidence interval in parentheses when appropriate. Normality was assessed with the Kolmogorov–Smirnov test. Groups were compared by means of unpaired t tests and change in groups by paired t test. $P < 0.05$ was considered significant.

3. Results

Each group was comprised of 105 subjects with mean age of about 38 years. Demographic information of the subjects was recorded at the beginning of the study (Table 1). Vitamin D level was about 13 mg/dL in both groups, indicating severe deficiency among the investigated population. The mean BMI of the subjects was classified as overweight (BMI = 31 ± 5 and 32 ± 4 in both groups), which seems rational according to the studies maintaining the correlation of weight control with vitamin D status [24,25].

Table 1
Characteristics of the patients.

	Intervention	Control	*p* value
n	105	105	
Women/men	81/24	80/25	
Age	38 ± 13	38 ± 11	1.0
Height (cm)	164 ± 7	164 ± 8	0.9
BMI	31 ± 5	32 ± 4	0.3
Waist (cm)	95 ± 14	95 ± 11	0.9
Calorie intake (kcal)	3286 ± 1358	3405 ± 1616	0.5
Serum Vit D (mg/dL)	13.8 ± 3.6	13.9 ± 3.7	0.8

After 8 weeks of vitamin D supplementation, along with a balanced weight maintenance diet (to prevent overweight), vitamin D serum level significantly increased in vitamin D supplementation group as compared to the placebo group (5.2 ± 13.7 versus 2.8 ± 0.8) (Table 2). Due to the changes in the amount of received calorie, relative to the baseline, weight and waist size changes were observed in both groups; however, these changes were greater in vitamin D supplementation group. Despite this, the major change occurred in metabolic serum variables, in which vitamin D supplementation significantly improved these indices, especially insulin serum indicators. As compared to the baseline and control group, the fasting/2-h-after-meal insulin levels were significantly lower in the Vitamin-D supplementation group than control group. The fasting/2-h insulin levels decreased by −6.8 ± 8.1/−31.1 ± 34.9 units in the supplementation group versus −2.3 ± 3.7/−4.5 ± 24.6 units in control group.

The homeostatic model assessment indices, which indicate insulin-resistance status of the body, beta-cells function (%), and target cells sensitivity to insulin, were improved by taking vitamin D supplements (Table 2).

4. Discussion

Results show that vitamin D serum increase decreased blood sugar and fasting/2-h insulin levels. It seems that higher vitamin D level increases cells sensitivity to insulin, as smaller amount of insulin is needed to maintain the blood sugar level within the normal range, especially in post-meal metabolic conditions.

Results from epidemiologic and in vitro studies suggest a correlation between vitamin D status and blood sugar control [26–29]. Vitamin D may directly increase insulin sensitivity through stimulating the expression of insulin receptor or activating peroxisome proliferator-activated receptor gamma (PPAR-γ), a factor that regulates fatty acid metabolism in skeletal muscle and adipose tissue. Vitamin D can also affect the insulin secretion and sensitivity through regulating intracellular calcium concentration [30]. It also influences insulin flow through beta cell membrane and peripheral insulin sensitive tissues [ibid].

It directly activates transcription of insulin receptor gene [4] and PPAR-δ [5], and enhances insulin-mediated glucose transport in vitro by stimulating the expression of insulin receptor [6]. In vitro studies have shown that vitamin D may have functional role in maintaining glucose tolerance through increasing insulin secretion and sensitivity. Animal studies have suggested that vitamin D deficiency impairs insulin-secretion, which can be corrected through vitamin D supplementation [7]. Mice with mutations in the VDR had impaired insulin secretion and lower glucose tolerance than those with active receptors [7]. In vitro, 1,25(OH)2D3 induces insulin biosynthesis in pancreatic islet cells [31].