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No Association between 25 (OH) Vitamin D Level And Hypothyroidism among Females

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Abstract

AIM: The aim was to investigate serum vitamin D (25-OH) level among females with hypothyroidism.

MATERIALS AND METHODS: A case-control study (58 in each arm) was conducted in Arar Central Hospital, Kingdom Saudi Arabia. The cases were females with hypothyroidism, and healthy females were controls. TSH, thyroid hormones: Free T3 (FT3) and Free T4 (FT4) and haemoglobin levels were measured in all participants. Serum vitamin D (25-OH) level was measured using the spectrophotometry.

RESULTS: While there was no significant difference in the age and haemoglobin level, body mass index (BMI) was significantly higher in the cases. Compared with the controls, cases had significantly higher TSH, had significantly lower T4, and there was no significant difference in FT3 and 25 (OH) vitamin D, [16.1 (8.8-26.7) vs. 14.0 (9.5-20.3 ng/ml; P = 0.577]. Linear regression showed no association between, age, BMI, haemoglobin, TSH, FT3, FT4 and the log of 25 (OH) vitamin D levels.

CONCLUSION: There was no significant difference in vitamin D level among females with hypothyroidism and healthy controls.

Introduction

Vitamin D deficiency is a global health problem where over a billion people worldwide have some vitamin D deficiency or insufficiency [1, 2]. The essential biological action of vitamin D is the regulation of calcium and phosphorus metabolism. Though the role of vitamin D in the regulation of immune system has recently been reported [3, 4]. Hypothyroidism is a common disease in the general population, most of which results as consequences of Hashimoto's thyroiditis with a tendency to increase with age and female are at 8 to 15 times at higher risk than men [5]. It has been observed that serum Vitamin D3 metabolites are elevated in hypothyroid subjects [6].

However, a reduced level has been reported in a patient with over-active thyroid gland [7]. Thyroid disorders may affect vitamin D status as subnormal levels of vitamin D were observed in a patient with Graves' disease [8]. The role of vitamin D is explored as an anti-inflammatory, anti-proliferative factor and association with many clinical disorders [9, 10]. Vitamin D has a direct and indirect role in inhibiting the production of cytokines (IL-12 and IFN-c), hence, enhances the immune and anti-inflammatory responses [11].

Vitamin D is circulating in the blood attached to a D-binding protein. Then hydroxylation takes place at the liver and the kidneys to produce 25(OH) D and the active metabolite, 1, 25 dihydroxy vitamin D (1, 25-(OH) 2 D) respectively [12]. The active form of vitamin D is called calcitriol or 1, 25-dihydroxyvitamin D3. Serum 25(OH) D is used to reflect vitamin D status because it is the major circulating precursor of active vitamin D and has a half-life, ranging from two to three weeks.

Interestingly, 1, 25-(OH) vitamin D has a short circulating half-life and is tightly under the influence of

parathyroid hormone, calcium and phosphate [13]. Moreover, low level of serum 1, 25-(OH) 2D may not observe until vitamin D deficiency is severe [14]. Hence 25(OH) level is used to assess vitamin D reserve. Vitamin D has a vital role in many physiological actions and an association with some clinical disorders.

Hence the current study was conducted to investigate serum vitamin D (25-OH) level among Saudi females with hypothyroidism.

Material and Methods

A case- control study was conducted at Arar Central Hospital, Kingdom of Saudi Arabia during the period 1st of November 2014 to 1st of May 2015. Cases were women with hypothyroidism. Moreover, those who had symptoms suggestive of hypothyroidism e.g. fatigue, cold intolerance, constipation, weight gain, dry skin and menstrual disturbance or those who had sounding features: puffy, hoarseness, depressed mood and bradycardia were screened and enrolled as new cases if proofed to have hypothyroidism. The cases were diagnosed by the high level of TSH (≥ 6.30 miU/L) with lower levels of FT3 and FT4 than normal value. The controls were healthy females. Those with chronic medical diseases, on vitamin D supplementation, children, pregnant females and non-Saudi citizen, were excluded.

Ethical approval was obtained from medical education and research centre at Arar Central Hospital, KSA.

After signing an informed consent, height and weight were measured using the conventional method and were used to calculate the body mass index (BMI) by using the formula: weight in kilogrammes (kg) divided by height in square meters (m^2).

Blood (5 ml) was withdrawn, kept for 30 minutes at the room temperature to clot and centrifuged for five minutes. Then TSH, FT3 and FT4 were measured using commercially available kits (Roche Diagnostics, Mannheim, Germany). Reference values for normal range of TSH (0.48 – 6.30 mU/l), FT3 (3.39-5.82, pmol/l) and FT4 (9.00-17.15, pmol/l) [15].

The 25-hydroxy vitamin D (25 (OH) vitamin D) was measured using spectrophotometry. The normal level of 25 (OH) D is 30 ng/ml or above [16]. Haemoglobin (Hb) level was checked too.

Fifty-eight participants in each arm of the study were calculated as to have the difference in the mean level of thyroid hormones and 25 (OH) vitamin D between the two groups and to have over 80% power to detect a difference of 5% at $\alpha = 0.05$. We assumed that 10% of participants might not respond or have incomplete data.

Statistical analysis

Data was analysed using the Statistical Package for the Social Sciences (SPSS) version 22 (Chicago, IL, USA). Chi-square test was used to compare proportions between the two groups. Kolmogorov –Smirnov test was used for testing the normality of the data. Student's t-test and Mann-Whitney test were used to compare the continuous parametric and non-parametric (thyroid hormones and 25 (OH) vitamin D) data, respectively between the two groups. Simple linear regression models with the log of 25 (OH) vitamin D as a continuous dependent variable was used. Socio-demographic character-critics, BMI, and thyroid hormones levels were the independent predictors of interest. A p value of <0.05 was considered significant.

Results

While there was no significant difference in the mean (SD) of age [34.1 (13.2)] vs. [37.3 (10.2) years, P =0.140] and haemoglobin [12.2 (1.4) vs. 12.6 (1.4) g/dl, P= 0.192] levels between the two groups, BMI was significantly higher in the cases compared with the controls, [33.2 (6.2) vs. 30.2 (6.1, kg/m^2, P=0.01], Table 1.

Table 1: **Comparing the mean (SD) of the age, body mass index and haemoglobin level between the cases and the controls**

Variables	Cases (*n* = 58)	Control (*n* = 58)	P
Age, years	34.1 (13.2)	37.3 (10.2)	0.140
Body mass index, k/m^2	33.2 (6.2)	30.2 (6.1)	0.010
Haemoglobin, g/dl	12.2 (1.4)	12.6 (1.4)	0.192

Compared with the controls, cases had significantly higher TSH, had significantly lower FT4, and there was no significant difference in FT3 (4.7 (3.8 -5.4) vs. 4.5 (3.9 ─ 5.3) pmol/l, P=0.685) and 25 (OH) vitamin D, 16.1(8.8─ 26.7) vs. 14.0 (9.5─ 20.3ng/ml; P= 0.577], Table 2, Figure 1.

Table 2: **Median (interquartile) of thyroid hormones and 25 (OH) vitamin D level in the cases and controls**

Variables	Cases (*n*= 58)	Control (*n*= 58)	P
TSH ,miU/l	4.9 (2.0 ─ 9.5)	2.2 (1.1─ 3.4)	< 0.001
FT3, pmol/l	4.7 (3.8 ─ 5.4)	4.5 (3.9 ─ 5.3)	0.685
FT4, pmol/l	13.3 (11.1─15.0)	14.0 (12.0─ 15.7)	0.028
25 (OH) vitamin D, ng/ml	16.1(8.8─ 26.7)	14.0 (9.5─ 20.3)	0.577

Linear regression showed no association between, age, BMI, haemoglobin, TSH, T3, T4 and the log of 25 (OH) vitamin D levels, Table3.

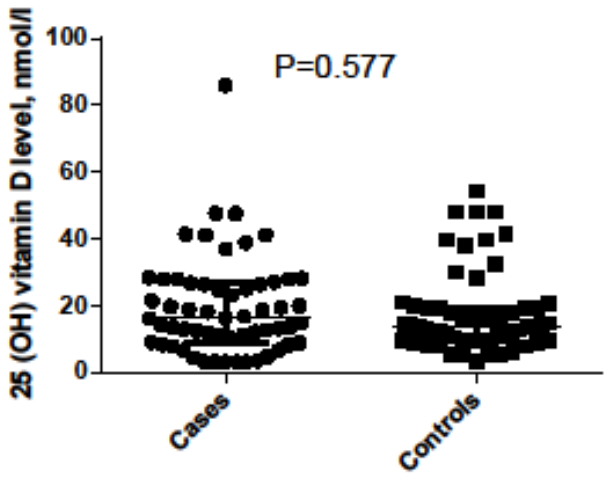

Figure 1: Median (interquartile) of 25 (OH) vitamin D level in the cases and the controls

Discussion

The main finding of the current study was a non-significant difference in the level of vitamin D among the women with hypothyroid compared to the control. This goes with Goswami et al., findings where they observed no significant difference between autoimmune thyroid disorders (AITD) and vitamin D levels [17]. Likewise, a non-significant association between vitamin D deficiency and autoimmune thyroid disorders (AITD) has been previously reported [18]. The aforementioned observation was further consolidated by a similar finding in hypothyroidism as the Hashimoto thyroiditis induced and Non-Hashimoto thyroiditis [18, 19].

Table 3: **Factors affecting log of 25 (OH) vitamin D level using multiple linear regression analysis**

Variables	Coefficient	Standard error	P
Age, years	0.003	0.003	0.189
Body mass index, kg,m^2	0.002	0.005	0.608
Haemoglobin, g/dl	0.013	0.021	0.525
TSH, miU/l	-0.002	0.008	0.814
FT3, pmol/l	0.000	0.034	0.998
FT4, pmol/l	− 0.001	0.011	0.913
Case (hypothyroidism) versus controls	0.023	0.068	0.741

The non-significant difference of low vitamin D level among both groups may be explained by the higher prevalence (61.5% to 83.6%) of vitamin D deficiency among Saudi population perhaps due and inadequate exposure to sensible sunlight or females are wearing black outer cloak which may reduce the benefit of sensible sunlight [20-22].

A significant correlation between vitamin D and hypothyroidism among female participants has recently been documented [23, 24]. Moreover, a recent study showed, the serum 25-OH vitamin D levels were significantly lower in a group of hypothyroid cases compared to healthy controls [25]. Some different studies documented a significant negative association between vitamin D levels in patients with Hashimoto's thyroiditis compared to the control group [1, 6, 26-31]

Interestingly, significantly high levels of vitamin D were found in cases with subclinical hypothyroidism compared to a healthy control group in a similar study that was conducted in Saudi Arabia with the majority of cases being females: female (39) vs. males (3) [32].

The current study showed a significant difference in BMI between the cases and controls. This goes with one study conducted in the Kingdom of Saudi Arabia that showed similar findings [32]. In a similar context, another two studies proposed that vitamin D deficiency can predict BMI [33, 34].

In this study, the median (interquartile) of serum thyroid stimulating hormone (TSH) levels and FT4 levels showed a significant difference between the two groups. This goes with the previous finding in one study that was conducted on the same nationality of participants [35]. Serum 25(OH)D levels were found to be significantly negatively correlated with serum thyroid stimulating hormone (TSH) levels and positively with T4 in some recent clinical data [36-38].

The key role in the development of autoimmune process is genetically dependent on aberrant expression of HLA-DR and other antigens on the thyrocyte surface hence are become vulnerable to an autoimmune insult [39]. Likewise, a different gene in the Vitamin D receptor was found to be the culprit to autoimmune thyroid disease such as Graves' disease and Hashimoto's thyroiditis [26, 36]. An indirect effect can be due to a higher serum level of calcium, low level of circulating parathyroid hormone and high phosphorous levels which may lead to suppression of renal 25(OH) D1-α hydroxylase activity. Therefore 1, 25 (OH) 2D productions will be reduced and this will be accompanied with marked elevation in both serum 24, 25(OH) and serum thyroid hormone levels [6]. It has to be mentioned that the beneficial effects of vitamin D could be due to prevention/correction of the potential risk of hypothyroidism and an improvement in the thyroid functions [27, 40-42]. Also correction of vitamin D with anti-thyroid drugs or thyroid hormone replacement is associated with better treatment response, besides, suppressing the autoimmune reaction as reflected by reducing serum levels of thyroid autoantibodies [43]. Furthermore, vitamin D supplementation is associated with prevention and development of different autoimmune diseases in both humans and animal models [27]. Both vitamin D and thyroid hormone bind to analogous receptors called steroid hormone receptors. Tissues express vitamin D receptor (VDR) and 1-alpha-hydroxylase, have a paracrine and autocrine effects to allow upregulation of calcitriol production, neither depends on

parathormone nor renal influence. [6, 39] Mutation of genes encoding for tissue hydroxylases and VDR hire a risk for development of thyroid cancer. [44, 45] Low levels of vitamin D (1, 25-(OH) 2D3) were observed in different types of thyroid cancers and correlated with cancer staging (I-IV) [45]

On the other hand, low levels of vitamin D may be related to hypothyroidism disorder. We can justify the presence of low levels of vitamin D among subjects with hypothyroidism for poor intestinal absorption in some autoimmune disorders that are associated with hypothyroidism such as celiac disease and pernicious anaemia. Moreover, the seasonal variation may affect the prevalence as one report documented higher rates of low serum level of the vitamin during winter compared to spring [46]. The seasonal variation of vitamin D was not one of the objectives of the current study. On the contrary, a lower prevalence of vitamin D deficiency among males compared with females was previously observed, when gender issue was considered [22, 36].

One of the limitations of this study is; calcium, phosphorous, parathyroid hormones and thyroid antibodies were not investigated.

In conclusion, there was no significant difference in vitamin D level among females with hypothyroidism and healthy controls.

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