International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 07, Issue 07, July 2022,
https://doi.org/10.23958/ijirms/vol07-i07/1443

Original article

Prevalence of Vitamin D Deficiency and the Associated Risk Factors in Adults with Thyroid Nodule in Royal Commission Hospital, Kingdom of Saudi Arabia

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Received 25 June 2022; Accepted 01 July 2022; Published 05 July 2022

Abstract

Vitamin D is an essential nutrient for the human body. Its deficiency is linked with many common chronic diseases, types of cancer and thyroid disorders. Recent data have shown high rates of vitamin D deficiency, thyroid nodules and an increase in the incidence of thyroid cancer in the Kingdom of Saudi Arabia (KSA). We conducted this study to evaluate the rates of vitamin D deficiency and associated risk factors in patients with thyroid nodules in the Eastern Region of the KSA.

Methods: A retrospective study was conducted between 1 January 2015 and 31 December 2021. The recruited patients had documented thyroid nodules based on the American College of Radiology's Thyroid Imaging Reporting and Data System (TI-RADS).

Results: There were 391 patients with thyroid nodules enrolled in the study. The median (interquartile range [IQR]) age was 46.00 (20.0) years, and 332 (84.9%) of the participants were women. The patients' median (IQR) body mass index was 30.26 (7.71) kg/m2, and the median (IQR) 25-hydroxyvitamin D (25[OH)]D) level was 14.50 (12.0) nmol/L. There was a high prevalence (89.8%) of vitamin D deficiency among patients with thyroid nodules. In the univariate analysis, there were significant associations between 25(OH)D level and age, hypertension, hyperthyroidism, thyroid-stimulating hormone level, free triiodothyronine level and thyroid ultrasound-based TI-RADS scores of 3 to 5.

In the multivariate analysis, age, free thyroxine level, free triiodothyronine level and hyperthyroidism were not significantly associated with 25(OH)D level. However, there were significant associations between 25(OH)D level and hypertension (odds ratio [OR]=0.438, 95% confidence interval [CI] 0.210–0.911) and higher TI-RADS scores (TI-RADS 4: OR=9.654 [95% CI 1.819–51.226] and TI-RADS 5: OR=7.784 [95% CI 1.473–41.135]).

Conclusion: There was a high prevalence of vitamin D deficiency among patients with nodular thyroid disease. TI-RADS ultrasound scores of 4 and 5 and the presence of hypertension were significantly associated with lower levels of vitamin D.

Keywords: ***prevalence, vitamin D deficiency, thyroid nodules.***

Introduction

Vitamin D, an essential nutrient for the human body, is a steroid hormone that regulates calcium levels and phosphorus metabolism and enhances bone health. It is also an immunomodulatory hormone, and its deficiency is associated with many common chronic diseases, including several thyroid diseases, [1]. Vitamin D receptors (VDRs) play important roles in influencing cellular functions and the morphology of thyrocytes, regulating microRNA expression (which may enhance cancer stem cell biology) and inhibiting mitogenic signalling by growth factors by inducing the increased expression of growth inhibitors, such as transforming growth factor-β [2-4]. Vitamin D has anti-inflammatory properties that inhibit the production of many pro-inflammatory cytokines, decreasing the risk for developing many common chronic diseases [3,5]. Several studies have reported different occurrence rates of thyroid nodules according to different methods: 2-6% with palpation, 19-35% with ultrasound, and 8-65% from autopsy data [6]. Recently, a higher prevalence of thyroid nodules (74.2%) was reported in China [7]. Many recently published clinical data pointed to a significant association between lower serum vitamin D levels and thyroid nodules across the globe [8-11]. Hence vitamin D deficiency is a modified risk factor [12] for thyroid nodular disease [13], risk of cancer [14]. Many risk factors for nodular thyroid diseases have been identified for example, high blood glucose levels, elevated serum lipid levels, increased weight, abnormal thyroid hormone levels and history of hypertension [9].

Thyroid ultrasound is a powerful new diagnostic tool for assessing goitres, thyroid nodules and adjacent tissues; thyroid nodules are exceedingly common, with a higher reported prevalence (68%) in adults using high-resolution ultrasound [15]. Moreover, ultrasound scoring according to the American College of Radiology's Thyroid Imaging Reporting and Data System (TI-RADS) improves the assessment and management of thyroid nodules [16,17]. Thyroid gland disorders are the most common endocrine abnormalities in the Middle East and in the Kingdom of

Saudi Arabia (KSA) in particular [18,19]. Similarly, an increase in the rate of thyroid cancer was observed in 2010 (9%) and 2012(11.7%) in the KSA [20,21]. Studies conducted in the KSA have reported higher rates of vitamin D deficiency, representing a public health issue [22-24]. Furthermore, a recently published study pointed to a link between vitamin D deficiency and nodular thyroid diseases in the KSA [22]. Based on the high prevalence of vitamin D deficiency, its association with thyroid nodules and the increasing global and local rates of thyroid cancer, the current study aimed to investigate the prevalence of vitamin D deficiency and the associated risk factors among adult patients with thyroid nodules in the Royal Commission Hospital in the Eastern Region of the KSA.

Methods

A retrospective study was conducted at the Royal Commission Hospital, lasted from 1 January 2015 to 31 December 2021. The records of patients (men and women) aged 18 years and older with documented thyroid nodules, based on the findings of ultrasound procedures conducted in the hospital, were retrieved. Records with incomplete data and thyroid ultrasound reports from other hospitals were excluded. The socio-demographic data, including each patient's age, gender, body mass index (BMI), thyroid status and comorbidities (diabetes mellitus, hypertension and bronchial asthma), were gathered using a data collection sheet. Moreover, laboratory tests for thyroid function, complete white blood cell counts, lipid profiles and vitamin D levels were obtained. Vitamin D deficiency is defined as a 25-hydroxyvitamin D (25[OH]D) level of <30 ng/mL; levels equal or above this cut-off point are considered normal [25]. Each thyroid ultrasound procedure was conducted in the hospital by a radiology specialist, and each report was reviewed and approved by a radiology consultant. Thyroid ultrasound reports based on the TI-RADS were used to assess the thyroid nodules (**Table 1**) [17].

Table (1) (TI-RADS) Category definitions

TI-RADS -1	Benign
TI-RADS -2	Not suspicion
TI-RADS -3	Mildly suspicion
TI-RADS -4	Moderately suspicion
TI-RADS -5	Highly suspicion

Statistical analysis

Data were analysed using SPSS for Windows (version 22.0). Continuous data were assessed for normality using the Shapiro-Wilk test; all variables were not normally distributed. Data were expressed as proportions, medians with interquartile ranges (IQRs) or numbers and proportions, as applicable. A univariate analysis was performed with the 25(OH)D level as the dependent variable. The independent variables were age, gender, thyroid status, thyroid function, haemoglobin, white blood cell count, platelet count, lipid profile and TI-RADS ultrasound score. A variable was analysed using logistic regression if its univariate p-value was <0.20, and backward-stepwise likelihood ratio regression was selected for adjustment. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and p-values of <0.05 were considered significant.

Ethics

The study was approved by the ethical committee of the Royal Commission Hospital, KSA (IB-RCH-012), that waived the need for verbal or written consent.

Results

Three hundred ninety-one patients who had thyroid nodules were enrolled in the study. The median (IQR) patient age was 46.00 (20.0) years, and 332 (84.9%) patients were women. The median (IQR) BMI was 30.26 (7.71) kg/m2, and the median (IQR) 25(OH)D level was 14.50 (12.0) nmol/L. The median (IQR) values for the thyroid function tests were as follows: thyroid-stimulating hormone (TSH), 1.72 (2.43) mmol/L; free thyroxine, 1.12 (0.45) ng/dL and free triiodothyronine, 2.69 (0.40) nmol/L. The median (IQR) of haematological index: haemoglobin 12.6 (1.70) gm/dl, platelet 276.15 (95.80) 103/dl and white blood cell count 7.01 (2.63) 109/L. The median (IQR) lipid profile values for total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides were 5.80 (3.89) mmol/L, 3.76 (0.80) mmol/L, 2.99 (1.71) mmol/L and 1.78 (1.11) mmol/L, respectively (Table 2). Most participants (n=250, 64%) had normal thyroid function, while 122 (28.6%) had hypothyroidism and 29 (7.4%) had hyperthyroidism. The percentages of patients with TI-RADS ultrasound scores of 2, 3, 4 and 5 were 21%, 40.7%, 36.3% and 2%, respectively.

There was a high prevalence of vitamin D deficiency (89.8%) among patients with thyroid nodules.

Table (2) general characteristics of patients with thyroid nodule in eastern region, KSA, 2015-2021.

Variables			
		Median	**Interquartile range**
Age, years		46.00	20.0
Body mass index, kg/m^2		30.26	7.71
Vitamin d , nmol/L		14.50	12.00
Thyroid-stimulating hormone, mmol/L		1.71	2.43
Free triiodothyronine, nmol/L		2.69	.40
Free thyroxine, ng/dL		1.12	.45
White blood cell, 10^9/L		7.01	2.63
haemoglobin, gm/dl		12.6	1.70
Platelet, 10^3/dl		276.15	95.80
Total cholesterol, mmol/L		5.8	3.89
Low-density lipoprotein, mmol/L		3.76	0.80
High-density lipoprotein, mmol/L		2.99	1.71
Triglyceride, mmol/L		1.78	1.11
		Number	Proportion
Gender	Female	332	84.9
	Male	59	15.1
Diabetes mellitus	No	297	76
	Yes	94	24.0
Hypertension	No	303	77.5
	Yes	88	22.5

Asthma	No	360	92.1
	Yes	31	7.9
Thyroid status	Euthyroid	250	64.0
	Hypothyroidism	112	28.6
	Hyperthyroidism	29	7.4
Malignant risk based on ACT TI-RADS	ACT TI-RADS 2	82	21
	ACT TI-RADS 3	159	40.7
	ACT TI-RADS 4	142	36.3
	ACT TI-RADS 5	8	2

In the univariate analysis, there was no association between 25(OH)D level and gender, BMI, lipid profile elements, diabetes mellitus, bronchial asthma, hypothyroidism or free thyroxine. Similarly, there was no significant association between 25(OH)D level and total cholesterol, low-density lipoprotein, high-density lipoprotein or triglycerides or between 25(OH)D level and any haematological index (haemoglobin, platelet or white blood cell count). However, there were significant associations between 25(OH)D level and age (OR=0.981, 95% CI 0.958–1.005), hypertension (OR= 0.496, 95% CI 0.247–0.998), hyperthyroidism (OR=0.214, 95% CI 0.027–1.687), TSH (OR=1.124, 95% CI 0.947–1.334), free triiodothyronine (OR=1.518, 95% CI 0.948–2.428) and TI-RADS ultrasound score (TI-RADS 3: OR=3.72, 95% CI 0.767–18.052; TI-RADS 4: OR=7.35, 95% CI 1.564–34.546 and TI-RADS 5: OR=5.96, 95% CI 1.28–27.794; Table (3).

Table (3) Univariate analysis of the factors associated with vitamin D deficiency in patients with thyroid nodules in eastern region, KSA, 2013- 2021

Variables		**Vit D deficient (n=351)**	**Normal vit D (n=40)**	**OR (95.0 %CI**	**P**
		Median			
Age, years		45.00 (20.0)	53.00 (20.8)	.981(.958 –1.005)	0.124
Body mass index, kg/m^2		30.09 (7.73)	31.11 (8.2)	1.004(.978–1.03)	0.769
Thyroid-stimulating hormone, mmol/L		1.71 (2.5)	1.64 (1.98)	1.124(.947–1.334)	0.183
Free triiodothyronine, nmol/L		2.69 (0.42)	2.69 (.36)	1.518(.948–2.428)	0.082
Free thyroxine, ng/dL		1.11 (0.41)	1.31(0.38)	.902(.760–1.07)	0.238
haemoglobin, gm/dl		12.54(1.7)	12.7 (1.92)	1.009(.937 – 1.088)	0.806
White blood cell, 10^9/L		7.07 (2.6)	6.7 (3.9)	1.003(.979–1.028)	0.800
Platelet, 10^3/dl		276.15 (97.8)	264.8 (62.25)	1.002(.998–1.005)	0.396
Total cholesterol, mmol/L		5.7 (3.95)	6.09 (3.6)	1.004(.98 – 1.029)	0.727
Low-density lipoprotein, mmol/L		3.76(0.8)	3.76 (0.77)	1.036(.881– 1.219)	0.665
High-density lipoprotein, mmol/L		3.00 (1.70)	2.16 (1.69)	1.133(.794– 1.617)	0.491
Triglyceride, mmol/L		1.80 (1.10)	1.66 (1.13)	1.349(.819 – 2.224)	0.240
Gender	Male	52(14.8)	7 (17.5)	Reference	0.654
	Female	299 (85.2)	33 (82.5)	.820(.344 –1.951)	
Thyroid status	Euthyroid	227 (64.7)	23 (57.5)	Reference	
	hypothyroidism	96 (27.4)	16 (40.0)	.351(.046 – 2.7)	0.314
	hyperthyroidism	28 (8.0)	1 (2.5)	.214 (.027–1.687)	0.143
Diabetes Mellitus	No	266 (75.8)	31(77.5)	Reference	0.810
	Yes	85 (24.2)	9 (22.5)	1.101(.504 –2.404)	
Hypertension	No	277 (78.9)	26(65.0)	Reference	0.049
	Yes	74 (21.1)	14 (35.0)	.496 (.247–.998)	
Bronchial asthma	No	321 (91.5)	39(97.5)	Reference	0.209
	Yes	30 (8.5)	1 (2.5)	3.645(.484–27.47)	
Ultrasound	ACR TIRADS2	70(20)	12(30.0)	Reference	
	ACR TIRADS3	147(41.9)	12(30.0)	3.72(.767–18.052)	0.103
	ACR TIRADS4	129 (36.8)	13(32.5)	7.35(1.564–34.546)	0.012
	ACR TIRADS5	5 (1.4)	3(7.5)	5.96 (1.28 –27.794)	0.023

IQR= Interquartile range. OR= odds ratio. CI=confidence interval

In the multivariate analysis, age, free thyroxine level, free triiodothyronine level and hyperthyroidism were not significantly associated with 25(OH)D level. However, there were significant associations between 25(OH)D level and hypertension (OR=0.438, 95% CI 0.210–0.911) and TI-RADS score (TI-RADS 4: OR=9.654, 95% CI 1.819–51.226; TI-RADS 5: OR=7.784, 95% CI 1.473–41.135; Table 4).

Table (4) Multivariate analysis of the predictors associated with vitamin D deficiency in patients with thyroid nodule in eastern region 2015-2021

Variables		**OR (95.0 %CI**	**P**
Age, years		0.991 (0.963 - 1.02)	0.546
Free triiodothyronine, nmol/L		1.437 (0.866 - 2.384)	0.160
Thyroid-stimulating hormone, mmol/L		1.123 (0.950 -1.329)	0.174

Hypertension	No	Reference	
	Yes	0.438 (0.210 - 0.911)	0.027
Bronchial asthma	No	Reference	
	Yes	4.545 (0.585 - 35.277)	0.148
Thyroid status	Euthyroid	Reference	
	Hyperthyroidism	.213 (0.026 - 1.786)	0.154
ACR TIRADS	ACR TIRADS 2	Reference	
	ACR TIRADS 3	4.178 (0.764 - 22.844)	0.099
	ACR TIRADS 4	9.654 (1.819 - 51.226)	0.008
	ACR TIRADS 5	7.784 (1.473 - 41.135)	0.016

IQR= Interquartile range. OR= odds ratio. CI=confidence interval

Discussion

The present study found a higher prevalence of vitamin D deficiency among adult patients with thyroid nodules (89.8%) than those previously reported among the general population in the same Eastern Province of Saudi Arabia (86.91%), the Eastern Region of Turkey (88.4%) and Brazil (84%) [22,26,27] On the other hand, a markedly lower prevalence of vitamin D deficiency (55%) was reported in the United States of America in a similar group of participants [28]. Furthermore, our study demonstrated a lower mean serum vitamin D level in patients with thyroid nodules; this is in concordance with the results of previous studies that examined similar populations in Egypt, Turkey, Brazil and China [7-12]. Interestingly, a negative correlation between vitamin D level and nodule diameter was documented (i.e., larger nodules were seen in patients with lower vitamin D levels) [29]. The higher prevalence of vitamin D deficiency obtained in this study may be explained by the higher prevalence of vitamin D deficiency that recent clinical studies have reported among the general Saudi population (80.1% in females and 76.1% in males) [23,24]. One study pointed to insufficient sunlight exposure and low dietary vitamin D intake as the culprits behind the higher prevalence of vitamin D deficiency in the KSA [25]. The proposed mechanisms underlying nodular thyroid disease in patients with lower levels of vitamin D include VDR binding, as vitamin D affects the expression of a single-nucleotide polymorphism that might influence the regulation of cellular functions and thyrocyte morphology. This notion was supported by statistically significantly higher rates of the FokI VDR gene polymorphism in patients with nodular goitres [2]. Moreover, vitamin D affects the growth and function of thyroid follicular cells by blocking the production of cyclic adenosine monophosphate, thereby blocking the activation of TSH, the main contributor to the growth of thyroid nodules [30]. Indeed, the administration of vitamin D3 has been associated with improved serum TSH levels [31]. Similarly, the incidence of thyroid nodules is considerably lower in the presence of a high level of serum 25(OH)D, suggesting a direct protective effect of 25(OH)D against the occurrence of thyroid nodules [9,12].

On the other hand, one study revealed that a lower level of 25(OH)D may not be considered a risk factor for the development of thyroid nodules [27]. The current study demonstrated a significant association between low vitamin D levels and TI-RADS ultrasound scores of 4 or 5, which indicate considerable risk for malignancy. To our knowledge, our study is the first to examine the relationship between vitamin D level and TI-RADS ultrasound score. Previously, the accuracy of the TI-RADS categories TR4 and TR5 in detecting malignant risk have been shown to be 69.3% and 88.3%, respectively [16]. Our study demonstrated that a lower level of vitamin D was a significant predictor for the risk of thyroid malignancy according to the TI-RADS. This was in concordance with the outcomes of recently published studies indicating that lower serum 25-hydroxyvitamin D levels were linked to increased risk for thyroid cancer in general, well-differentiated thyroid carcinoma and papillary thyroid cancer [14,32-36]. Vitamin D has direct and indirect roles in regulating multiple signalling pathways that enhance many cellular processes (e.g., cellular proliferation, differentiation, apoptosis, inflammation, invasion, angiogenesis and metastasis [4] and regulates microRNA expression that may influence cancer stem cell biology [3]. Furthermore, it is responsible for the inhibition of mitogenic signalling by many growth factors, such as insulin-like growth factor 1 and epidermal growth factor; it also induces the increased expression of growth inhibitors, such as transforming growth factor-β [4]. Additionally, the anti-inflammatory actions of vitamin D are exerted through the inhibition of prostaglandin synthesis and prostaglandin signalling, leading to the suppression of p38 stress kinase signalling and, ultimately, switch-off production of pro-inflammatory cytokines [3,5]. Likewise, the polymorphisms of genes encoding for vitamin D receptors and genes encoding for the participating hydroxylating enzymes in thyroid tissue are involved in the development of thyroid cancer [37]. Furthermore, a high level of circulating 25(OH)D is associated with a decreased risk of thyroid cancer [3,12].

"Therefore, an individual's vitamin D level may be considered the first modifiable risk factor for thyroid cancer; it is possible to modify VDR signalling [34,37,38], inhibit cell proliferation via anti-neoplastic factors [5], and enhance intracellular kinase pathways that repress proto-oncogenes, thereby blocking high telomerase activity [3,5]". However, some other studies have reported no association between 25(OH)D levels and the risk of developing thyroid carcinoma or its prognosis [27,33].

Our study documented a significant association between vitamin D level and hypertension among patients with thyroid nodules. A significant association between hypertension and nodular thyroid disease was also demonstrated in recent clinical trials [9,39,40]. Similarly, isolated systolic hypertension was observed in patients with thyroid cysts and participants without evidence of atherosclerosis who were not taking medications for hypertension, indicating that the thyroid gland can produce a sufficient amount of thyroid hormone [41,42]. This may be explained by the fact that hypertension is an element of metabolic syndrome that is characterised by insulin resistance, which might enhance the proliferation of thyroid cells, promote the formation of nodules and increase the risk of progression to carcinoma [43,44]. Furthermore, vitamin D deficiency stimulates renin expression, whereas the administration of 1,25-dihydroxyvitamin D3 has been observed to reduce renin synthesis [45]. This was confirmed by similar results in a transgenic mouse model, with mice over-expressing the human vitamin D receptor in renin-producing cells that were suppressed with the administration of 1,25-dihydroxyvitamin D3, independent of parathyroid hormone and calcium levels [46]. The results of the present study are in concordance with the outcomes of many studies that have shown no significant associations between vitamin D and other associated predictors (age, gender, BMI, thyroid hormone levels, hypothyroidism and hyperthyroidism [28,47-51]. This may be explained by the very high prevalence of vitamin D deficiency in patients with thyroid nodules in the present study (89.8%), which confirms the results of a previous study from Saudi Arabia [49].

Limitations

This study was retrospective and from one centre. Additional factors, such as thyroid antibodies, iodine levels, nutritional patterns, exposure to radiation, genetic factors and environmental factors were not assessed.

Conclusion

A high prevalence of vitamin D deficiency was documented among patients with nodular thyroid disease in the Eastern Region of the KSA. TI-RADS ultrasound scores of 4 and 5 and the presence of hypertension were significantly associated with lower levels of vitamin D in patients with thyroid nodules.

Abbreviations

KSA: Kingdom of Saudi Arabia
VDRs: Vitamin D receptors
(25[OH)] D): 25-hydroxyvitamin D
1,25(OH)2D3:1,25-dihydroxyvitamin D
AOR: Adjusted odds ratio
BMI: Body mass index
CI: confidence interval
SD: Standard deviation
TI-RADS: Thyroid ultrasound reports based on thyroid imaging reporting and data system.

Data Availability

On request

Acknowledgments

Not applicable

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Author contributions

Conceptualization: IRM, NAA, ZAA and HY. Methodology: HY, MAS, AS AHH Data Curation HY, MAS, AS AHH, ZAAand NA. Formal Analysis: IRM, HY Investigation: HY, MAS, AS AHH, ZAA and NAA. Writing – Original Draft Preparation: IRM, HY and. All contributors reviewed the manuscript.

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