

## Hypothyroidism Associated with Low Vitamin D Deficiency among Type 2 Diabetic Mellitus Patients - A Cross Sectional Study

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### Abstract

**Introduction:** Vitamin D deficiency (VDD) has been identified as a risk factor for diabetes mellitus and autoimmune diseases. We conducted a cross sectional study to investigate the prevalence of hypothyroidism and vitamin D deficiency in patients with T2DM.

**Method:** A cross-sectional single centre study was conducted in 4053 patients with T2DM. Patients with T2DM attended the Diabetes Centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia between January 2018 and December 2018 were recruited. The serum concentration of 25-OHD, Thyrotropin level (TSH), Free thyroxine (FT4) and HbA1c were measured.

**Results:** There were 2019 patients with T2DM, 481 (23.8%) male and 1538 (76.2%) female. The mean age was  $51.3 \pm 16.4$  years. The mean and median 25-OHD concentrations were  $58.1 \pm 38.7$  and 51.9 respectively. Hypothyroidism was found in 402 (19.9%). The mean TSH and FT4 value was  $3.5 \pm 8.9$  mIU/l and  $13.9 \pm 4.3$  pmol/l respectively. VDD (25-OHD < 50 nmol/l) was found in 959 (47.5%). Moreover, VDD was significantly more prevalent among females than males with male to female ratio 1:2.6 (72.6% vs. 27.4% respectively,  $p < 0.0001$ ). In addition, Vitamin D deficient patients were statistically significant younger than non-vitamin D deficient ( $47.6 \pm 16.0$  vs.  $54.7 \pm 16.1$  respectively,  $p < 0.0001$ ). Vitamin D deficient patients have statistically significant higher HbA1c than non-vitamin D deficient ( $8.0 \pm 2.2$  vs.  $7.2 \pm 1.9$  respectively,  $p < 0.0001$ ). As expected, the mean 25-OHD concentration was statistically significant lower in the vitamin D deficient patients compared to non-vitamin D deficient ( $33.8 \pm 9.8$  vs.  $80.2 \pm 28.3$  respectively,  $p < 0.0001$ ). Hypothyroidism was statistically significant more prevalent in vitamin D deficient than non-vitamin D deficient (22.1 vs. 17.9,  $p = 0.02$ ). The mean TSH concentration was statistically significant higher in the vitamin D deficient patients compared to non-vitamin D deficient ( $4.0 \pm 11.6$  vs.  $3.1 \pm 5.4$  respectively,  $p < 0.0001$ ). On the opposite, the mean FT4 concentration was statistically significant lower in the vitamin D deficient patients compared to non-vitamin D deficient ( $13.3 \pm 2.8$  vs.  $14.3 \pm 5.3$  respectively,  $p < 0.0001$ ). There were statistically significant differences between subjects vitamin D deficient patients compared to non-vitamin D deficient for female gender ( $P < 0.0001$ ), 25-OHD ( $P = 0.02$ ), TSH ( $P < 0.0001$ ), FT4 ( $P = 0.02$ ). Multivariable logistic regression analysis of independent predictors for the presence of VDD showed female gender (OR: 1.617, 95% CI: 1.257 - 2.080,  $P < 0.0001$ ), age (OR: 0.971, 95% CI: 0.963 - 0.978,  $P < 0.0001$ ) and HbA1c (OR: 1.174, 95% CI: 1.105 - 1.247,  $P < 0.0001$ ) were considered at higher risk as predictors of VDD among T2DM patients. The prevalence of VDD associated hypothyroidism decreased as age advanced with highest frequency of hypothyroidism was found statistically significant in the fifth and sixth decades.

**Conclusions:** The prevalence of hypothyroidism among T2DM patients was higher in patients with than without VDD. Young age, female gender and high Hba1c but not the presence of hypothyroidism are identified as an independent predictors of VDD. There is a strong positive associations between the VDD and hypothyroidism population among T2DM patients.

**Keywords:** Type 2 Diabetes Mellitus; Hypothyroidism; Vitamin D Deficiency

### Introduction

Vitamin D is recognized to be an essential element for bone metabolism and skeletal health [1]. In addition, it may also affect extraskel-etal health. Indeed, vitamin D deficiency (VDD) has been identified as a risk factor for diabetes mellitus and autoimmune diseases [2-5]. On the other hand, immune-mediated pathophysiology comprises the major etiology of hypothyroidism in iodine-replete areas [6].

The prevalence of type 2 diabetes mellitus (T2DM) in Saudi Arabia is one of the highest reported in the world, reaching up to 30% [7]. VDD remains a major health problem in many parts of the world [8]. VDD has received special attention lately because of its high incidence and its implication in the genesis of multiple chronic illnesses. The high prevalence of VDD in general population underlines the fact that VDD is more common in chronic diseases like diabetes mellitus.

T2DM and hypothyroidism are the main threats in developed and developing countries and impairs the health and economic status [9,10]. T2DM increases the risk of thyroid dysfunction in the long-term [11-17]. T2DM and thyroid dysfunction are the primary reasons for mortality and morbidity in most high income and developing countries [13-17]. Thyroid disorders and diabetes are the two most widespread endocrinological medical conditions seen in general clinical medical practice [12]. However, several studies have shown a higher prevalence of thyroid dysfunction occurring among T2DM patients [15-20]. Moreover, positive correlations between VDD and thyroid dysfunction among T2DM patients have been reported by several authors [1,19-22].

Few published researches have been found that surveyed the prevalence of VDD in patients with hypothyroidism among patients with T2DM in Saudi Arabia. We conducted a cross sectional study to investigate the prevalence of hypothyroidism in patients with VDD among patients with T2DM.

### Methods

A cross-sectional single centre study was conducted in 2019 patients with T2DM attended the Diabetes Centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia between January 2018 and December 2018. Eligible patients were 20 years or older. Exclusion criteria were known hepatic or renal disease, metabolic bone disease, malabsorption, hypercortisolism, malignancy, immobility for more than one-week, pregnancy, lactation, and medications influencing bone metabolism. The serum concentration of 25-HydroxyVitamin D(25-OHD) was measured by competitive protein binding assay using kits (Immunodiagnostic, Bensheim, Germany). VDD was defined as serum 25-OHD concentration < 50 nmol/L [1]. Glycosylated hemoglobin (HbA1c) was measured by the high performance liquid chromatography method (Bio-Rad Laboratories, Waters, MA, USA). Patients with Thyrotropin level (TSH) above the normal range of TSH for our laboratory reference, history of hypothyroidism and taking thyroid replacement therapy were included as hypothyroidism. The reference range values of TSH 0.22 - 4.2 MIU/L and Free thyroxine (FT4) 12.0 - 22.0 pmol/L. The total number of cohort were separated on basis of age values into six groups: 20 - 29 years, 30 - 40 years, 40 - 49 years, 50 - 59 years, 60 - 70 years and  $\geq$  70 years. The study was approved by the ethical committee board of King Fahad Armed Forces Hospital.

### Statistical analysis

Data are presented as means  $\pm$  standard deviation (SD) or numbers (%). Quantitative variables were compared between two groups by using the Student's test. Differences in categorical variables were analysed using the chi-square test. The relationship between continuous variables was assessed using coefficients of correlation. Logistic regression analysis was carried out to identify the independent predictors of vitamin D deficiency considering age, gender and HbA1c as risk factors and to estimate odds ratio (OR) and 95% CI. P value < 0.05 indicates significance. The statistical analysis was conducted with SPSS version 23.0 for Windows.

### Results

There were 2019 patients with T2DM, 481 (23.8%) males and 1538 (76.2%) females (Table 1). The mean age was  $51.3 \pm 16.4$  years. The mean and median 25-OHD concentrations were  $58.1 \pm 38.7$  and 51.9 respectively. Hypothyroidism was found in 402 (19.9%). The

mean TSH and FT4 value was  $3.5 \pm 8.9$  mIU/l and  $13.9 \pm 4.3$  pmol/l respectively. VDD (25-OHD < 50 nmol/l) was found in 959 (47.5%) (Table 2). Moreover, VDD was significantly more prevalent among females than males with male to female ratio 1:2.6 (72.6% vs. 27.4% respectively,  $p < 0.0001$ ). In addition, Vitamin D deficient patients were statistically significant younger than non-vitamin D deficient ( $47.6 \pm 16.0$  vs.  $54.7 \pm 16.1$  respectively,  $p < 0.0001$ ). Vitamin D deficient patients have statistically significant higher HbA1c than non-vitamin D deficient ( $8.0 \pm 2.2$  vs.  $7.2 \pm 1.9$  respectively,  $p < 0.0001$ ). As expected, the mean 25-OHD concentration was statistically significant lower in the vitamin D deficient patients compared to non-vitamin D deficient ( $33.8 \pm 9.8$  vs.  $80.2 \pm 28.3$  respectively,  $p < 0.0001$ ). Hypothyroidism was statistically significant more prevalent in vitamin D deficient than non-vitamin D deficient (22.1 vs. 17.9,  $p = 0.02$ ). The mean TSH concentration was statistically significant higher in the vitamin D deficient patients compared to non-vitamin D deficient ( $4.0 \pm 11.6$  vs.  $3.1 \pm 5.4$  respectively,  $p < 0.0001$ ). On the opposite, the mean FT4 concentration was statistically significant lower in the vitamin D deficient patients compared to non-vitamin D deficient ( $13.3 \pm 2.8$  vs.  $14.3 \pm 5.3$  respectively,  $p < 0.0001$ ).

Variable	Values	
Total	2019	
Age (years)	$51.3 \pm 16.4$	
Gender	Male	481 (23.8)
	Female	1538 (76.2)
HbA1c (%)	$7.5 \pm 2.0$	
25-hydroxyvitamin D (nmol/L)	$58.1 \pm 38.7$	
Hypothyroidism	402 (19.9)	
TSH (mIU/l)	$3.5 \pm 8.9$	
FT4 (pmol/l)	$13.9 \pm 4.3$	

**Table 1:** Patient characteristics [mean  $\pm$  standard deviation or number (%)].

Variable Present	Vitamin D deficiency		P values
	Absent		
Numbers	959 (47.5)	1060 (52.5)	
Age (years)	$47.6 \pm 16.0$	$54.7 \pm 16.1$	< 0.0001
Gender	Male	263 (27.4)	< 0.0001
	Female	696 (72.6)	
HbA1c (%)	$8.0 \pm 2.2$	$7.2 \pm 1.9$	< 0.0001
25-hydroxyvitamin D (nmol/L)	$33.8 \pm 9.8$	$80.2 \pm 28.3$	< 0.0001
Hypothyroidism	212 (22.1)	190 (17.9)	0.02
TSH (mIU/l)	$4.0 \pm 11.6$	$3.1 \pm 5.4$	0.02
FT4 (pmol/l)	$13.3 \pm 2.8$	$14.3 \pm 5.3$	< 0.0001

**Table 2:** Vitamin D deficiency among Type 2 diabetes mellitus patients [mean  $\pm$  standard deviation or number (%)].

Table 3 gives clinical biochemistry baseline based on VDD with and without hypothyroidism among T2DM. There were statistically significant differences between subjects vitamin D deficient patients compared to non-vitamin D deficient for female gender ( $P < 0.0001$ ), 25-OHD ( $P = 0.02$ ), TSH ( $P < 0.0001$ ), FT4 ( $P = 0.02$ ).

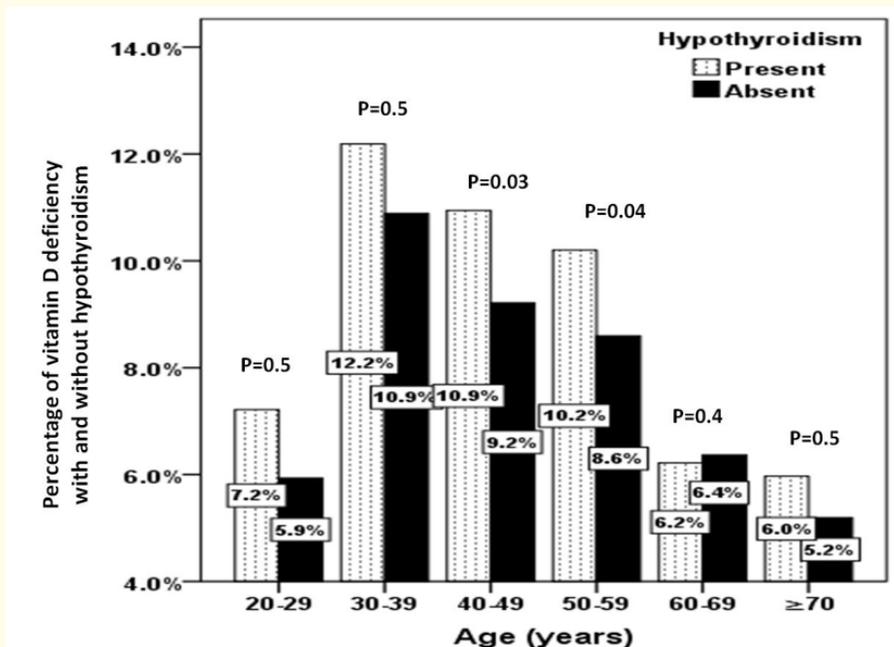
Variable With hypothyroidism	Vitamin D deficiency		P values
	Without hypothyroidism		
Numbers	959 (47.5)	1060 (52.5)	
Age (years)	47.6 ± 16.6	47.5 ± 15.8	0.9
Gender	Male	46 (21.7)	< 0.0001
	Female	166 (78.3)	
HbA1c (%)	8.0 ± 2.1	7.8 ± 2.2	0.3
25-hydroxyvitamin D (nmol/L)	32.3 ± 10.8	34.2 ± 9.4	0.02
TSH (mIU/l)	11.2 ± 23.2	2.0 ± 1.0	< 0.0001
FT4 (pmol/l)	12.9 ± 2.9	13.4 ± 2.8	0.02

**Table 3:** Clinical biochemistry baseline based on vitamin D deficiency with and without hypothyroidism among T2DM [mean ± standard deviation or number (%)].

Table 4 gives multivariable logistic regression analysis of independent predictors for the presence of VDD. Female gender (OR: 1.617, 95% CI: 1.257-2.080, P < 0.0001), young age (OR: 0.971, 95% CI: 0.963-0.978, P < 0.0001) and high HbA1c (OR: 1.174, 95% CI: 1.105-1.247, P < 0.0001) were considered at higher risk as predictors of VDD among T2DM patients.

Parameters	Odd Ratio	95% Confidence interval	P value
Female gender	1.617	1.257 - 2.080	< 0.0001
Age (years)	0.971	0.963 - 0.978	< 0.0001
HbA1c	1.174	1.105 - 1.247	< 0.0001
Hypothyroidism	1.118	0.822 - 1.521	0.5

**Table 4:** Multivariate logistic regression analysis for predictors presence of vitamin D deficiency among T2DM patients.



**Figure 1:** The percentage of vitamin D deficiency in patients with and without hypothyroidism in patients with type 2 diabetes in correlation to age groups.

The prevalence of VDD associated hypothyroidism decreased as age advanced, with statistically significant highest frequency of hypothyroidism was found in the fifth and sixth decades (Figure 1).

### Discussion

Diabetes mellitus is a worldwide epidemic and currently the most prevalent chronic illness in the world having a prevalence of around 9% in the adult population and 30% of Saudi adults [7,23]. Moreover, VDD has received special attention lately because of its high incidence and its implication in the genesis of multiple chronic illnesses. VDD and T2DM are usually recognized as a complication and risk for thyroid disease.

There are very few studies which determine the relationship between VDD and hypothyroidism among T2DM patients as a worldwide. Our study has revealed a higher prevalence of hypothyroidism in VDD with T2DM patients. The present study demonstrated low mean vitamin D level with hypothyroidism compared to VDD without hypothyroidism. This is confirmative with the previous reported studies [19,20,24,25]. In fact, T2DM and thyroid diseases are highly correlated as the two commonest endocrinological medical conditions reported and linked with the vitamin D deficiency in general clinical practice [13-22]. Additionally, a study has investigated the role of environmental and lifestyle factors [11]. It is worth to note that the possible role of VDD can be considered in the pathogenesis of both DM and thyroid disease. However, VDD could be also secondary to these diseases. Oral anti-diabetic medications as well as therapeutic dietary restriction could affect vitamin D levels in patients with diabetes. In addition, thyroid dysfunction could also modify vitamin D intake, absorption or metabolism. 25-OHD exerts its effect by binding to 25-OHD 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 [26]. Moreover, the association between autoimmune thyroid disorders such as Hashimoto's disease with low levels of 25-OHD has been described [27,28]. In one report, the frequency of 25-OHD deficiency is higher among patients with autoimmune thyroid disorders compared to those with non-autoimmune thyroid problem or healthy controls [21]. Metabolism of 25-OHD 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 [29]. 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 [30]. There is a strong suggestion that the epidermal barrier function is probably impaired in hypothyroidism with a speculation that synthesis of 25-OHD is decreased in patients with overt hypothyroidism and high TSH [31]. Finally, the body may not activate vitamin D properly [32].

In the multivariate linear regression model constructed using serum VDD as the dependent variables, age, female gender and Hba1c but not the presence of hypothyroidism are identified as an independent predictors of VDD in the present study. It has been shown that age has shown a positive correlation with 25-OHD level in our population ( $r = 0.2$ ,  $p < 0.0001$ ) and the prevalence of VDD with hypothyroidism was decreased with age, in addition, VDD was more prevalent in the fifth and sixth decades in discordance with other [33]. As such as the study population grow older, the serum concentrations of 25-OHD increase. We speculate that the observation is due to the fact that our population consists of population with a tendency to include subjects in the seventh and eighth decades of their lives. Interestingly in two other reports as the current study, higher levels of 25-OHD have been reported in older population in comparison with their younger counterparts [33,34]. This could be due to the higher rate of consumption of 25-OHD supplements in this age group.

Hypothyroidism are more common in females by 5 - 10 times, while their frequency increases with age [35,36]. Our results revealed decreased serum 25-OHD levels in patients with than without hypothyroidism. Moreover, there was non statistical significant different of serum 25-OHD levels between female and males ( $33.2 \pm 8.9$  vs.  $34.0 \pm 10.1$ )  $p = 0.3$  respectively in discordance with other.37 Otherwise this decrease was non-significant but we can refer this non-significant decrease to the small sample size of our study.

We had several limitations. study was done at only one centre and was done at one point of time. The study sample confined to patients with T2DM but without comparable groups.

### Conclusion

This study suggests that the prevalence of hypothyroidism among T2DM patients was higher in patients with than without VDD. There is a strong positive associations between the VDD and thyroid diseases population among T2DM patients. Young age, female gender and high Hba1c but not the presence of hypothyroidism are identified as an independent predictors of VDD.

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