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Original Research Article

Study of Vitamin D3 Level in Non-Diabetic Patients with Subclinical Hypothyroidism

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Abstract:

Introduction: The deficiency of vitamin D is a major health problem worldwide. In recent studies vitamin D deficiency has been shown to be associated with increased risk of diabetes mellitus, atherosclerosis and autoimmune condition like autoimmune thyroiditis. There has not been any clear research that shows the association between the vitamin D deficiency and hypothyroidism. The present study aims to explore the levels of vitamin D in the subjects with subclinical hypothyroidism. Subclinical hypothyroidism is defined by normal serum T3, T4 levels and serum TSH level falling between 4.2 to 10 mU/L without any clinical signs and symptoms. The aim of the current study was to study the vitamin D level in nondiabetic subclinical hypothyroid subjects and to compare the vitamin D level with controls.

Materials & Methods: The cross-sectional study was conducted among 100 subjects of subclinical hypothyroidism (S. TSH level between 4.2 – 10 mU/L, normal S. T3 and S. T4) while, the control group consisted of 100 healthy individuals at Shree Krishna Hospital and H. M. Patel Centre for Medical Care and Education - Gujarat. The vitamin D levels are measured using Electrochemiluminescence method on Cobas E411 analyser.

Results: There is no significant difference between the case and the control groups for the age, sex, fasting blood sugar, HbA1c, S. T3 and S. T4 level. The vitamin D levels are significantly lower in the cases with subclinical hypothyroidism than the controls.

Conclusion: Our study suggest that the subjects with subclinical hypothyroidism showed vitamin D insufficiency or deficiency and there is strong negative linear correlation between the levels of S. TSH and vitamin D in all the study subjects.

Keywords: Subclinical hypothyroidism, Non-Diabetic, vitamin D, Electro chemiluminescence.

Introduction

A normal T4 and elevated Thyroid Stimulating Hormone (TSH) are signs of subclinical hypothyroidism (SCH). Vitamin D deficiency is very common in SCH patients [1]. It has been demonstrated that vitamin D deficiency is associated with autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE), inflammatory bowel disease (IBD), multiple sclerosis (MS), and type 1 diabetes mellitus (T1DM). Vitamin D supplementation, on the other hand, has been shown to prevent the onset and/or development of these autoimmune diseases [2]. Also, it was reported that people with Hashimoto's thyroiditis, an autoimmune thyroid disease, had lower levels of vitamin D (3). Vitamin D is important for maintaining calcium homeostasis and the skeleton's development and maintenance [4, 5].

Importantly, both vitamin D and thyroid hormone bind to similar receptors called steroid hormone receptors, located in intranuclear. A different gene in the vitamin D receptor was shown to predispose people to autoimmune thyroid disease including Graves' disease and Hashimoto's thyroiditis. For these reasons, it is important to understand how the vitamin D system works in the patients with thyroid problems. Vitamin D mediates its effect though binding to vitamin D receptor, and activation of vitamin D receptor responsive genes, while vitamin D receptor gene polymorphism was found to associate with autoimmune thyroid diseases (AITDs) [6]. Sudha K. et al. Study establishes the fact that 1,25 dihydroxy cholecalciferol may play an important role in altering thyroid hormones and TSH levels in subclinical hypothyroidism. Vitamin D insufficiency is associated with subclinical hypothyroidism[7]. From this point of view, we have undertaken to study the level of vitamin D in the subjects of subclinical hypothyroidism (S. TSH > 4.2 to < 10 mU/L) [8] without diabetes, that is, those having HbA1c < 6.5 %.[9].

Material & Methods

This retrospective case-control study was conducted in the Shree Krishna Hospital and H. M. Patel Centre for Medical Care and Education Hospital attached to Pramukhswami Medical College, Karamsad from January 2016 to November 2017. Ethical clearance was obtained from Institutional Ethics Committee, H.M. Patel Centre for Medical Care and Education, Karamsad. The history of the participants, required for the study was collected from the health check-up files and the data of laboratory reports required for the study were obtained from the online Laboratory Information System (LIS) and the online HMPC Helpdesk software database.

A total of 200 individuals were considered for the study, 100 cases with a diagnosis of Non-Diabetic Patients with Subclinical Hypothyroidism and 100 individuals as a control group.

All the subjects (Aged >18 years) coming to "Hello Health Scheme" at Shri Krishna Hospital, Karamsad for routine health check-ups were included in the study after applying the inclusion and exclusion criteria and used for research purposes.

Inclusion Criteria:

Cases: This study group consisted of 100 subjects coming for the routine health check-up scheme in Shri Krishna Hospital with the following inclusion criteria.

- Age between 20 to 70 years
- HbA1c < 6.5 % (According to recent guideline of ADA)
- S TSH > 4.2 to < 10 mU/L (Subclinical Hypothyroidism)

Controls: The control group consisted of 100, age and sex-matched normal healthy individuals with

- Age between 20 to 70 years

- HbA1c < 6.5 % (According to recent guideline of ADA)
- S TSH > 0.27 to < 4.2 mU/L

Exclusion Criteria: The exclusion criteria were as follows:

- Known Diabetic patients
- Patients on thyroxine or anti-thyroid drugs supplements
- Liver diseases (on the basis of LFT)
- Renal diseases (on the basis of RFT)

Patients with Non-Diabetic Patients with Subclinical Hypothyroidism who met the inclusion criteria (n=100) were included and 100 individuals who met the inclusion criteria in the controls group were included.

Routine health check-up scheme includes basic information, clinical history and laboratory investigations [Fasting Blood Sugar, Glycated Hemoglobin (HbA1c), Thyroid Function Tests (TFT), Liver Function Tests (LFT), Renal Function Tests (RFT), Vitamin B_{12}, Vitamin D_3, Histogram, Urine - Routine & Microscopy, etc.].

Statistical analysis: Statistical analysis was performed using the commercially available statistical software MedCalc Version 14.8.1 and Microsoft Office 2016. The P value of less than 0.05 was considered statistically significant.

Results:

A total of 200 participants were included in this study, of which 100 participants were as cases group and 100 participants were as control groups. The mean and SD age for the cases group was 53.75 ± 11.06 years and 54.8 ± 9.77 for the control group. All the subjects were in the age groups between 21-70 years. Both groups were statistically similar in the age groups with P value of 0.48. So, there was no significant difference in the mean age between these two groups. The mean fasting blood sugar levels were 96.28 mg/dl and 97.17 mg/dl in the case and the control groups respectively. There was statistically insignificant difference with P value of 0.29. The mean HbA1c levels were 5.95 (%) and 5.89 (%) in the case and the control groups respectively. There was no statistically significant difference with P value of 0.31. The mean S. T3 levels were 1.76 nmol/L and 1.74 nmol/L in the case and the control groups respectively. There was no statistically significant difference with P value of 0.71. The mean S. T4 levels were 106.75 nmol/L and 107.36 nmol/L in the case and the control groups respectively. There was no statistically significant difference with P value of 0.80. The mean S. TSH levels were 6.4 mU/L and 2.5 mU/L in the case and the control groups respectively. There was statistically significant difference with a P value of <0.0001. Level of S. The mean Vitamin D3 levels were 20.1 nmol/L and 31.5 nmol/L in the case and the control groups respectively. There was statistically significant difference with a P value of <0.0001. Level of Vitamin D3 was significantly lower in the case group compared with the control group as shown in the Box and Whisker Plot.

Table 1: Comparison of various parameters in the case and the control groups (The independent t tests)

Variables	Cases(Mean ± SD) N = 100	Control(Mean± SD) N = 100	P value*
Age(Year)	53.75 ± 11.06	54.8 ± 9.77	0.48
FBS(mg/dl)	96.28 ± 6.31	97.17 ± 5.64	0.29
HbA1c (%)	5.95 ± 0.38	5.89 ± 0.40	0.31
S. T3(nmol/L)	1.76 ± 0.31	1.74 ± 0.30	0.71
S. T4(nmol/L)	106.75 ± 18.54	107.36 ± 15.31	0.80
S. TSH(mU/L)	6.4 ± 1.5	2.5 ± 0.9	< 0.0001
Vitamin D_3 (nmol/L)	20.1 ± 5.0	31.5 ± 8.1	< 0.0001

***P < 0.05 = Statistically Significant**

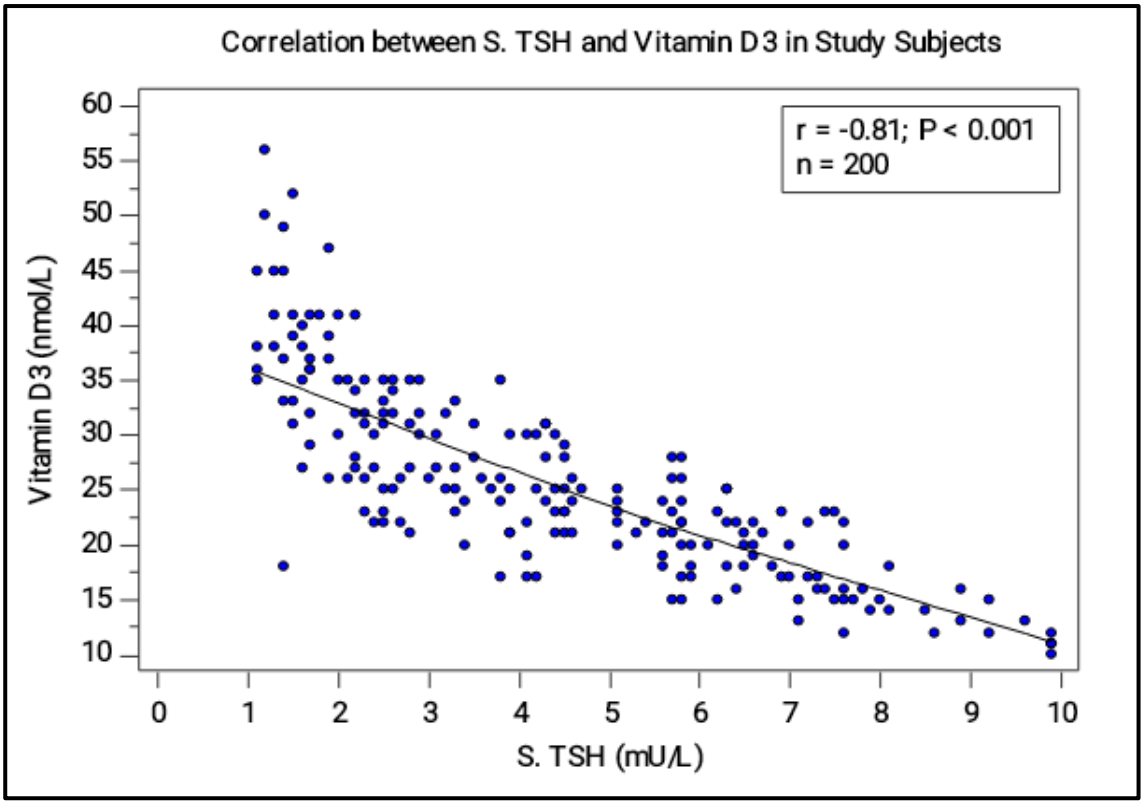

Figure 1: Showing the correlation between S. TSH (mU/L) levels and Vitamin D_3 (nmol/L) levels in all of the Subjects of the Study by Pearson's correlation coefficient.

The results presented in this Figure were showing that the levels of S. TSH have strong negative linear relationship with the levels of Vitamin D3 in the study subjects by Pearson's correlation coefficient ($r = -0.81$, $P < 0.0001$).

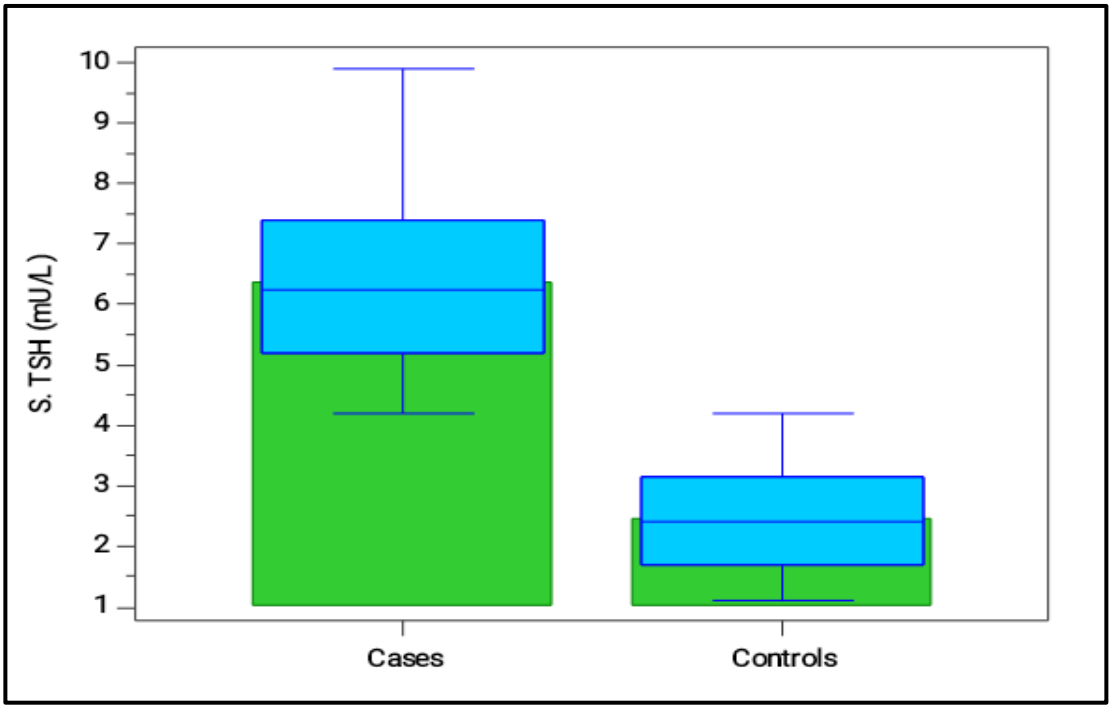

Figure 2: Showing S. TSH (mU/L) level in the case and the control groups with Box and Whisker Plot

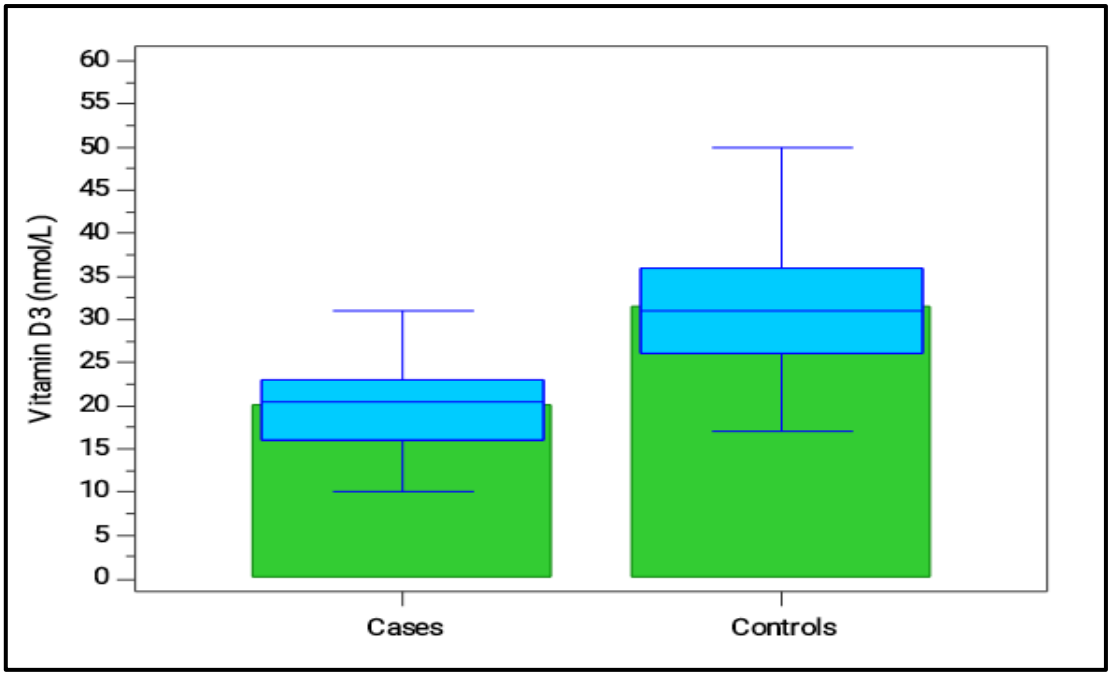

Figure 3: Showing Vitamin D_3 (nmol/L) level in the case and the control groups with Box and Whisker Plot.

Discussion

This study was a cross-sectional done over a period from January 2016 to November 2017 and included subclinical hypothyroidism patients as cases and healthy individuals as controls. The levels of S. TSH in all the cases were between 4.2 to 10 mU/L but, other parameters like S. T3 and S. T4 levels were normal. All the controls had normal thyroid function tests.

The mean S. TSH levels in the case group(subclinical hypothyroidism) were higher than in the control group(normal healthy individuals). There was a statistically significant difference with a P value of < 0.0001. But we observed that the mean vitamin D3 levels were higher in the control group(normal healthy individuals) compared with the case group (subclinical hypothyroidism). There was a statistically significant difference with a P value of < 0.0001. As there was no statistically significant difference between the cases with subclinical hypothyroidism and the controls with normal healthy individuals for the age, sex, FBS, HbA1c, S. T3, and S. T4 levels. Also, we found that there was a statistically significant correlation between S. TSH and vitamin D3 levels in all the study subjects by Pearson's correlation coefficient (r = - 0.81, P < 0.0001). According to the above observations, we can say that the levels of S. TSH have a strong negative linear relationship with the levels of vitamin D3.

Studies association between TSH and Vitamin D:

Sudha K et al. in a study from Manipal University, India for the relation between vitamin D deficiency, thyroid hormones, and TSH in subclinical hypothyroidism found that vitamin D insufficiency is associated with subclinical hypothyroidism. In this study 100 newly diagnosed patients with subclinical hypothyroidism were divided into three groups according to vitamin D levels and they found that mean plasma TSH and T3 values decreased with increasing vitamin D values and T4 increased with increasing vitamin D values. The study establishes the fact that vitamin D may play an important role in altering thyroid hormones and TSH levels in subclinical hypothyroidism and conclude that further studies are needed to determine whether vitamin D insufficiency

is a causative factor in the pathogenesis of subclinical hypothyroidism or rather a consequence of the disease[7].

A cross-sectional study by Halder et al. carried out at Kolkata showed that all hypothyroid patients had significantly low serum vitamin D levels and there was a significant inverse association between serum vitamin D and Hashimoto's Thyroiditis. The study also found that serum TSH levels also showed a significant negative correlation with serum vitamin D levels[10].

A cross sectional study by Nirensingh Koch et al. 173 conducted on 152 clinically suspected hypothyroid subjects in the age group of 20 - 60 years at Meerut reported that all the patients were subjected to complete examination and the levels of vitamin D, T3, T4 and TSH were measured. The patients categorized into euthyroid (TSH = 0.25-5 μIU/ml), subclinical hypothyroid (TSH > 5-7 μIU/ml) and overt hypothyroid (TSH > 7 μIU/ml) based on serum TSH cut off values and they were also defined as vitamin D sufficient (> 30 ng/ml), insufficient (20 – 30 ng/ml) and deficient (< 20 ng/ml) based upon the vitamin D cut off values. This study found that the mean value of vitamin D in subclinical hypothyroid (16.73 ± 12.46 ng/ml) and overt hypothyroid (13.23 ± 10.08 ng/ml) were significantly lower than the euthyroid (29.07 ± 19.01 ng/ml) with the P value of < 0.05. The study also found a significant negative correlation between vitamin D and TSH with Pearson's correlation analysis (r= -0.314, P <0.01) and conclude that vitamin D deficiency negatively correlates with TSH [11].

The case control study Fawzy E. et al. carried out in Egypt showed that the levels of serum total vitamin D were significantly decreased in subclinical (28.80 ± 12.25 nmol/L) and hypothyroid groups (11.57 ± 3.70 nmol/L) as compared to control group (90.86 ± 12.60 nmol/L), (p< 0.001) and the study also found a highly significant negative relation between serum TSH and total vitamin D levels (P < 0.001) [12].

A study from Saudi Arabia, Amal Mohammed Husein Mackawy et al. found that patients with hypothyroidism suffered from hypovitaminosis D with hypocalcaemia. The study also showed the positive significant correlation between serum vitamin D with thyroid hormones and that negative significant correlation with TSH levels [13].

We acknowledge the study's limitations, which include a cross-sectional design, a small sample size, and the exclusion of multiple confounders such as dietary vitamin D intake, which has been shown to affect vitamin D levels. However, the study also demonstrates the need for larger studies with larger sample sizes to resolve the debates surrounding vitamin D deficiency in subclinical hypothyroidism and the subsets in which it may play such a significant and beneficial role.

Conclusion

In conclusion, our data showed that vitamin D insufficiency or deficiency is associated with subclinical hypothyroidism and the levels of S. TSH have a strong negative linear relationship with the levels of Vitamin D3 in all the study subjects.

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