

Vitamin D Status and its Relationship with Thyroid Function Parameters in Patients with Hypothyroidism

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ABSTRACT

Background and Objectives: Vitamin D is an essential secosteroid that plays a crucial role in the homeostasis of a few mineral elements, particularly calcium. Since vitamin D deficiency and thyroid diseases are two important global health problems, we aimed to investigate a possible relationship of vitamin D and calcium levels with hypothyroidism in an Iranian population.

Methods: This case-control study was conducted on 175 subjects with hypothyroidism (75 males and 100 females) and 175 euthyroid controls (85 males and 90 females) who were referred to a laboratory in Gorgan, Iran. Serum levels of 25-hydroxyvitamin D, calcium, thyroid-stimulating hormone (TSH), free triiodothyronine (free T3) and thyroxine (total T4) were measured in all participants.

Results: Vitamin D and calcium were significantly lower in patients with hypothyroidism ($P < 0.0001$). Free T3 and calcium levels differed significantly among hypothyroid patients based on their vitamin D status ($P < 0.0001$), but vitamin D levels were within sufficient range in all groups. Moreover, there was a positive correlation between free T3 with vitamin D ($r = 0.337$, $P < 0.0001$) and calcium ($r = 0.361$, $P < 0.0001$) levels.

Conclusions: Our results suggest that there may be a relationship between decreased vitamin D levels and thyroid function parameters.

Keywords: Vitamin D Deficiency, Hypocalcemia, Hypothyroidism, Thyrotropin, Thyroxine.

INTRODUCTION

Vitamin D is a fat-soluble compound with a steroid-like structure that plays a key role in maintaining phosphorus and calcium homeostasis as well as bone health. Approximately one billion people suffer from vitamin D deficiency or insufficiency worldwide (1). This vitamin is normally produced in response to ultraviolet radiation exposure and is converted to its active form (calcitriol) in the liver and kidney (2).

Nowadays, investigating the role of vitamin D and treatment procedures for vitamin D deficiency has attracted much attention. Previous clinical and animal studies have revealed that vitamin D deficiency may be involved in numerous skeletal disorders such as rickets and osteoporosis, as well as non-skeletal disorders, such as immune system disorders (3). The rising prevalence of vitamin D deficiency has become a major public health issue, but neither international nor governmental health organizations have come up with effective countermeasures (2). Vitamin D deficiency could lead to development of various endocrine disorders such as type 1 and type 2 diabetes, adrenal insufficiency and polycystic ovary syndrome (4-6). Moreover, it may be involved in the pathogenesis of some autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and multiple sclerosis. It has been proposed that vitamin D supplementation could prevent the onset and/or progression of autoimmune diseases (7-9). The association of vitamin D levels with thyroid disorders such as Hashimoto thyroiditis and autoimmune thyroid disease has been well established, but few studies have investigated the relationship of hypothyroidism and vitamin D level (10-12). Clinical manifestations of hypothyroidism include dry skin, cold intolerance and severe fatigue along with distinct laboratory findings in serum thyroid-stimulating hormone (TSH) levels greater than 5 mIU/L and serum T4 levels less than 4.5 µg/dL (13). Both vitamin D and thyroid hormones bind to a similar type of receptors, such as intracellular steroid hormone receptors, which may play important roles in the expression of various genes in metabolic pathways (14). In the present study, we aimed to assess vitamin D and serum calcium levels in patients with hypothyroidism and euthyroid subjects.

MATERIALS AND METHODS

This case-control study that was carried out between April and October 2015 on people with suspected hypothyroidism who were referred to the Kavosh laboratory (Gorgan, Iran). Based on results of thyroid tests, 175 subjects (75 men and 100 women) with hypothyroidism (TSH > 5 mIU/L and T4 < 4.5 µg/dL) were enrolled in the study. In addition, 175 euthyroid (0.5 < TSH < 5 mIU/L and 5 < T4 < 12 µg/dL) individuals (85 men and 90 women) were enrolled as a control group. The two groups were matched in terms of age. Informed written consent was taken from all subjects. The subjects had no history of thyroid disease or interfering chronic disorders and were not taking any medication or supplement that could alter thyroid hormones or vitamin D/calcium levels.

Serum 25-hydroxyvitamin D levels were measured by the Chemiluminescence immunoassay (CLIA analyzer Maglumi, China). A serum vitamin D level of ≥ 30 ng/ml was considered normal, while values lower than 20 ng/ml and in the 21-29 ng/ml range indicated vitamin D deficiency and vitamin D insufficiency, respectively (1, 15). Serum levels of TSH, T4 and free T3 were measured by Chemiluminescence immunoassay (Siemens Inc, Germany). Serum calcium levels were evaluated by a photometric method using an automated biochemistry analyzer (Mindray Medical International Limited, China). The Shapiro–Wilk test was used to evaluate normal distribution of data in both groups.

Comparison of variables between the two groups was made using the independent samples t-test and the Mann-Whitney U test. Pearson's bivariate correlation coefficient was performed to investigate the possible relationship of serum vitamin D and calcium levels with TSH, T4 and free T3 values. All statistical analyses were performed in SPSS software (version 16) and at a significance level of 0.05.

RESULTS

The mean age was 44.21±8.49 years in hypothyroid subjects and 43.19±8.54 years in euthyroid subjects (P=0.61). Serum level of 25-hydroxy vitamin D and calcium was significantly lower in hypothyroid patients than in euthyroid subjects (P<0.0001) (Table 1).

Table 1- Laboratory findings of the subjects in the two study groups

Parameters	Hypothyroid	Euthyroid	P-value
25-hydroxyvitamin D (ng/ml)	46.87±29.7	78.17±44.58	<0.0001
Calcium (mg/dL)	8.74±1.21	9.11±0.47	<0.0001
TSH (mIU/L)	8.72±2.32	1.95±1.1	<0.0001
free T3 (pg/ml)	1.06±0.45	1.14±0.36	0.006
Total T4 (µg/dL)	2.57±1.61	7.72±1.78	<0.0001

Table 2. Comparison of serum TSH, T4 and free T3 levels in hypothyroid patients based on vitamin D levels

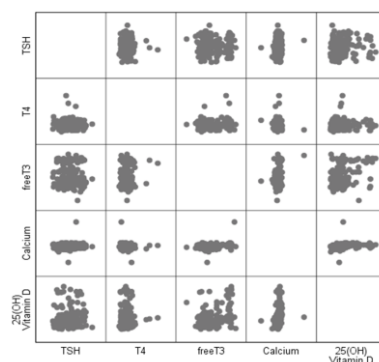
Parameters	Vitamin D deficiency	Vitamin D insufficiency	Vitamin D sufficiency	P-value
TSH (mIU/L)	8.79 ± 2.80	8.62 ± 2.26	8.73 ± 2.26	0.98
Serum T4 (µg/dL)	2.51 ± 0.91	2.49 ± 0.87	2.60 ± 1.26	0.98
Free T3 (pg/mL)	0.99 ± 0.49	0.76 ± 0.19	1.15 ± 0.47	<0.0001
Calcium	8.29 ± 0.71	8.28 ± 0.54	8.93 ± 1.35	<0.0001

Data are presented as mean ± standard deviation

Based on the vitamin D levels, the subjects were divided into vitamin D sufficiency, insufficiency and deficiency groups. Only free T3 was different among the hypothyroid patients (Table 2). Serum TSH in hypothyroid individuals did not differ significantly between men and women ($P=0.91$, CI= -0.66 - 0.74), while serum levels of 25-hydroxyvitamin D, calcium and free T3 differed significantly between men and women ($P<0.0001$ for all parameters).

There were positive and significant correlations between free T3 and serum 25-hydroxyvitamin D ($r=0.337$, $P<0.0001$) and calcium ($r=0.361$, $P<0.0001$) levels among hypothyroid patients. However, hydroxyvitamin D and calcium levels had no significant association with TSH and T4 levels (Figure 1). In euthyroid subjects, there was a positive correlation between serum 25-hydroxyvitamin D and free T3 levels ($r=0.168$, $P=0.026$).

Figure 1- Correlation analysis for laboratory parameters in hypothyroid individuals



DISCUSSION

The role of vitamin D in bone and minerals homeostasis has been well documented (16, 17). Recent studies have demonstrated the association between vitamin D deficiency and various disorders including cardiovascular disease, cancer, infection, obesity and osteoporosis (18-21). Vitamin D levels vary depending on the amount of vitamin D produced in the skin and dietary intake of vitamin D (2, 22). In the present study, vitamin D level differed significantly between the hypothyroid and euthyroid subjects. Numerous studies have addressed the role of vitamin D in the onset and progression of thyroid disorders. Tamer et al. reported a significant association between Hashimoto's disease and vitamin D

insufficiency, but found no significant correlation between overt or subclinical hyperthyroidism and vitamin D insufficiency (10, 11, 23). Studies on the possible association of vitamin D level and development of hypothyroidism have been limited and controversial (24, 25). In the present study, vitamin D, calcium and free T3 levels differed significantly between hypothyroid men and women but not among euthyroid individuals. Results of the studies on variation of serum 25-hydroxyvitamin D levels between men and women have been contradictory (26-28). In Muslim countries, vitamin D level is generally lower in women than in men, which is mainly due to wearing

hijab and social-religious behaviors. However, in a large-scale study in Iran, Heshmat et al. found no difference in vitamin D status between men and women (29).

We observed that only free T3 differed significantly between vitamin D deficient, insufficient and sufficient individuals. Moreover, free T3 was significantly correlated with vitamin D and calcium levels. Vitamin D and triiodothyronine receptors are both members of DNA-binding transcription factors family and can be activated by a low nanomolar concentration of lipophilic molecules as small as cholesterol (30). Several in vivo studies have reported a positive interaction between triiodothyronine and vitamin D in bone, calcium and vitamin D metabolism. In a study by Colston and Cleeve, treatment of vitamin D deficient rats with T3 improved intestinal absorption of vitamin D through alkaline phosphatase stimulation (31, 32). On the other hand, TSH, T4 and T3 secretion can be influenced by sex hormones, genetic Susceptibility and even environmental factors, which might be also involved in the relationship of vitamin D status with TSH, T4 and free T3 levels. Two possible mechanisms for the decreased vitamin D levels in patients with hypothyroidism are poor intestinal vitamin D absorption and improper vitamin D activation (32-34). Although vitamin D level was significantly lower among hypothyroid patients compared to euthyroid individuals, the mean level of vitamin D in hypothyroid patients was still within the sufficient range

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(≥ 30 ng/ml). Since the present study was conducted during spring and summer, it is likely that increased sun exposure might have a compensatory effect on vitamin D level of hypothyroid subjects.

CONCLUSION

Our findings indicated a significant positive correlation between serum free T3, vitamin D and calcium levels, suggesting that vitamin D might alter T3 secretion. In addition, vitamin D level was significantly lower among hypothyroid patients compared to euthyroid individuals, but the mean level of vitamin D in hypothyroid patients was still within the sufficient range. This suggests that reduced secretion of thyroid hormones might have a negative effect on the absorption or activation of vitamin D. However, a certain mechanism has not yet been suggested or approved. Given our findings, screening for vitamin D and calcium deficiency as well as vitamin D supplementation are strongly recommended for patients with hypothyroidism.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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