

Vitamin D Deficiency in Subclinical Hypothyroid Dysfunction Patients: A Case Control Study

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Abstract

Background: the prevalence of subclinical hypothyroidism worldwide is commoner than the overt disease. Limited studies discussed the vitamin D levels in subclinical hypothyroid patients. Giving vitamin D supplements may prevent from developing overt hypothyroidism. In this cross-sectional case-control study, we described the differences in the vitamin D of adult Saudis with and without subclinical hypothyroid dysfunction. **Methods:** This is an observational single-center, retrospective, age, and sex matched, case-control study. A total of 60 subjects [41 healthy controls, 19 subclinical hypothyroid case] were included. 25(OH) vitamin D, TSH, free T4 and free T3 are measured in both groups. **Results:** Subjects with subclinical hypothyroid dysfunction had a significantly lower serum Vitamin D than controls (p value 0.016) although both groups fall below vitamin D sufficiency levels. Correlation is found between both vitamin D and TSH, p value 0.036. but it was found to be less statistically significant positive relation, r value is 0.279, (R square = .078, beta regression coefficient = -.055 and p value <0.0005) **Conclusion:** Patients with hypothyroid dysfunction showed much lower serum vitamin D compared to controls but it has not that big role in early hypothyroid disorders as shown in less significant relation.

Key words: Vitamin D, Hypothyroidism, Subclinical hypothyroidism

Introduction:

Vitamin D has pleiotropic physiological effects in healthy state as it helps in intestinal calcium absorption and bone mineralization [1].

Also it has assumed associations with various disorders like arterial hypertension [2], fatty liver disease [3], cancer incidence reduction

[4], inflammatory bowel disorders [5], diabetes mellitus [6] and thyroid diseases [7].

A recent large metanalysis showed that vitamin D deficiency patients had 2.99 Odd ratio for having thyroid diseases with an autoimmune etiology in comparison to controls [8]. Limited studies discuss association between early hypothyroid disorders and vitamin D deficiency [9]. Giving vitamin D supplements may prevent from developing overt hypothyroidism [10,11].

The prevalence of abnormal biochemical thyroid function in adults is substantial [12]. The subclinical hypothyroid dysfunction is by far more prevalent than clinically overt disease globally [13]. In USA, the prevalence of subclinical hypothyroidism and overt disease reaches 8.5 % and 0.4 % respectively [14,15]. In Saudi Arabia Subclinical hypothyroidism has a prevalence of 10% of Saudi Arabia adults [16].

Methods:

Subjects

This is an observational single-center, retrospective, age, and sex matched, case-control study. Electronic medical records were reviewed of patients that attended the outpatient clinic located at northern area of Saudi Arabia between March 2019 and

December 2019. A total of 60 subjects [41 healthy controls, 19 subclinical hypothyroid case] were included. It was conducted in 2020. Detailed clinical history and laboratory finding (TSH, FT4, Vitamin D3) were collected on preformed data collection sheet.

Vitamin D3 status of the two groups was tested statistically, correlation between different thyroid hormones and serum Vitamin D3 was observed. Eligible patients were 20 years or older who had a subclinical hypothyroid dysfunction confirmed by thyroid profile (elevate TSH with normal FT4 levels). Control subjects had normal thyroid profile without any history of thyroid disorders

We excluded from the study any individual with a known hepatic or renal disorders, metabolic bone disease, malignancy, pregnancy, lactation, or having medications altering bone metabolism.

The study protocol approval and patient consents were waived from Institutional Review Board (IRB) of Tabuk Hospital administration after reviewing the Declaration of Helsinki standards as it is designed retrospectively using electronic medical records that masks the subject's identities.

Methods

Blood samples were drawn for serum TSH and FT4 levels. There were no restrictions on eating or requests to discontinue medication before testing. Serum TSH, and FT4, were measured by chemiluminescent immunoassay. Serum TSH had a laboratory reference range of 0.22–4.2 mIU/L. The laboratory reference range for FT4 was 12.0–22.0 pmol/L.

Laboratory data were extracted from the medical information system of the hospital and added to the data collection form. The serum concentration of 25-HydroxyVitamin D (25-OHD) was tested with ELISA in accordance with the instructions provided by the manufacturer, Roche Cobas e 411, Lot number 47457802.

Vitamin D deficiency was considered if Vitamin D levels were less than 30 ng/ml and if the levels were between 20-30 ng/ml, it was regarded as insufficient; Sufficient Vitamin D levels are between 30-100 ng/ml. Euthyroid patients had normal serum FT4 and TSH levels, while subclinical hypothyroid patients had normal serum FT4 and TSH > 4.2 mIU/l but < 10 mIU/l.

Statistical analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 (Chicago, Ill, USA). Frequencies

were referred by N. Mean (\pm standard deviation) was used with normal distributed

variables and median (inter-quartile range) was used in non-parametric distributed variables. Shapiro wick test (small sample size in both groups) was used to evaluate normality.

For group comparisons (subclinical hypothyroid dysfunction versus healthy controls), independent T-test and Mann-Whitney U-test were used for parametric and non-parametric data. when $p < 0.05$, it is considered significant statistically

Results

Demographic characteristics of subclinical hypothyroid cases and healthy controls are represented in the table 1 below. The two groups are age and sex matched. Mean age in subclinical hypothyroid patients is 46.6 (± 11.7) year old while in healthy controls is 42.15 (± 14.33) year old. Female represented 73.7 % of subclinical hypothyroid cases and 68.3 % of healthy controls.

The results show significant difference among both groups vitamin D and TSH levels ($p < 0.05$). In subclinical hypothyroid patients, Median (and IQR) of serum vitamin D level is lower than it is found in euthyroid subjects 18.5 (12.9-32) ng/ml versus 14.6 (10.1-18.7) ng/ml, p-value 0.006.

The data shows that all subclinical hypothyroid patients (n=19/19) had vitamin D deficiency compared to only 73.17 % (n=30/41) of Euthyroid healthy controls.

By using Mann-Whitney U test, Subjects with subclinical hypothyroid dysfunction had a significantly higher TSH (as expected, according to definition) and lower serum Vitamin D than controls (p value 0.016) although both groups fall below vitamin D sufficiency levels.

With using Spearman test, a correlation between both vitamin D and TSH was found, (p value 0.036), but it was found to be less statistically significant positive relation when linear regression is done, r value is 0.279, (R square = .078, beta regression coefficient = -.055 and p value <0.0005)

Odd ratio of vitamin D deficiency and subclinical hypothyroidism was 1.36 that means subclinical hypothyroid patients are 1.36 times as likely to have vitamin D deficiency compared to healthy controls.

By using one sample t test, the data showed there was a difference between levels of vitamin D across all subjects' ages (p value < 0.001). To test a correlation between age and vitamin D level, a Pearson test shows coefficient ratio $r = 0.27$, p value 0.035 and R square 0.075. Size of correlation means that it is a low correlation that might warrant further studies (fig 1).

The study data is available from corresponding author, upon request.

Table 1: General characteristics of both subclinical hypothyroid cases and healthy controls

	Subclinical hypothyroidism cases	Healthy Controls	P values
Frequency N (%)	19 (31.7%)	41(68.3%)	
Gender	Female N (%)	28 (68.3 %)	0.678
	Male N (%)	13 (31.7 %)	
Age mean (SD)	46.6 (11.7)	42.15 (14.33)	0.359
TSH (Median and IQR) *	5.4 (4.5-6.3)	1.5(1.1-2.4)	0.000
Vitamin D level (Median and IQR) *	14.6(10.1-18.7)	18.5 (12.9-32)	0.016

Note *: denotes non-Gaussian distribution and presented as median with interquartile range; p-value significant at < 0.05. Age and gender were normal distributed but serum vitamin D and TSH values showed non gaussian distributions

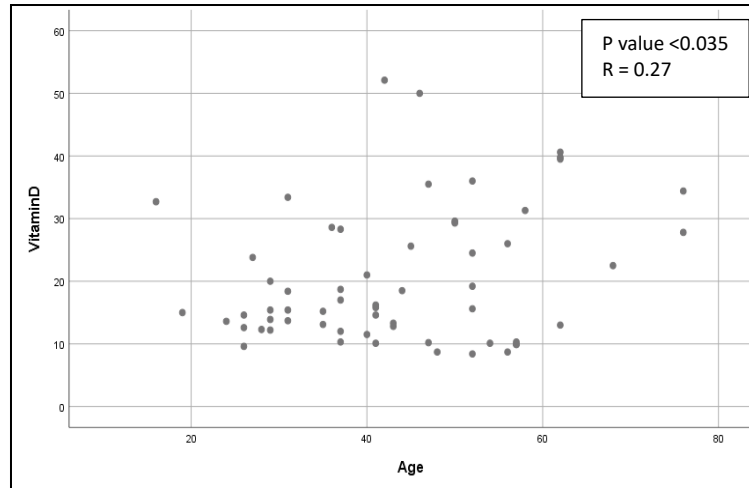


Fig 1: scatter plot represents relation between vitamin D level and age

Discussion

In the current study the subclinical hypothyroid patients (n=19/19) had vitamin D deficiency compared to only 73.17 % (n=30/41) of euthyroid healthy controls. This high prevalence of vitamin D deficiency in Saudi Arabia individuals matched with other studies that was conducted earlier [16]. In a meta-analysis that had been conducted on studies published (from 2008 to 2015) showed that vitamin D deficiency is around 60% on the Saudi Arabian population [17].

Many studies were conducted to find if there is an association between vitamin D deficiency and hypothyroid disorders, whether vitamin D involved in pathogenesis

or even a sequelae of a thyroid illness [13,18,19].

Vitamin D was compared between subclinical hypothyroid patients and euthyroid controls. We also examined the association and predictive relation of vitamin D level with subclinical hypothyroidism.

In this research, subjects with subclinical hypothyroid dysfunction had a significantly lower serum Vitamin D than controls (p value 0.016) although both groups fall below vitamin D sufficiency levels. Conflicting results are found in this era, where some articles found the same results [13], others showed the opposite [20]. These differences may be explained by several

unmeasured confounders which include varied dietary intake, BMI differences, other comorbidities which may be not documented.

Moreover, we reported a positive relation between vitamin D levels and age (coefficient ratio $r = 0.27$, p value 035). Although this is a less statistically significant positive relation, our data does not match with other studies that showed decreased vitamin D with age [21,22]. This can be described by some limitation in our article like variable BMI, sun exposure and socioeconomic status through all participants.

While many authors showed that serum vitamin D level decreases in several thyroid disorders [19, 23], our data showed less statistically significant positive relation between serum vitamin D level and TSH when linear regression was done, (r value is 0.279, R square = .078, beta regression coefficient = -.055 and p value <0.0005) which would confirm the Dutch study that showed that low vitamin D is not a causation to genetic thyroid disorders predisposition or TPO antibody positive euthyroid participants [24].

Also our results were against the beneficial effect that had been shown when vitamin D replacements had been given to subclinical

hypothyroid [20,25,26], but this can be explained by specific inclusion of autoimmune TPO-positive subclinical hypothyroid participants in these clinical trials and natural history of subclinical hypothyroid disorders that may spontaneously resolve [27].

We acknowledge several limitations which include the cross-sectional study methodology, the small sample size, and multiple confounders like BMI. Also, dietary vitamin D intake were not included which has proven effects on vitamin D level. Nevertheless, the study has its own strength as it explores the need for further large sample size studies to clear the controversies in vitamin D deficiency in early thyroid disorders and in which subsets it may play a such significant beneficial role.

Conclusions

In summary, adult patients with subclinical hypothyroidism have much lower serum vitamin D. My study shows that there is no statistically significant correlation between vitamin D and TSH levels in subclinical hypothyroid dysfunction patients. So, large sample size studies are needed to explore the controversies in vitamin D deficiency in that early thyroid dysfunction.

Key message

- Adult patients with subclinical hypothyroidism have much lower serum vitamin D
- No statistically significant correlation between serum 25 hydroxy vitamin D levels and TSH levels in subclinical hypothyroid dysfunction patients

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