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ORIGINAL ARTICLE

The association between serum 25OHD levels and hypothyroid Hashimoto's thyroiditis

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Abstract
Background Vitamin D is shown to be a potent immunomodulator. Considering the potential role of low serum vitamin D levels in autoimmune disorder, we evaluated the association between Hashimoto's thyroiditis (HT) (with subclinical or overt hypothyroidism) and serum 25-hydroxyvitamin D (25OHD) levels in an Iranian population.
Methods A total number of 86 individuals were enrolled. The case group included 41 patients with hypothyroid HT (overt or subclinical). The control group comprised 45 healthy euthyroid persons. Serum 25OHD levels were measured in all subjects.
Results The case:control ratio of geometric means of 25OHD levels was 0.66 (95 % CI: 0.49–0.90; $P = 0.008$). There was a significant inverse association between serum 25OHD levels and HT (OR: 0.81 for 5 ng/ml increase in 25OHD level, 95 % CI: 0.68–0.96; $P = 0.018$). This association remained significant after adjustment for potential confounding factors including age, sex and BMI.
Conclusions Our study suggested that higher serum 25OHD levels was associated with decreased risk of HT so that each 5 ng/ml increase in the serum 25OHD levels results in 19 % decrease in odds of HT.

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Keywords 25-Hydroxyvitamin D · Hashimoto's thyroiditis · Hypothyroid (overt or subclinical)

Introduction

Vitamin D is an essential regulator of calcium homeostasis through its action in the kidney, intestine, bone and parathyroid gland [1]. Furthermore, It has been demonstrated that 1,25-dihydroxyvitamin D3, the active metabolite of vitamin D3, is also a potent immunomodulator [2]. 1,25-dihydroxyvitamin D3 inhibits cellular differentiation, proliferation and apoptosis. T cells and B cells are considered to be the target for the immunomodulatory effects of different forms of vitamin D [3].

Hashimoto's thyroiditis (HT) is the most common cause of thyroid gland dysfunctions in areas of the world where there is not an iodine deficiency in the diet. This disorder arises due to interactions between genetic and environmental factors and is characterized by reactivity to self-thyroid antigens [4]. In fact, in Hashimoto's disease and other autoimmune thyroid disorders there is a hereditary susceptibility to thyroid disease that allows the survival of T cells and B cells towards thyroid antigens [5].

It has been shown that vitamin D deficiency is associated with autoimmune diseases, including systemic lupus erythematosus [6, 7] multiple sclerosis [8, 9] and type 1 diabetes [10, 11]. Furthermore, some studies, recently reported that patients with HT had lower vitamin D levels [12–14].

Considering the potential role of low serum vitamin D levels in autoimmune disorder, we attempted to evaluate the association between Hashimoto's disease (with subclinical or overt hypothyroidism) and serum 25-hydroxyvitamin D (25OHD) levels in a sample of Iranian population.

Materials and methods

A total number of 86 individuals were enrolled in this cross-sectional study. The case group included 41 persons who diagnosed as HT with hypothyroidism (7 with overt hypothyroidism, 34 with subclinical hypothyroidism) in the endocrine clinic of Imam Reza Hospital during the autumn months of 2012. HT was documented with high titers of serum anti-thyroid peroxidase antibodies. The control group comprised 45 healthy euthyroid persons. Subjects with history of other autoimmune disease, diabetes, malignancy, chronic renal or liver disease were excluded. Furthermore, subjects who took vitamin or calcium supplements and medications that may interfere with serum levels of 25OHD were not included in this study. All participants gave informed consent.

Serum concentrations of 25OHD, calcium, phosphorus, T4, T3 and TSH were measured in control group and case group before the start of treatment. Serum 25OHD levels were measured using a semi-automated solid-phase extraction reverse-phase high-performance liquid chromatography assay. The levels of TSH were determined using ELISA method (Enzaplate N-TSH, Ciba Corning Japan). Anti-thyroid peroxidase (anti-TPO) antibodies were also measured using commercially available ELISA kits in the case group in the same laboratory. Subjects with Anti-TPO >35 IU/mL were considered as "positive" for thyroid autoimmunity.

Anthropometric parameters were obtained while the subject was standing erect and barefoot. Height and weight were determined using standardized conventional methods. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

Statistical methods

By studying 41 cases and 46 controls, the study has a power of 90 % to detect a mean difference in 25OHD of 13.3 ng/ml between case and control groups at the 5 % significance level, assuming the standard deviations of 25OHD to be 10.4 and 25.5 ng/ml in case and control groups, respectively [12]. Continuous variables are presented as mean (standard deviation), and categorical variables are shown as proportions (percentages). Categorical vitamin D variable was defined based on serum 25OHD levels as follows: (a) Normal: serum 25OHD levels >30 ng/ml, (b) vitamin D insufficiency: serum 25OHD levels between 20 ng/ml and 30 ng/ml, (c) vitamin D deficiency: serum 25OHD levels lower than 20 ng/ml. The associations between continuous and categorical vitamin D variables and HT were tested using independent *t* test and Chi-squared test, respectively. The linear associations between 25OHD on the log scale and the logarithm of the variables anti-TPO and TSH in the case group were presented as Pearson correlation coefficient. The association between 25OHD and HT was summarized as (a) case:control ratio of 25OHD geometric means of 25OHD levels (95 % confidence interval): As the distribution of 25OHD was positively skewed, the 25OHD variable was log-transformed and the mean difference in log-25OHD between case and control groups was estimated and then antilogged to derive the geometric means ratio, (b) the odds ratio (95 % confidence interval) for HT per 5 unit increase in 25OHD: this is estimated using a simple logistic regression model with HT as the response variable and 25OHD as an explanatory variable. Both fractional polynomials and LOWESS (locally weighted scatter plot smoothing) algorithm (Fig. 1) suggest that including 25OHD as a linear term in the logistic regression model provides a descent fit, and (c) odds ratios (95 % confidence intervals) between normal group and vitamin D insufficiency, and between normal group and vitamin D deficiency. Multiple logistic regression model was used to estimate odds ratios in (b) and (c) adjusted for potential confounding variables including age, sex and BMI. All analyses were performed using STATA version10 (Stata Corporation, College Station, TX).

Results

Demographic and clinical characteristics of the study participants are presented in Table 1. The case:control ratio of geometric means of 25OHD levels was 0.66 (95 % CI: 0.49–0.90; $P = 0.008$). There was a significant inverse association between serum 25OHD levels and HT (OR: 0.81 for 5 ng/ml increase in 25OHD levels, 95 % CI: 0.68–0.96; $P = 0.018$). This association remained

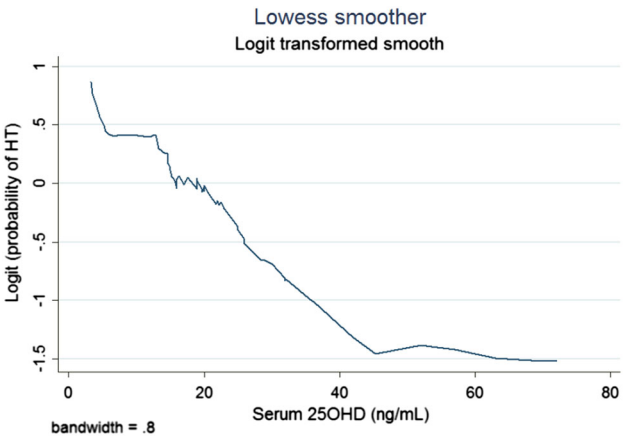

Fig. 1 The LOWESS regression curve for the association between HT and 25OHD

Table 1 Clinical and demographic characteristics of subjects

Variable	Case ($n = 41$)	Control ($n = 45$)	P value**
Age (years)	42.3 (15.3)	39.2 (12.9)	0.32
Sex (female), n (%)	34 (83)	33 (73)	0.28
BMI (kg/m^2)	27.1 (4.7)	26.8 (4.7)	0.79
TSH (mIU/l)	18.1 (20.1)	2.3 (1.5)	<0.001
25OHD (ng/ml)	15.9 (12.1)	24.4 (17.3)	0.008

Mean (SD), except where otherwise indicated

** Based on Chi-squared test for sex and independent t tests for other variables; TSH and 25OHD are log-transformed before testing

Table 2 Multiple logistic regression model for HT

Variable	OR (odds ratio)	95 % CI	P value
Age (years)	1.02	0.99–1.06	0.17
Sex	0.77	0.24–2.42	0.65
BMI (kg/m^2)	1	0.91–1.10	0.99
25OHD (ng/ml)	0.80	0.66–0.97	0.02

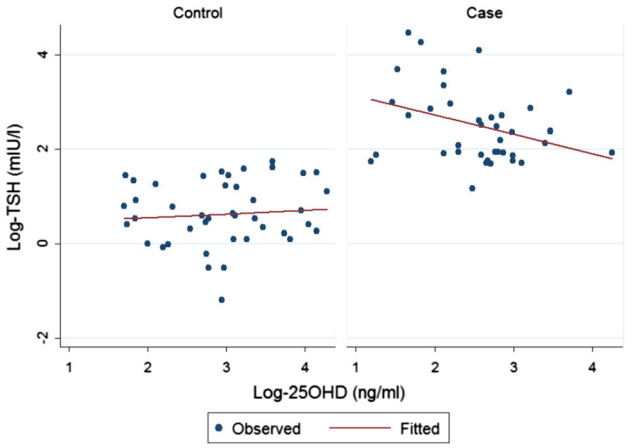

Fig. 2 The scatter plots between log-TSH and log-25OHD and fitted regression lines in case and control groups

significant after adjustment for potential confounding factors including age, sex and BMI (Table 2).

There was no significant correlation between serum 25OHD and anti-TPO levels (on the log scales) among the case group (Pearson $r = -0.06$; $P = 0.73$). Serum 25OHD and TSH levels (on the log scales) were negatively correlated among the case group (Pearson $r = -0.34$; $P = 0.03$), but not among the control group (Pearson $r = 0.08$; $P = 0.61$). Figure 2 shows the scatter plots between serum TSH and 25OHD levels (on the log scales) and fitted regression lines in case and control groups.

The frequency distributions of the categorical vitamin D variable among case and control groups are shown in Table 3. The categorical vitamin D variable was associated with HT (Chi-squared $P = 0.014$). The odds ratios for vitamin D deficiency and vitamin D insufficiency groups relative to normal group were 0.82 (95 % CI: 0.15–4.63; $P = 0.83$) and 3.90 (95 % CI: 1.11–13.70; $P = 0.034$), respectively.

Table 3 Frequency distribution of the categorical vitamin D in study subjects

	Case ($n = 41$)	Control ($n = 45$)	Total
Normal	4 (10)[a]	11 (24)	15 (17)
Vitamin D insufficiency	3 (7)	10 (22)	13 (15)
Vitamin D deficiency	34 (83)	24 (53)	58 (67)

[a] n (%)

Discussion

The relationship between the serum 25OHD levels and autoimmune disorder has been the subject of many recent studies [12–14]. In this study, we investigated the association between the serum 25OHD levels and Hashimoto's disease with hypothyroidism (overt or subclinical) in an Iranian population. Our study suggested that higher serum 25 hydroxyvitamin D levels were associated with decreased risk of HT after adjustment for potential confounding factors, so that each 5 ng/ml increase in the serum 25OHD level results in about 20 % decrease in HT.

Although there is no consensus on the optimal serum 25OHD levels for skeletal health, many experts agree that levels lower than 20 ng/mL are suboptimal for skeletal health, and in addition, optimal serum 25OHD concentrations for extraskeletal health have not been established. As mentioned above, we classified subjects into three groups based on 25OHD levels in this study. The odds of HT in the vitamin D deficiency group (serum 25OHD levels lower than 20 ng/ml) were significantly (about fourfold) higher than the odds of in the normal group, but the subjects with vitamin D insufficiency (serum 25OHD levels between 20 ng/ml and 30 ng/ml) were not at greater risk of disease than the normal subjects. The latter is probably an artifact of small sample sizes in normal and vitamin D insufficiency groups, as suggested by LOWESS regression curve shown in Fig. 1. The figure indicates that the logit of HT generally decreases with vitamin D levels.

Regarding the association of serum 25OHD levels with Hashimoto's disease, our findings are in agreement with most of the previous studies. Tamer and colleagues [12] reported lower serum vitamin D levels in patients with HT compared to healthy subjects. In a similar study, Kivity et al. showed that vitamin deficiency (serum 25OHD levels below 10 ng/ml) was higher in patients with HT compared

to control subjects [13]. A recent study in a Turkish population showed that serum 25OHD levels of patients with HT were lower than that of controls and severity of vitamin D deficiency was correlated with the duration of HT, thyroid volume and antibody levels. Moreover, this study showed that subjects with HT treated with levothyroxine had the lowest serum 25OHD levels [14]. In contrast, Effraimidis et al. [15] did not find any association between low 25OHD levels and early stages of thyroid autoimmunity in a cohort of euthyroid subjects with genetic susceptibility for autoimmune thyroid disease.

There was a positive correlation between serum TSH and serum 25OHD levels in patients with HT. However, we did not find any correlation between serum anti-TPO and 25OHD levels. The latter is inconsistent with two previous studies in Turkish and Indian populations, which showed an inverse correlation between 25OHD and anti-TPO [14, 16]. Although in Hashimoto's disease, anti-TPO may be complement-fixing and cytotoxic, the thyroid gland is infiltrated by both B cells and T cells and cell-mediated autoimmune mechanisms are involved [17].

In summary, our data provide the first evidence for an association between low serum vitamin D levels and decreased risk of Hashimoto's disease with hypothyroidism (subclinical or overt) in an Iranian population. The main limitation of our study is that the observed association between vitamin D and HT cannot be interpreted as the causal effect of vitamin D on HT due to cross-sectional data. The low serum vitamin D levels may be a consequence of HT rather than its risk factor. This is particularly important since overt HT may be associated with malabsorption. Another limitation of the study is the low precision of the study estimates of the odds ratios for HT per unit increase in 25OHD or between vitamin D deficiency and HT, even though they are statistically significant at 5 % level. For example, 95 % confidence limits of 1.11 and 13.70 for the odds ratio between vitamin D deficiency and HT indicate that data are compatible with a very small to a large association between vitamin D deficiency and HT. Large cohort studies are needed to precisely estimate the causal effect of low serum vitamin D levels on the HT.

Conflict of interest The authors declare no conflict of interest.

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