Original Article

The Association of Vitamin D Deficiency with Hypothyroidism

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ABSTRACT

Objective: To identify whether or not there was a correlation between low serum 25(OH)D and hypothyroidism
Design: Retrospective study
Setting: King Abdulaziz University Hospital, from June 2014 to June 2016
Subjects: One thousand and forty-two patients suffering from hypothyroidism were enrolled in this retrospective study and serum 25(OH)D levels were measured in all patients. We divided them into two groups; the first included 373 patients with post radioactive Iodine (RAI) ablation hypothyroidism and the second group included 669 patients with Hashimoto's hypothyroidism.
Main outcome measures: Vitamin D states in hypothyroid patients
Results: In the first group, 335 patients (90%) were afflicted with vitamin D deficiency and 636 patients (95%) from the second group were afflicted with vitamin D deficiency. Furthermore, it was also found that levels of serum 25(OH)D were lower in the Hashimoto's group at 13.7 ng/mL in comparison with the post-RAI group at 15.6 ng/mL. There was no significant correlation between the serum thyroid-stimulating hormone (TSH) and the 25(OH)D parameter in patients with post-RAI hypothyroidism as per the Pearson scale reading ($r = -0.004$, $p = 0.94$). Similarly, the patients afflicted with Hashimoto's disease had no significant correlation between their serum 25(OH)D and TSH levels since the Pearson scale read $r = -0.04$, $p = 0.3$.
Conclusion: Low serum 25(OH)D levels was found to be common amongst the patients affected with hypothyroidism.

KEY WORDS: Hashimoto's thyroiditis, post RAI, Saudi Arabia, serum 25(OH)D

INTRODUCTION

One of the most common illnesses in the Kingdom of Saudi Arabia is thyroid disease, which could be linked to vast numbers of people suffering from a vitamin D deficiency[1,2]. This deficiency is a consequence of many different traditional and cultural traits alongside religious teachings which are followed by the vast majority of the Saudi population. Firstly, traditional factors include the men wearing white clothing, also known as the thobe, to protect themselves from the sun. As for women, religious teachings instruct them to cover up, exposing only their faces and hands, and there are some who even cover up their faces, further reducing the chance for sun exposure. However, perhaps the main cause of the deficiency is the lack of physical activities outdoors, again further reducing their exposure to the sun's rays[3,4].

Hashimoto's thyroiditis (HT) is a disorder which arises due to either genetic factors or environmental factors. HT is differentiated from other disorders by its reactivity to the self-thyroid antigens[5]. Hashimoto's disease is also an autoimmune thyroid disease; furthermore, it has been shown that Vitamin D deficiency has been associated with autoimmune diseases, including autoimmune thyroid disease, systemic lupus erythematosus, multiple sclerosis and type 1 diabetes[6,7]. Therefore, a link could be established between Hashimoto's disorder and vitamin D deficiency.

Similarly, post radioactive Iodine (RAI) ablative hypothyroidism tended to be more prevalent in patients with Graves disease, which is also an autoimmune disorder, or thyroid cancer treated by RAI[8].The objective of this retrospective study was to evaluate the association of low serum 25(OH)D and hypothyroidism due to either Hashimoto's disease or post RAI treatment.

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MATERIALS AND METHODS

To begin with, data was collected from the master database of the Department of Clinical Biochemistry at King Abdulaziz University (KAU) Hospital during the period of two years from June 2014 to June 2016. The data included age, sex, nationality, thyroid function test (TFT), thyroid antibodies, RAI treatment, serum 25(OH) D, calcium, phosphorous, hemoglobin and sodium. All the clinical parameters were measured at the same time or close to the date of serum 25(OH)D measurement.

A total of 1042 patients were enrolled in this retrospective study. They were divided into two groups, the first group which consisted of 373 patients with post-RAI hypothyroidism and the second group comprising of 669 suffered solely from Hashimoto's disease.

Patients with high titres of serum antithyroid peroxidase (antiTPO) and high antithyroglobulin (antiTG) were diagnosed with Hashimoto's disorder. As for the post-RAI hypothyroidism, it was diagnosed after receiving RAI treatment for thyroid cancer or Graves disease.

Serum 25(OH)D levels were measured using a semi-automated, solid-phase extraction followed by reverse-phase high-performance liquid chromatography assay. As for the levels of thyroid stimulating hormone (TSH), they were determined using the enzyme-linked immunosorbent assay (ELISA) method. Furthermore, immunocitometry kits were used to measure the anti-TPO antibodies of all patients in the same laboratory.

All 1042 patients had TSH values greater than the normal limit ranging from 0.27 to 4.2 IU/mL, and serum levels 25(OH)D < 30 ng/mL.

The exclusion criteria for this study were patients who received vitamin D or calcium supplements and medications that could have interfered with the levels of serum 25(OH)D. The study was approved by the Clinical Research Ethics Committee at KAU.

Statistical Methodology

Firstly, the categorical data was summarized using frequency and percentages, whilst the continuous data was summarized using mean and standard deviation. The independent test was then performed to find out the difference in average of continuous variable in the two groups, whereas the chi-square test of association was used for the categorical variables.

Patients with an odds ratio of 95% confidence interval (CI) were calculated to have a greater risk of vitamin D deficiency alongside hypothyroidism between the two groups.

As for Pearson's correlation r, it was calculated to find out the strength of the relationship between TSH and other laboratory parameters. If the p-value was less than 0.05, all statistical tests were defined as statistically significant.

Furthermore, a box-plot was drawn to compare the descriptive statistics of vitamin D_3 (25(OH)D) among the two groups. For simplification and better understanding, log transformation was done for vitamin D_3 values. A bar graph was drawn to highlight the difference in frequency between the groups. All statistical analysis was carried out using Statistical Packages for Social Sciences (SPSS) version 20.1.

RESULTS

Characteristics of HT versus post-RAI hypothyroidism

The baseline characteristics of the 1042 hypothyroid patients are presented in Table 1. Of the 1042 patients, 669 were diagnosed with Hashimoto's hypothyroidism, 508 (75.9%) of those patients were females and the median age of the group was 45 years. Furthermore, 357 of the patients (53.5%) were expatriates. The second group consisted of 373 patients with post-RAI hypothyroidism, 283 (75.6%) of them were female with a median age of 42 years. In this group, the majority were also expatriates due to only 196 (47%) of them being Saudi. Statistically speaking, the age difference between the two groups is p > 0.011, which is significant.

Table 1: Demographic characteristics of subjects

Variable	Hypothyroidism		P - Value
	Post-radioactive iodine n = 373	Hashimotos n = 669	
Age [a]	42 (15)	45 (18)	0.011*
Sex [b]			
Male	90 (36)	161 (64)	0.982
Female	283 (75.6)	508 (75.9)	
Nationality			
Saudi	196 (47)	312 (61)	0.670
Non-Saudi	177 (33)	357 (53.5)	

[a]: Mean (SD) , [b]: Frequency (percentage) , * statistically significant with p-value < 0.05

Laboratory abnormalities: HT versus post-RAI hypothyroidism

The mean value of TSH for HT and post-RAI hypothyroidism was 79.2 IU/mL and 77.16 IU/mL respectively; due to the difference being very small, there is no statistically significant difference. However, there was a difference between both groups regarding their FT4 and FT3 figures with the post-RAI group, with a significant p-value < 0.0001. As for the antiTPO and antiTG patients with HT disorder, they incurred high titres with antiTPO at 496 ± 83 and antiTG at 510 ± 129.

The prevalence of vitamin D deficiency was 335 (90%) and 636 (95%) in groups 1 and 2 respectively. Furthermore, the vitamin D levels were lower in the

Hashimoto's group (13.7) in comparison to the post-RAI group (15.6). However, there was no statistical significance since the p-value was 0.144.

Similarly, there was no significant difference in the sodium, calcium and PO_4 levels between the two groups. However, the hemoglobin and serum iron were significantly lower in Hashimoto's group in comparison to the post-RAI group (p-values 0.004 and 0.005, respectively) (Table 2 (A,B), Fig 1) .

Table 2 (A): Laboratory parameters

Variable	Hypothyroidism Mean (SD)		P - Value
	Post radioactive iodine n = 373	Hashimotos n = 669	
TSH	79.21(20.3)	77.16 (22.3)	0.143
25(OH)D	15.62 (20.4)	13.78 (17.5)	0.144
HB	11.01 (06.3)	10.05 (3.5)	0.001*
Iron	1.01(03.7)	1.74 (4.4)	0.005*
Na	111.3 (52.7)	117.60 (44.9)	0.051
Ca	1.6 (0.9)	2.08 (10.9)	0.39
PO_4	0.78 (5.2)	0.6 (0.56)	0.39

* statistically significant with p-value < 0.05
TSH: thyroid-stimulating hormone; 25(OH)D: 25-hydroxy-vitamin D; HB: haemoglobin; Na: sodium; Ca: calcium; PO_4: phosphate

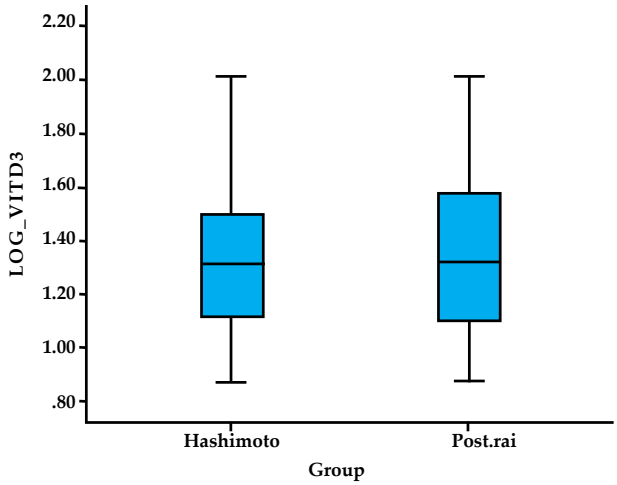

Fig 1: Box-plots for vitamin D3 (25OHD) with respect to hypothyroid groups

and its p-value at 0.028; yet in the post-RAI group, the correlation between TSH and PO_4 was insignificant due to the Pearson r value being at -0.001 and its p-value totaling to 0.99 (Fig 2).

Table 2 (B): Logistic regression model for categorical data

Variables	Hypothyroidism		Odds ratio (95% CI)	P- Value
	Post radioactive iodine (n = 373)	Hashimotos (n = 669)		
25 (OH) D-Deficiency				
Yes	335 (90)	636 (95)		
No	38 (10)	33 (05)	0.46 (0.28 - 0.78)	0.002*

* statistically significant with p-value < 0.05; 25(OH)D: 25-hydroxy-vitamin D

To begin with, the Chi-square test of association was used to figure out the categorical variables (Table 3). Patients with an odds ratio with 95% CI were associated to having a greater risk of vitamin D deficiency. However, the odds ratio for normal level of 25(OH)D in the two groups at 95% CI ranged from 0.2 to 0.78, with a significant p-value of 0.002.

The relation between serum 25 (OH)D and the TSH parameters in patients with post-RAI hypothyroidism was not statistically significant due to the Pearson r being at -0.004, and the p-value at 0.94. Correspondingly, patients with HT disorder did not have a strong correlation between serum 25(OH)D and TSH due to the statistics of Pearson r being at -0.04 and the p-value at 0.3. Similarly, there was no significant relationship observed between TSH and the haemoglobin, sodium and calcium parameters. However, in the Hashimoto's group, there was a significant correlation between the TSH and PO_4 values with the Pearson r value at -0.085

DISCUSSION

Vitamin D deficiency is a global health problem with an estimate of over one billion people worldwide suffering from the deficiency[9]. Here in Saudi Arabia, the deficiency is one of the most common disorders faced by both males and females. It has even been reported by the Ardawi Group, that in Saudi Arabia,

Table 3: Association between 25(OH)D and hypothyroid groups

Variables	Hypothyroidism		P-Value
	Post radioactive iodine (n = 373)	Hashimotos (n = 669)	
25(OH)D			
Low	335 (34)	636 (66)	
Normal	35 (56)	28 (44)	0.002*
High	03 (38)	05 (62)	

* statistically significant with p-value < 0.05; 25(OH)D: 25-hydroxy-vitamin D

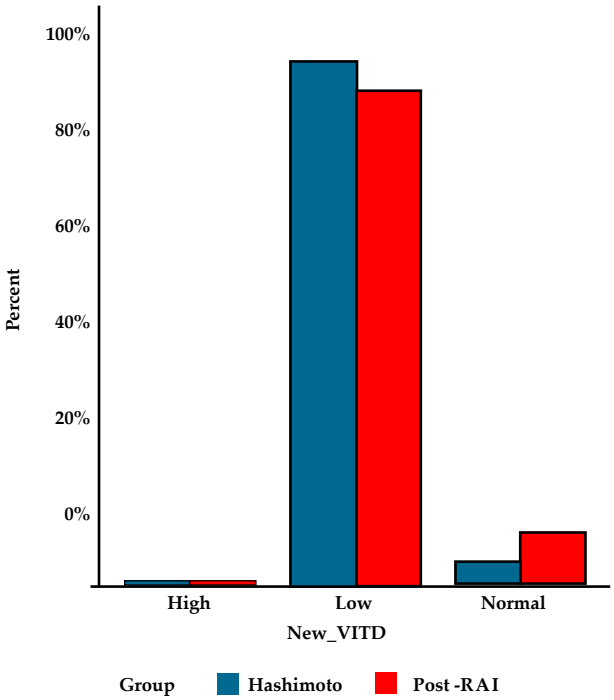

Fig 2: Percentage of Vitamin D_3 levels among post-RAI and Hashimoto's

Table 4: Correlation between TSH and laboratory parameters

Variable	Hypothyroidism			
	Radioactive iodine (n = 373)		Hashimotos (n = 669)	
	R	P-Value	R	P-Value
25(OH)D	0.004	0.94	- 0.040	0.30
HB	- 0.027	0.60	0.008	0.83
Iron	- 0.076	0.14	- 0.022	0.56
Na	- 0.015	0.77	- 0.050	0.19
Ca	- 0.002	0.97	- 0.029	0.45
PO_4	- 0.001	0.99	- 0.085	0.028*

* statistically significant with p-value < 0.05
TSH: thyroid-stimulating hormone; 25(OH)D: 25-hydroxy-vitamin D; HB: haemoglobin; Na:sodium; Ca: calcium; PO_4: phosphate

the United Arab Emirates, Australia, Turkey, India, and Lebanon, 30 to 50% of both children and adults had serum 25(OH)D levels which were under 30 ng/ml[10].

Such a case may seem to be quite peculiar, especially since Saudi Arabia, a country which lies close to the equator, is well known for belonging to one of the sunniest and warmest continents in the world. However, such a matter may be easily explained due to the habits, traditions and religious practices which the vast majority of the Saudi citizens and expatriates abide by, which range from the hijab and abaya which all ladies must wear, to the traditional thobe which the men generally wear, to even the prevalent habit of preferring to avoid the heat during the morning and instead carrying out their activities at night[11].

In many recent studies, the relationship between the serum 25(OH)D levels and the autoimmune thyroid disorder has been thoroughly investigated[12,13]; and our aim was to investigate whether or not an association of low serum 25(OH)D (Vitamin D), and hypothyroidism, either due to Hashimoto's disease or post-RAI ablation treatment, existed.

The data provided from the patients at KAU supported the association between the low serum 25(OH)D and hypothyroidism. The logistic regression model for the categorical data confirmed that in both groups 1 and 2, there was a relationship between the two disorders due to a significant p-value at <0.002. However, in all our patients, no significant correlation was observed between TSH and 25(OH)D, haemoglobin, sodium and calcium parameters.

Such a relationship between low levels of vitamin D and HT or post-RAI hypothyroidism was also established in many other researches. Recently, there were many studies which established a correlation between low levels of vitamin D and Graves' disease[14,15], as well as HT[16,17]. However, fewer studies provided an association between low levels of 25(OH) D and thyroid cancer[18].

Overall, our data supports the thesis statement and provides evidence for an association between low serum 25(OH)D and hypothyroidism, either due to Hashimoto's disease or post RAI ablation treatment of thyroid cancer or Graves' disease, in the western region of the Kingdom of Saudi Arabia. However, such an association may not be due to a link between the two disorders but rather a consequence of overt hypothyroidism which causes malabsorption of 25(OH)D. Another factor which may trigger both the disorders simultaneously could be due to the lack of sun exposure in the country, causing a vitamin D deficiency in the majority of the citizens, even those who do not suffer from a thyroid disorder[19,20].

The study acknowledges several limitations; firstly and most importantly, this was a retrospective and cross-sectional study. Secondly, due to the fact that it is a retrospective study, we were not able to distinguish and adjust the analysis accordingly to the actual cause of the vitamin D deficiency, whether it is due to nutrition, or even a lack of sun exposure. Nonetheless, the study has much strength which includes a large sample of patients whose serum 25(OH)D was measured at a given time frame and in one institution, which removes a selection bias and increases the generalization of present results.

CONCLUSION

Regardless of any environmental factors, vitamin D deficiency is overwhelmingly common amongst patients with hypothyroidism at King Abdulaziz University Hospital. Moreover, although FT3 and FT4 established a strong relationship with serum 25(OH) D, there was no significant correlation between TSH and the serum 25(OH)D parameter.

Irrespective of the cause of hypothyroidism, we recommend hospitals to measure the vitamin D levels that the patients have due to the exceptionally strong link between the two, as seen in this study.

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REFERENCES

1. AlGhalayini K. Prevalence of hypothyroidism in a cohort of Saudi women with heart failure and effect on systolic and diastolic function. J Pak Med Assoc 2015; 65:1300-1304.
2. Malabu UH, Alfadda A, Sulimani RA, Al-Rubeaan KA, Al-Ruhaily AD, Fouda MA, *et al.* Graves' disease in Saudi Arabia: a ten-year hospital study. J Pak Med Assoc 2008; 58:302-304.
3. Elsammak MY, Al-Wosaibi AA, Al-Howeish A, Alsaeed J. Vitamin D deficiency in Saudi Arabs. Horm Metab Res 2010; 42:364–368.
4. Tuffaha M, El Bcheraoui C, Daoud F, Al Hussaini HA, Alamri F, Al Saeedi M, *et al*. Deficiencies under plenty of sun: Vitamin D Status among adults in the Kingdom of Saudi Arabia, 2013. N Am J Med Sci 2015; 7:467-475.
5. Effraimidis G, Wieringa WM. Mechanisms in endocrinology: autoimmune thyroid disease: old and new players. Eur J Endocrinol 2014; 170:R241-252.
6. Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y. Vitamin D in systemic and organ-specific autoimmune diseases. Clin Rev Allergy Immunol 2013; 45:256–266.
7. Delvin E, Souberbielle JC, Viard JP, Salle B. Role of vitamin D in acquired immune and autoimmune diseases. Crit Rev Clin Lab Sci 2014; 51:232–247.
8. Yaqub A, Choudhry MI, Wheaton J, Gress T. Post-ablative hypothyroidism. W V Med J 2011; 107:37-40.
9. Haq A, Svobodova J, Imran S, Stanford C, Razzaque MS. Vitamin D deficiency: A single centre analysis of patients from 136 countries. J Steroid Biochem Mol Biol 2016; 164:209-213.
10. Ardawi MS, Sibiany AM, Bakhsh TM, Qari MH, Maimani AA. High prevalence of vitamin D deficiency among healthy Saudi Arabian men: relationship to bone mineral density, parathyroid hormone, bone turnover markers, and lifestyle factors. Osteoporos Int 2012; 23:675-686.
11. Farahati J, Nagarajah J, Gilman E, Mahjoob S, Zohreh M, Rosenbaum-Krumme S, *et al*. Ethnicity, clothing style, and body mass index are significant predictors of vitamin D insufficiency in Germany. Endocr Pract 2015; 21:122–127.
12. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K, *et al*. Vitamin D and autoimmune thyroid diseases. Cell Mol Immunol 2011; 8:243–247.
13. Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, *et al*. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocr Pract 2013; 19:479–484.
14. D'Aurizio F, Villalta D, Metus P, Doretto P, Tozzoli R. Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases? Autoimmun Rev 2015; 14:363–369.
15. Zhang H, Ling L, Xie Z. Low Vitamin D status is associated with increased thyrotropin-receptor antibody titer in Graves Disease. Endocr Pract 2015; 21:258–263.
16. Mazokopakis EE, Kotsiris DA. Hashimoto's autoimmune thyroiditis and vitamin D deficiency. Current aspects. Hell J Nucl Med 2014; 17:37-40.
17. Goswami R, Marwaha RK, Gupta N, Tandon N, Sreenivas V, Tomar N, *et al*. Prevalence of vitamin D deficiency and its relationship with thyroid autoimmunity in Asian Indians: a community-based survey. Br J Nutr 2009; 102:382–386.
18. Grant WB. A critical review of vitamin D and cancer: a report of the IARC working group. Dermatoendocrinol 2009; 1:25–33.
19. Al-Daghri NM, Al-Attas O, Yakout S, Aljohani N, Al-Fawaz H, Alokail MS. Dietary products consumption in relation to serum 25-hydroxyvitamin D and selenium level in Saudi children and adults. Int J Clin Exp Med 2015; 8:1305-1314.
20. Ritu G, Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. Nutrients 2014; 6:729-775