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Research Article
Association of Autoimmune Hypothyroid Disease and Obesity with Vitamin D Deficiency in Female Patients

[1]Sadia Batool, [1]Dalia Almaghaslah, [1]Amira Abdel Motaal, [1]Abdulrhman Alsayari, [1]Arwa Khaled, [2]Zuha Dirki and [2]Shahid Attique

[1]College of Pharmacy, King Khalid University, Abha, Saudi Arabia
[2]Department of Medical, Khamis Mushayt General Hospital, Khamis Mushayt, Saudi Arabia

Abstract

Background and Objective: Vitamin D deficiency is becoming a global problem and is linked to many immune disorders. In regard to autoimmune hypothyroidism, the data is still controversial. This study aimed to evaluate the link between autoimmune hypothyroidism, BMI and vitamin D in the female population of Saudi Arabia. **Materials and Methods:** This was a prospective cross-sectional study. Blood samples for vitamin D (25 OH) and thyroid function (TSH, T3 and T4) were taken from 51 autoimmune hypothyroid female patients (diagnosed after testing positive for autoimmune thyroid antibodies). Vitamin D deficiency was designated at levels lower than 20 ng mL^{-1} and compared with thyroid function tests. **Results:** The results indicated low levels of vitamin D in up to 90% of these patients. Of the total 51 patients, 5 patients (9.8%) had normal vitamin D levels, 2 patients (3.9%) had insufficient levels and 44 patients (86.3%) had deficient levels. A significant inverse correlation was noted between vitamin D and TSH ($r = -0.28$, $p = 0.046$) indicating an increase in TSH levels as vitamin D levels decrease. T3 and T4 were found to be in their normal range. In regard to body mass index (BMI), 10 of the 51 patients (9.6%) had normal body weight, 5 patients (9.8) were overweight and 36 patients (70.6) were obese. The results, however, were statistically non-significant. **Conclusion:** The results indicated that patients with autoimmune hypothyroidism suffered from hypovitaminosis D that was significantly associated with the degree and severity of the disease.

Key words: Vitamin D, immune disorders, body mass index, thyroid profile, autoimmune hypothyroidism

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Corresponding Author: Sadia Batool, College of Pharmacy, King Khalid University, Abha, Saudi Arabia Tel: 00966557316186

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Vitamin D is an important vitamin, required for the regulation of calcium and bone health. This vitamin increases the uptake of calcium from the gastrointestinal tract (GIT) and links the re-absorption of bone calcium to osteoclast stimulation, thus contributing to bone health. However, evidence has identified other effects as well. Its role in the maintenance of immune function, control of hypertension, certain malignancies and autoimmune diseases was also observed[1].Recently, VDR receptors have been found in various organ systems, including the cells of bone marrow, large intestine, breast and brain[2]. Thus, many tissues can convert inactive vitamin D to an active form, as they carry the enzyme 1 alpha hydroxylase, thus pointing to roles beyond bone regulation[3]. T-cells, B-cells and antigen presenting cells have also been shown to express VDR receptors and are capable of synthesizing the active form of vitamin D (1, 25, dihydroxy)[4].

Thyroid dysfunction is considered a common endocrine disease and its prevalence has recently increased[5]. Thyroid problems are divided into hypothyroidism and hyperthyroidism. A defect in the gland could be due to primary or secondary causes[6]. The etiology of autoimmune thyroid disease (ATD) is multifactorial, including genetic, hormonal and environmental factors. Hypothyroidism could also be due to various causes, with an autoimmune disorder being one of the main etiologies[7]. It is characterized by lymphocytic infiltration of the thyroid parenchyma. This disease affects up to 1.5% of the population, predominantly females. The prevalence of hypothyroidism among adult females of different age groups ranges from 3-7.5% and is more frequent among elderly women[5].

Vitamin D deficiency has been linked to many chronic diseases and autoimmune disorders, such as multiple sclerosis, diabetes mellitus Type 1, rheumatoid arthritis and systemic lupus erythematosus (SLE)[8-10]. However, the relationship between vitamin D and AITD is still a controversial issue[11]. Many studies have pointed out a correlation between a low concentration of vitamin D and ATD, while other studies have discounted the role of vitamin D in autoimmune hypothyroid disease[12,13]. Most of these studies were carried out on existing cases of autoimmune hypothyroid disease. This study aimed to evaluate the vitamin D status of newly diagnosed autoimmune hypothyroid female patients, who have not undergone any treatment at the time of presentation. This study also examined the correlation between body mass index (BMI) and vitamin D levels.

MATERIALS AND METHODS

Study design and setting: The study was designed as a single centre, prospective cross-sectional study. It was conducted at the Endocrinology Outpatient Department Clinic, Khamis Mushayt General Hospital, southern region, Kingdom of Saudi Arabia, between October, 2018 and January, 2019. The Research Ethics Committee at College of Medicine, King Khalid University approved the research protocol (REC# 2018-05-37) and consent forms were obtained from participants before the beginning of the study.

Study participants: The sample size was based on a previous study from Qassim, Saudi Arabia[14]. The inclusion criteria was as follows: female gender, between the age of 18-45 years, newly diagnosed with autoimmune hypothyroidism and tested positive for ATA (thyroid peroxidase antibody test and anti-thyroglobulin antibody test)[14]. The exclusion criteria was as follows: patients with a history of liver or renal disorders, thyroid surgery, primary hyperparathyroidism, medication history that involved taking calcium/vitamin D supplements or drugs that alter the thyroid status, such as amiodarone, lithium or immune modulators. Patients with renal or liver disease, cancer, severe weight loss, gall bladder disease, lipid abnormalities, bowel diseases and those who were pregnant, or were on immunosuppressive medications, insulin, sulfonamides or any supplements including vitamin D were also excluded.

Patients who met the inclusion criteria were invited to participate during their visit to the Endocrinology Outpatient Clinic and were then asked to sign a written informed consent. Blood samples were collected for hematological and chemical analyzed. A total of 51 female patients were included in the study.

Laboratory testing: All biochemical tests were conducted by photometric assays (BT2000) using a Pars kit. TSH was measured by the chemiluminescent immunoassay method (Advia Centaur CP, Siemens Healthcare Diagnostic Inc., USA)[15]. Vitamin D levels were measured by an enzyme-linked immunosorbent assay kit (Immunodiagnostic Systems Limited, UK). All samples were taken in a single sitting and without fasting. Blood was drawn from the arm vein using a standard technique. The samples were kept in red top or serum separator vacutainers and stored at -20°C until further analysis.

Data collection form: The data collection form consisted of two sections. Section 1 gathered information on the patient's socio-demographic characteristics, including age, sex, weight, height and nationality. Section 2 collected information regarding laboratory test results, including serum 25 (OH) vitamin D levels and thyroid blood profile (TSH, T3 and T4). The identity of each patient was kept anonymous by assigning codes, P1-P51, to study participants.

Serum TSH, T3 and T4 and Vitamin D (25-OH vitamin D): Patients' blood was evaluated for thyroid profile and vitamin D levels with the following reference ranges[16]:

- TSH: 0.27-4.5 ml U L^{-1}
- T3: 2.8-7 pmoL L^{-1}
- T4: 12-22 pmoL L^{-1}
- Vitamin D (25 OH vitamin D): Normal: >30 ng mL^{-1}, Insufficiency: >20 and <30 ng mL^{-1}, Deficiency: <20 ng mL^{-1}

Body mass index (BMI): Patients BMI was measured as follows; Measures of weight and height were collected in person by the Endocrinology Clinic nurse. Weight measurements were taken on digital scales and heights were measured using portable audiometers. BMI was defined as weight in kilograms divided by height in meters squared. BMI was categorized according to the World Health Organization classifications: underweight (BMI<18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), class I obese (BMI 30.0-34.9), class II obese (BMI 35.0-39.9) and class III obese (BMI≥40.0).

Statistical analysis: In this research, data was expressed as counts and percentages for categorical variables and as Mean±standard deviation for continuous variables. Data was assessed for normality using the Kolmogorov-Smirnov test and frequencies, means and standard deviations were calculated by descriptive statistics. Correlations between variables were tested using the Pearson or Spearman's correlation analysis. Values between 0-0.3 indicated a weak correlation, 0.3-0.7 indicated intermediate and 0.7-1.0 indicated a strong correlation. A p-value <0.05 was considered statistically significant. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS version 24 for Windows).

RESULTS

A total of 51 female patients were included in the study, almost half of them (25, 49%) were between 40 and 50 years of age, while 21 (41.2 %) were between 30-39 years and only 5 (9.8%) were between 20-29 years, as shown in Table 1.

Correlation between serum Vitamin D and thyroid profile: Of the total 51 patients, 5 (9.8%) had normal vitamin D status, 2 (3.9%) were insufficient and 44 (86.3%) patients were deficient (Table 1). The mean and standard deviation were calculated for vitamin D and thyroid blood profile (i.e., T3, T4 and TSH) as summarized in Table 1.

A significant inverse correlation was found between vitamin D and TSH (r = -0.281, p = 0.046) as vitamin D decreased, the level of TSH increased. In this study, participants presented high levels of TSH with a mean of 13± 11.1 mL μ L^{-1} and vitamin D deficiency levels with a mean of 18.8±10.8 ng mL^{-1}. Since all study participants were newly diagnosed with ATD, this finding indicated a possible link between vitamin D deficiency and the occurrence of autoimmune hypothyroidism.

Table 1: Correlation between Serum Vitamin D levels and Thyroid Profile (TSH, T3, T4)

Demographic characteristics			Number of patients (%)
Age			
20-29			5(9.8%)
30-39			21(41.2%)
40-50			25(49%)
Diagnostic criteria			Number of patients (%)
Vitamin D serum levels			
Normal: >30 ngmL^{-1}			5 (9.8%)
Insufficient: >20 and <30 ng mL^{-1}			2 (3.9%)
Deficiency: <20 ng mL^{-1}			44 (88%)
Mean values of vitamin D, TSH, T3 and T4			
Vitamin D			18.8±10.8 ng mL^{-1}
TSH			13±11.1
T3			4.3±1.6
T4			13±3.3
Parameter 1	Parameter 2	r-value	p-value
Correlation between vitamin D, TSH, T3 and T4			
Vitamin D	TSH	-0.281*	0.046
Vitamin D	T3	-0.034	0.811
Vitamin D	T4	0.355*	0.011
TSH	T3	-0.081	0.572
TSH	T4	-0.319*	0.023
T3	T4	-0.291*	0.039

*Correlation is significant at the 0.05 level (2-tailed)

Table 2: Correlation between Serum Vitamin D levels and BMI

Distribution			Number of patients (%)
BMI Characteristics			
Normal			10 (19.6%)
Overweight			5 (9.8%)
Obese			36 (70.6%)
Parameter 1	Parameter 2	r-value	p-value
Correlation between Vitamin D and BMI			
Vitamin D	BMI	0.272	0.054

*Correlation is significant at the 0.05 level (2-tailed)

Correlation between serum Vitamin D and BMI: Fifty-one patients were categorized into the BMI classifications. The participants BMIs were classified as normal (10 and 19.6%), overweight (5 and 9.8%) or obese (36 and 70.6%). However, the correlation between vitamin D and BMI was statistically non-significant, with r-value of 0.272 (Table 2).

DISCUSSION

The results indicated a strong association with low levels of vitamin D and higher TSH levels in up to 90% of the participants with statistical significance. The levels of T3 and T4 were in the normal range, which conformed to the presentation of autoimmune hypothyroidism[17]. Out of 51 patients, 36 patients were obese and had a deficiency in vitamin D; or however, the correlation between vitamin D and BMI had no statistical significance. Vitamin D deficiency is quite prevalent in adult population of Saudi Arabia, with a higher incidence in females[18]. The link between low vitamin D and autoimmune hypothyroidism is still under debate, some denying any role and others suggested a strong association[19-21]. The present study has validated the findings of previous studies which supported a role of low vitamin D levels and occurrence of autoimmune thyroid disease. A study conducted on 208 patients in Japan observed serum vitamin D deficiency (value below 25 nmoL L^{-1}) was found in 40% of female patients and in 18% of male patients ($p<0.005$)[22]. Another study conducted on autoimmune hypothyroid patients in Greece revealed that more than 85% had low levels of vitamin D as well as high levels of anti-thyroid antibodies[23]. Further on, supplementation with vitamin D in these patients for 4 months (cholecalciferol, CF) resulted in a significant decrease (20.3%) in serum anti-thyroid peroxidase, which is an important marker of autoimmunity. Similar to the present study, Mackawy *et al.*[14] indicated a strong association between hypovitaminosis D and hypothyroidism. The findings included significantly lower serum vitamin D 25 (OH) levels in hypothyroid patients than in controls ($t = -11.128$, $p = 0.000$). In addition, Kivity *et al.*[24] confirmed higher titre of autoantibodies in patients who presented with low vitamin D levels. The study also indicated higher prevalence of vitamin D deficiency in patients with AITDs compared with healthy individuals (72% versus 30.6%; $p<0.001$). A similar study was also conducted on three types of autoimmune thyroid disease, including Grave's disease (GD), Hashimoto's thyroiditis (HT) and post-partum thyroiditis (PPT). The levels of vitamin D were significantly low in patients with AITD (GD and HT) when compared with healthy control[25]. Studies have shown an important role of vitamin D in regulation of immune system, VDR receptors have been found on cells linked to immunity (macrophages, dendritic cells. T and B Cells)[26]. An important effect of vitamin D is the suppression of dendritic cells, which function mainly in production of autoimmunity and destruction of self-tolerance[27].

The association between vitamin D deficiency and obesity is still not very clear. Thus far, the quality of studies and the methods used have not been very conclusive. In a study carried out in Norway, Vitamin D and calcium levels were found to be deficient in obese men and women[28]. It is possible that obese individuals expose less skin to the sun less often than non-obese individuals, resulting in reduced synthesis of vitamin D. BMI, body fat % and sunbathing have been shown to be related in a population-based sample, although another study found no relationship in individuals aged over 65 years[29, 30].

A variety of mechanisms by which vitamin D may influence adiposity and energy balance have been proposed, but interventional studies have thus far been inconclusive at least in part due to methodological issues [31]. In summary, the data pertaining to this topic is limited and larger scale prospective studies are required. These findings further supported the association of low vitamin D and occurrence of autoimmune disorders. The present study not only supported the existing data on association of hypovitaminosis and AITD, but also further validates the findings by providing significant statistical correlation between low serum vitamin D levels and TSH. According to the results of this study, the recommendation is to evaluate and replace vitamin D levels in all patients presenting with autoimmune hypothyroid disease.

CONCLUSION

The current study aimed to evaluate the correlation between vitamin D and autoimmune hypothyroidism, as well as the correlation between vitamin D and BMI. The majority 90% of the female patients with newly diagnosed autoimmune hypothyroidism had low vitamin D levels. The diagnosis of autoimmune hypothyroid was confirmed with high levels of TSH, normal level T3 and T4 and testing positive for ATA. On the other hand, no correlation was noted between BMI and vitamin D levels.

SIGNIFICANCE STATEMENT

This study has validated the association between low vitamin D levels and the occurrence of autoimmune hypothyroidism. This study can be beneficial in terms of

planning recommendations for the treatment of autoimmune hypothyroid disease. Furthermore, vitamin D supplementation may reduce the duration and improve the recovery of patients suffering from this disease.

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