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Research Article

Association of Vitamin D Deficiency and Thyroid Function in Postmenopausal Women

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Abstract

Pupose: Although there are reports of vitamin D (VitD) insufficiency in immune-mediated hypothyroidism, an association between VitD and thyroid-stimulating hormone (TSH) levels has yet to be shown. We aim to examine VitD and TSH levels among postmenopausal women, as both conditions are more prevalent in elderly women.

Methods: The clinic records of postmenopausal women during their routine maintenance visits were reviewed. All patients were examined for the symptoms related to thyroid function and osteoporosis. Participants were divided into three subgroups according to their TSH levels (below <0.5 mIU/L, 0.51-4.0 mIU/L and >4.0 mIU/L). Patient characteristics and VitD levels were compared between these subgroups. Multivariate linear regression model was constructed using serum VitD and serum TSH as the dependent variables to identify factors independently associated with these laboratory values.

Results: Two-hundred and nighty nine postmenopausal women were included. Average age was 62.2±7.5 years old. VitD was insufficient (10-30 ng/mL) in 12.0% and deficient (<10 ng/mL) in 60.9% of the participants. In 11.3%, TSH was low and in 7.6% of women, TSH was high, while the remaining 80.1%, had normal TSH levels. Subjects with low TSH had significantly higher VitD concentrations (34.2±29.1 ng/mL) compared to the other two groups (P-value: 0.039). In multivariate regression analysis, TSH was not a contributing factor, as age was the only significant predictor of VitD levels. Meanwhile, no predictor (including age and VitD) was identified for TSH levels in linear regression analysis.

Conclusion: Age was the only independent predictor of serum VitD in this study population. Though suppressed TSH was associated with higher VitD levels, the association was not linear between TSH and VitD in postmenopausal women.

Introduction

Vitamin D (VitD) insufficiency is present in over half of population worldwide.[1] It has been long known that VitD insufficiency contributes to development of osteopenia and osteoporosis.[2-4] As the VitD receptors are present in all human cells regardless of their different embryologic origins, several studies have focused on the extra-skeletal effects of VitD and the way it affects general health of patients.[5] In addition to the limited oral intake and age-related decline in its absorption, decreased exposure to sunlight is among the leading causes of VitD insufficiency in women.[6] Age-related changes that contribute to the reduced serum levels of this vitamin are mediated through the attenuation of hypodermal synthesis of VitD precursor, as well as reductions in alimentary absorption of cholesterol-based provitamin molecules in daily nutritional intake.[7]

VitD insufficiency has been implicated in increasing prevalence of autoimmune diseases, including type I diabetes mellitus,[8] rheumatoid arthritis[9] and systemic lupus erythematosus.[10-12] On the other hand, immune-mediated pathophysiology comprises the major etiology of hypothyroidism in iodine-replete areas.[13] Moreover, aging is linked to the increased prevalence of subclinical forms of hypothyroidism.[14-16] Interestingly low VitD levels is reported in patients with hyperthyroidism presumably due to the acceleration of its metabolism.[17] Studies have yielded conflicting results on the frequency of VitD insufficiency among patients with an ongoing autoimmune process in humans. VitD levels have been found to be lower in patients with autoimmune thyroid disorders compared to the healthy volunteers in one study.[18] Yet, other studies have not yielded similar results.[19]

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VitD insufficiency is very common among women in the geographic region where this study is conducted.[20] In view of these conflicting reports, we aim to examine the association between serum levels of VitD and thyroid stimulating hormone (TSH) among postmenopausal women. We hypothesize that serum levels of VitD would be lower in postmenopausal women with elevated serum concentrations of TSH presumably due to the diminished synthesis.

Materials and Methods

Inclusion and Exclusion criteria

The clinic records of all postmenopausal women who presented to the primary care clinic for routine check up visits between January and April 2008 were screened by a member of research team for the availability of serum levels of VitD and TSH. Patients who had simultaneous measurements during this period were considered for enrollment. They were enrolled only if they had been postmenopausal for at least past 48 consecutive months. Patients older than 80 years, and those with diabetes mellitus, rheumatoid arthritis, chronic kidney disease with an estimated glomerular filtration rate < 60 mL/min/1.73 m^2, hypo or hyperparathyroidism, cirrhosis, malnutrition and malabsorption were excluded.

Study variables

Data regarding participant's age, age at menopause, body mass index (kg/m^2), number of pregnancies, and smoking status were recorded. Additionally, the findings of physical examination were reviewed and information on vital signs, presence of peripheral edema, hoarseness and tremor were recorded in the research database. Nutritional information on daily intake of dairy products, calcium supplementation, medications and exposure to sunlight were also recorded.

Laboratory analysis

TSH levels between 0.5-4.0 mIU/L were regarded normal.[21] Subjects with serum 25-OH VitD levels below 10 ng/ml were considered 'deficient', whereas those with levels between 10-30 ng/ml were considered 'insufficient'. VitD levels > 30 ng/ml were considered 'sufficient'. Participants were divided to three subgroups according to their TSH level (below <0.5 mIU/L, 0.51-4.0 mIU/L and >4.0 mIU/L).[22]

Statistical Analysis

All pertinent clinical and laboratory information were entered to SPSS version 22.0 (IBM®, Chicago, IL). Descriptive analysis was performed to compare the patients after they were grouped based on their serum TSH concentrations. Categorical data were analyzed using chi square test (degree of freedom = 2) and reported with 95% confidence interval (CI). Numerical variables were analyzed using two-tailed one-way analysis of variance (ANOVA) with Bonferroni correction for post hoc inter-group comparisons. These data were presented as mean ± standard deviation (SD). Linear regression analyses were performed to examine the factors that predicted serum concentrations of VitD. Multivariate linear regression model was constructed using serum VitD and serum TSH as the dependent variables and factors with either a P-value less than 0.15 in the univariate analysis or a previously reported association with either VitD or TSH as independent variables. Null hypotheses were rejected where p values were less than 0.05.

Results

A total of 299 participants were included in this study. Average age of the study population was 62.2±7.5 years. Expectedly, only 27.1% of the population had normal serum VitD level. Overall, 12.0% had VitD insufficiency and 60.9% had VitD deficiency. In 34 (11.3%) of the cases, TSH was lower than 0.5 mIU/L and in 242 (81.0%) TSH was within normal reference range. Abnormally high levels of TSH (>4.0 mIU/L) were reported in 23 (7.7%) subjects. Table 1 summarizes the characteristics of the three subgroups of study population according to their serum TSH level. Serum VitD level was significantly different among the study subgroups (P = 0.039). In post hoc analysis, it was determined that subjects with TSH levels <0.5 mIU/L had significantly higher VitD concentrations (34.2 ± 29.1 ng/mL) compared to subjects with normal TSH levels (22.9 ± 23.9 ng/mL; P= 0.032) and those with elevated TSH concentrations (17.5 ± 11.0 ng/mL; P = 0.030). However the difference in serum VitD concentrations was not significant between subject with normal and those with elevated TSH levels (P = 0.892).

In order to identify the independent factors affecting VitD levels, a multivariate linear regression model was constructed using the serum VitD concentrations as the dependent factor. The constructed model is shown in Table 2. Age was the only independent predictor of VitD levels (correlation coefficient: 0.681, CI: 0.112-1.250; p-value = 0.019), whereas serum TSH levels were not found to be an independent predictor of VitD concentrations. The second linear regression analysis using serum TSH concentrations as the dependent variable was performed with age, age at menopause, serum VitD, current smoking, BMI and number of pregnancies as independent variables. In the constructed model, neither age nor VitD was found to be independent predictors of serum TSH level (Table 3).

Table 1. Distribution of patients based on TSH categories of suppressed TSH, normal TSH and elevated TSH

-	TSH < 0.5	TSH 0.51-4.0	TSH > 4.0	Total	P-Value
	N = 34	N = 242	N = 23	N = 299	
Age (year)	63.2 ± 5.1	63.3 ± 4.8	64.0 ± 4.6	63.4 ± 4.8	0.678
Age at Menopause (year)	46.1 ± 6.3	46.6 ± 5.3	46.9 ± 4.4	46.5 ± 5.3	0.862
Body Mass Index (Kg/M^2)	27.4 ± 5.1	28.0 ± 5.0	29.9 ± 5.4	28.1 ± 5.1	0.178
Current Smoking	0.0%	1.2%	4.3%	1.3%	0.381
Number of Pregnancies	7 [3-11]	6 [1-14]	5 [1-12]	6 [1-14]	0.351
Weight Loss > 10%	17.6%	12.4%	0.0%	12.0%	0.033
Adequate Sun Exposure	0.0%	1.7%	4.3%	1.7%	0.398
Supplemental Calcium Intake	14.7%	16.1%	30.4%	17.1%	0.250
History of Bone Fracture	32.4%	18.6%	39.1%	21.7%	0.030
Evidence of Osteoporosis	5.9%	3.3%	4.3%	3.7%	0.745
Heart Rate (beats/min)	79.1 ± 6.8	79.4 ± 6.3	80.1 ± 6.9	79.4 ± 6.3	0.823
Systolic Blood Pressure (mmHg)	129 ± 22	131 ± 21	128 ± 24	130 ± 21	0.772
Diastolic Blood Pressure (mmHg)	80 ± 14	81 ± 14	80 ± 13	81 ± 14	0.920
Tremor	14.7%	7.4%	13.0%	8.7%	0.318
Peripheral Edema	8.8%	10.3%	17.4%	10.7%	0.579
Hoarseness	5.9%	4.5%	4.3%	4.7%	0.943
Normal Vitamin D	38.2%	26.4%	17.4%	27.1%	0.039
Vitamin D Insufficiency	23.5%	10.3%	13.0%	12.0%	-
Vitamin D Deficiency	38.2%	63.2%	69.6%	60.9%	-
Serum Vitamin D ng/mL	34.2 ± 29.1	22.9 ± 23.9	17.5 ± 11.0	23.8 ± 24.1	0.016

Table 2. Linear regression analysis using serum vitamin D3 concentrations as the dependent variable. Age was the only significant factor, which significantly predicted serum vitamin D3 levels. TSH: Thyroid Stimulating Hormone

Regression Model	Coefficients	Std. Error	P-Value	95.0% Confidence	Interval
TSH (mIU/L)	-0.06	0.21	0.77	-0.47	0.35
Age (year)	0.68	0.29	0.02	0.11	1.25
Age at Menopause (year)	-0.21	0.26	0.43	-0.71	0.30
Frequent Sun Exposure	-15.83	10.65	0.14	-36.79	5.13
Current Smoking	-15.63	11.84	0.19	-38.94	7.68
Calcium Supplementation	2.94	3.79	0.44	-4.52	10.41
Dairy Product used at least once a day	0.68	2.04	0.74	-3.34	4.71

Table 3. Linear regression analysis using serum concentrations of thyroid stimulating hormone (TSH) as the dependent variable.

Model	Coefficients	Std. Error	P-Value	95.0% Confidence	Interval
Age (year)	0.12	0.10	0.25	-0.08	0.32
Age at Menopause (year)	0.03	0.09	0.78	-0.15	0.20
Current Smoking	0.71	3.72	0.85	-6.62	8.05
Serum Vitamin D3 (ng/mL)	0.00	0.02	0.92	-0.04	0.04
Body Mass Index (Kg/M^2)	0.01	0.09	0.92	-0.17	0.19
Number of Pregnancies	-0.11	0.18	0.56	-0.47	0.26

Discussion

Expectedly, VitD inadequacy was found to be very common in the current study. As the main finding of this study, suppressed levels of TSH have been associated with higher VitD levels, though no linear association between TSH and VitD has been noticed in postmenopausal women. Though higher levels of VitD in women with suppressed TSH levels might presumably be due to an increased absorption of VitD in hyperthyroid state, the concept has not been studied. Thyroid disorders are more common in women by 5–10 times,[23] while their frequency increases with age.[15]

Accordingly, the linkage between VitD and the function of thyroid gland is best to be examined among the postmenopausal women. TSH is a physiologic indicator of thyroid function and its elevated level is particularly the most sensitive screening test for hypoactive thyroid function.[23] The linkage between these two prohormonal molecules may be viewed from two different angles.

VitD is an omnipotent regulator of the innate immunity, and inadequate serum levels of this vitamin have been linked to autoimmune reactions.[24] In patients with systemic lupus, a decrease in the amount of immunoglobulin produced by B cells once the cells are pre-incubated with VitD have been observed.[25] VitD suppresses interleukin (IL-12) production, which is a type-1 cytokine that polarizes T-helper lymphocytes. As a result of IL-12 suppression, there is a shift toward type-2 T-helper (TH2) responses that include expression of IL-4, IL-5, IL-6 and IL-10.[26] TH2 response is a much stronger activator of B-cells leading to antibody secretion, particularly IgE responses in type-1 hypersensitivity reactions. VitD exerts its effect by binding to VitD receptor, which is present on many cells of immune system, and thereby regulating the activity of the immune cells. Individuals with genetic polymorphisms of these receptors are particularly prone to autoimmune thyroid disorders.[27] Moreover, the association between autoimmune thyroid disorders such as Hashimoto's disease and Grave's disease with low levels of VitD has been described.[28,29] In one report, the frequency of VitD deficiency is higher among patients with autoimmune thyroid disorders compared to those with non-autoimmune thyroid problem or healthy controls.[18]

Metabolism of VitD is also reciprocally regulated by thyroid hormones. Provitamin D3 is synthesized from 7-dehydrocholesterol and the enzymatic reaction takes place principally in keratinocytes located in the basal and spinous strata of the epidermis layer.[30] On the other hand, thyroid hormone exerts important effects on skin. Histologic examination of the skin in hypothyroid patients has shown changes indicative of epidermal thinning and hyperkeratosis.[31] There is a strong suggestion that the epidermal barrier function is probably impaired in hypothyroidism with a speculation that synthesis of VitD is decreased in patients with overt hypothyroidism and high TSH.[32] One would have expected an association between elevated levels of TSH and reduced VitD depots. However we did not observe such an association probably due to the relatively low number of patients with high TSH, and lack of cases with very high TSH levels.

In the multivariate linear regression model constructed using serum VitD and serum TSH as the dependent variables, age is identified as the only independent predictor of VitD level in the present study. It has been shown that serum levels of VitD decrease with age. The decrease in serum VitD level is more pronounced in women and the decline is noticed to start in perimenopausal phase.[33] Unexpectedly, age has shown a positive correlation with VitD level in our population. As such as the study population grow older the serum concentrations of VitD increase. We speculate that the observation is due to the fact that our population consists of post-menopausal women with a tendency to include subjects in the seventh decade of their lives (average 63.4 ± 4.8 years old). Interestingly in two other reports from the same region as the current study, higher levels of VitD have been reported in older women in comparison with their younger counterparts.[34,35] This could be due to the higher rate of consumption of VitD supplements in this age group.

The study is limited by its retrospective design. Though TSH is the initial test for evaluation of hypoactive thyroid function, further tests are needed to objectively determine the overall function of this gland. As other laboratory indicators of thyroid function such as serum levels of free T3 and T4 are missing, it is impossible to examine the direct effects of thyroid hormones on serum VitD. Additionally, the sporadic availability of anti-thyroid peroxidase antibody measurement in our patient population makes it difficult to comment on autoimmune nature of thyroid disorders affected by VitD inadequacy.

Conclusion

VitD inadequacy is very common in postmenopausal women in the region the study took place. Though suppressed TSH was associated with higher VitD levels, the association was not linear between TSH and VitD among postmenopausal women where age is the only independent predictor of serum VitD concentrations. This linkage between VitD and TSH levels may be merely an association and this study like several others does not add much information to the causality of the observation. Prospective longitudinal studies with larger subject numbers and more comprehensive measurement of thyroid function along with examining the indicators of innate immunity may shed light into the underlying pathophysiology and mechanisms involved in the interaction between thyroid function and VitD metabolism.

Ethical Issues

The study design and the informed consent process were reviewed and approved by the Research Ethics Committee at Tabriz University of Medical Sciences. The study was exempted from written informed consent process due to its retrospective design and non-interventional nature of the study protocol. The study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects. Patient identifiable information was handled cautiously to maintain patient privacy.

Conflict of Interest

The authors declare no conflict of interests.

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