Original Article

Correlation of Serum Vitamin D with Serum Calcium Level in Hypothyroid Patients

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Background : Vitamin D is necessary for the normal functioning of many organs, including the thyroid gland. It's deficiency is considered a risk factor for the development of many thyroid disorders, including autoimmune thyroid diseases and thyroid cancer. However, the interaction between Vitamin D and thyroid function is still not fully understood.

Aims and Objectives : The aim of the study was to evaluate the association between hypothyroidism and serum Vitamin D3 levels in the Indian population and its association with ionized calcium.

Materials and Methods : A cross-sectional analytical study was carried out among 100 patients with sub-clinical hypothyroidism or overt primary hypothyroidism who met the inclusion criteria from November, 2019 to November, 2020 in a tertiary care centre in Salem. Basic demographic details were obtained and the estimation of serum calcium, Vitamin D and thyroid profile was done by an automated analyzer.

Results : In this study, two-thirds of the patients were female. The bulk of the patients (82%) had overt hypothyroidism. Though, Vitamin D and TSH levels had a significant negative correlation (r = -0.333, P value = 0.001), there is a positive relationship between Vitamin D levels and serum calcium (r = 0.047, P value = 0.644). Serum calcium levels were negatively correlated with TSH levels but this finding was statistically not significant (r = -0.141, P value = 0.162).

Conclusion : This study indicates that patients with hypothyroidism suffer from low serum levels of Vitamin D, which correlate with TSH. These findings may suggest a potential role for 25-OH Vitamin D in the development of hypothyroidism. This study recommends that patients with hypothyroid disorders be regularly checked for levels of Vitamin D and serum calcium.

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Key words **: Hypothyroidism, Thyroid Function Tests**, **Thyrotropin, Vitamin D Deficiency.**

Hypothyroidism, the clinical condition of thyroid hormone deficiency, is a common disorder in the general population[1]. It is defined mainly by biochemical criteria due to the wide diversity in clinical presentation and the overall lack of a specific symptom[2]. TSH levels above the reference range suggest clinical or overt primary hypothyroidism. On the other hand, free thyroxine levels below the reference range suggest primary hyperthyroidism. TSH levels above the reference range and free thyroxine concentrations within the normal range indicate mild or sub-clinical hypothyroidism, which is frequently encountered as an early indication of thyroid dysfunction[3]. It is a common condition in India, with a prevalence of 1.9 percent in women by 2020 and the prevalence increases with age[4]. Thyroid hormones are universal determinants of organ function. Hence, there may be a multiplicity of symptoms. Especially in the elderly, clinical presentations may be atypical and go undiagnosed[4].

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Editor's Comment :

- Vitamin D is necessary for the normal functioning of many organs, including the thyroid gland. Its deficiency is considered a risk factor for the development of many thyroid disorders.
- This study indicates that patients with hypothyroidism suffer from low serum levels of Vitamin D, which correlate with TSH.
- These findings may suggest a potential role for 25-OH Vitamin D in the development of hypothyroidism.

Vitamin D plays a major role in physiological processes that modulate mineral metabolism and immune function with probable link to several chronic and infectious conditions[5]. Vitamin D is a steroid molecule, mainly produced in the skin, that regulates the expression of a large number of genes[6]. Calcium and phosphate levels are two minerals that Vitamin D aids in controlling. Healthy bones, teeth and muscles require these nutrients. Deformities of the bones, such as rickets in children and bone pain in adults due to Osteomalacia, can result from insufficient Vitamin D in the body[7].

Vitamin D deficiency is a global health problem[8]. Over one billion people Worldwide are Vitamin D deficient or insufficient[9]. Vitamin D deficiency prevails in epidemic proportion all over the Indian subcontinent. With a prevalence of 70%-90% in the general

population in India[10]. This prevalence is remarkably high. Several studies have shown that Vitamin D may play a role in many biochemical mechanisms, in addition to bone and calcium metabolism[11]. The role of Vitamin D as an immune modulator has been emphasized in recent years and low levels of the hormone were observed in several autoimmune diseases, including multiple sclerosis[12], SLE[13], Type 1 diabetes mellitus and rheumatoid arthritis. Most effects of Vitamin D are mediated via the Vitamin D3 Receptor (VDR). The immune modulator properties of Vitamin D are attributed to its effect on T and B lymphocytes, all of which harbors VDRS. Low Vitamin D may increase the degree of auto-immunity and subsequently increase the prevalence of Auto-immune Thyroid Diseases (AITDs)[14]. Thyroid diseases are among the most common endocrine abnormalities. The pathogenesis of AITDs, like other auto-immune diseases, is multifactorial, combining genetic, immune, environmental and hormonal influences such as Vitamin D.

Few past studies have reported the impact of Vitamin D deficiency on thyroid diseases. Currently, there is no consensus regarding the optimal role of Vitamin D deficiency in hypothyroid patients or its association with hypothyroidism. In the present study, we explored the probable interaction between Vitamin D status and hypothyroidism and also tried to find any correlation between serum calcium levels and hypothyroidism.

Materials and Methods

Study Settings :

Salem District is one of the 38 districts of Tamil Nadu State in Southern India. A hospital-based cross-sectional analytical study was carried out among patients diagnosed with sub-clinical hypothyroidism and overt primary hypothyroidism in a tertiary care centre in Salem. The Tertiary Care Centre is located in the rural area of Salem and the hospital has 560 beds. The Department of General Medicine normally provides 24-hour service to more than One Lakh Outpatients per year, mainly to the people of Salem and partly to the neighboring districts of Erode and Namakkal.

Study Period and Study Population :

This study was conducted for a period of 1 year, ie, from November, 2019 to November, 2020. All patients 18 years of age and older, of both genders, diagnosed with sub-clinical hypothyroidism and overt primary hypothyroidism who fulfilled the inclusion criteria were recruited for the study.

Ethical consideration : The approval for this study was obtained through the ethical clearance of the Institutional Ethics Committee on Human Subjects (Approval No. VMKVMC&H/IEC/19/65). After obtaining approval from the Institutional Ethics Committee, the data was collected from the patient who fulfilled the inclusion criteria and protocol for enrolling in the study after receiving their signed informed consent.

Selection of Study Participants :

Inclusion Criteria :

- Patients with sub-clinical hypothyroidism aged over 18 years with a TSH level greater than 5.1 and less than 10 mIU/ml
- Patients with overt primary hypothyroidism aged over 18 years with a TSH level greater than 10 mIU/ml

Exclusion Criteria :

Patients on Vitamin D supplementation or calcium supplements; patients with central hypothyroidism; hepatic dysfunction; renal dysfunction and patients on anti-epileptic medications

Sample Size Determination and Sampling Method :

In the cross-sectional study by Amer et al. in India by 2019, the prevalence of Vitamin D deficiency in sub-clinical and clinical hypothyroidism cases was 90%[15]. Considering this prevalence, the minimum sample size of 96 was calculated using the formula $3.84*pq/d^2$, where prevalence (p) = 90, q (1-p) = 10, and precision (d) = 6, with a 95% confidence interval. All consecutive patients (100 in number) who fit the inclusion criteria were enrolled in the study.

Data Collection Procedure :

A semi-structured questionnaire was used by the principal investigator using a one-on-one interview method to collect data. Each individual was given a thorough clinical examination, a history was obtained, and a clinical diagnosis was determined. After overnight fasting, 3 ml of venous blood was withdrawn from the patients in the plain vacutainer. Blood was allowed to clot, and a centrifuge was used to separate serum. Serum thus separated was stored at 4-8°C until the analysis was done. Estimation of serum T3, T4 and TSH was done by a fully automated analyzer, Minividas and serum calcium was analyzed by the Arsenezo method in a semi-automated analyzer. Serum concentrations of Vitamin D3 in patients were measured by the immuno-metric assay method (competitive principle). The quantitative determination of 25-OH Vitamin D was carried out by a direct, competitive chemiluminescence immunoassay (direct chemiluminescent reactions).

Operational Definition :

(1) Vitamin D deficiency :

In our study, Vitamin D deficiency was defined, in accordance with the manufacturer, as serum levels

of Vitamin D3 less than 20 ng/mL in adults. Vitamin D insufficiency was defined as serum levels of Vitamin D3 between 20 and 29 ng/mL in adults. Vitamin D sufficiency was defined as serum levels of Vitamin D3 greater than 30 ng/mL in adults[16].

(2) Hypothyroidism :

Hypothyroidism cases were classified into two subgroups according to their thyroid function status measured by the ELIZA technique[17].

Sub-clinical hypothyroidism describes a situation in which no overt clinical feature of hypothyroidism is present, with serum levels of T4 and T3 still in the normal range but with higher levels of TSH.

Clinical hypothyroidism describes the condition in which an overt clinical feature of hypothyroidism is present, with lower levels of T4 and T3 and higher levels of TSH.

Thyroid Stimulating Hormone (TSH)

Normal : 0.5-5.0 mIU/l

Sub-clinical Hypothyroidism : 5.1 to <10 mIU/l

Overt Hypothyroidism : >10 mIU/l

Triiodothyronine (T3) – Normal level: 1.2 – 4.4 pg/ml

Thyroxine (T4) – Normal Level: 0.8-2.0 ng/dl

(3) Serum Calcium :

Calcium sufficiency was defined as serum levels of calcium between 8.6 mg/dl and 10.3 mg/dl in adults.

Data Processing and Analysis :

Data analysis was performed using IBM-SPSS version 21.0 (IBM-SPSS Science Inc, Chicago, IL). Descriptive statistics like mean and Standard Deviation were used for continuous variables like age, TSH, T3, T4, etc, while frequency and percentage were used for gender variables. An independent sample T-test was used for comparing two means and Pearson's correlation was done to see the correlation between two continuous variables. A P value of 0.05 was considered significant.

Results

Almost half (45%) of the patients were 36-45 years of age and more than one-third were 26-35 years of age. 67% of the patients were female and 33% were male. Most (82%) of the patients had overt hypothyroidism. Almost 73% of patients were deficient in Vitamin D and 27% of patients had an insufficient amount of Vitamin D. Table 1 describes the basic characteristics of the study population.

Table 2 describes the gender-based clinical characteristics and their association as expressed by the independent T test. No statistical difference (P <0.05) was seen in all variables, except for the age variable, where a difference in the mean age of Males is 37.18±7.23 and Females is 33.44 ±7.56 (P value = 0.02). The mean concentration of Vitamin D is higher in Females compared to Males, but this difference was statistically not significant (P value = 0.42). The mean concentration of serum calcium is almost equal between Females and Males. Thus, this difference was statistically not significant (P value = 0.92).

Table 3 describes the association of thyroid status with vitamin D and serum calcium by an independent T test. The mean concentration of Vitamin D is higher in sub-clinical hypothyroidism (20.66 ± 4.68) in comparison to overt hypothyroidism with a mean of 16.67 ± 4.60 and this difference was statistically significant (P value = 0.001). Conversely, the mean concentration of calcium is higher in sub-clinical hypothyroidism (9.21 ± 0.62) in comparison to overt hypothyroidism with a mean of 9.01 ± 0.62 and this difference was not statistically significant (P value = 0.235).

Table 4 describes the correlation between Vitamin D, serum calcium and thyroid hormone levels. Thyroid Stimulating Hormone (TSH) levels correlate negatively with Vitamin D levels (r = -0.333, P value = 0.001). Vitamin D concentrations increase along with calcium levels in the blood. There is a positive correlation between Vitamin D levels and serum calcium, but there is no statistical significance (r = 0.047, P value = 0.644). T3 and T4 levels had no statistically significant change (P values = 0.644, 0.466, and 0.650, respectively). TSH levels were

Table 1 — *Basic Characteristics of the Study Population*

Patients Characteristics		Frequency (N = 100)	Percentage
Age group	≤25	13	13.0%
	26-35	36	36.0%
	36-45	45	45.0%
	>45	6	6.0%
Gender	Male	33	33.0%
	Female	67	67.0%
Hypothyroidism	Sub-clinical	18	18.0%
	Overt	82	82.0%
Vitamin D	Insufficient	27	27.0%
	Deficient	73	73.0%

Table 2 — *Gender-based Clinical Characteristics*

Parameters	Male, N=33	Female, N=67	*P* value
Age (in Years)	37.18±7.23	33.44 ±7.56	0.02*
Serum 25 (OH) Vitamin D (ng/ml)	16.83±5.03	17.66±4.76	0.42
Serum Calcium (mg/dl)	9.04±0.70	9.05±0.59	0.92

Table 3 — *Association of Thyroid Status with Vitamin D and Serum Calcium*

Thyroid Status	Sub-Clinical Hypothyroidism (N=18)	Overt Hypothyroidism (N=82)	*P* value
Vitamin D (ng/ml)	20.66±4.68	16.67±4.60	0.001*
Serum Calcium (mg/dl)	9.21±0.62	9.01±0.62	0.235

Table 4 — *Correlation Co-efficients of Vitamin D and Calcium with Thyroid Function Tests*

Variables	Vitamin D	Serum Calcium	TSH	T3	T4
Vitamin D :					
Pearson Correlation	1	0.047*	-0.333	0.074	0.046*
P value	-	0.644	0.001*	0.466	0.650
Serum Calcium :					
Pearson Correlation	0.047	1	-0.141	0.101	0.003*
P value	0.644	-	0.162	0.318	0.977

negatively linked with serum calcium levels, but this finding was not statistically insignificant (r = -0.141, P value = 0.162).

Discussion

Various previous studies have documented a relationship between the occurrence of hypothyroidism and serum concentrations of Vitamin D[8,18-20]. A literature review has reported that Vitamin D deficiency plays a critical role in thyroid disease development, including thyroid cancer[21,22].

We observed in this study that more than two-thirds (67%) of the patients were Female. In addition, almost half of them fall under the age group of 36 to 45. These findings suggest that hypothyroidism is more common among Females than Males. Similar findings were also observed in India by Sinha R, *et al* in 2019. They found that 67.1% of the patients were female and more than half of the patients fell under the 40-59 age group[23]. A study in India by Unnikrishnan, *et al* in 2013 also found a greater number of female patients with hypothyroidism[24]. Similar observations were also noted in a study by Mackawy, *et al* which had a greater number of female subjects with hypothyroidism[8].

In this study, patients with clinical or overt hypothyroidism had significantly lower serum levels of Vitamin D than those with sub-clinical hypothyroidism (P value 0.001). It may be associated with insufficient intestinal absorption of Vitamin D or the body's inability to activate Vitamin D correctly. Parallel to our findings in India, Amer AH, *et al* noticed in 2019 that patients with overt hypothyroidism had lower levels of Vitamin D than those with sub-clinical hypothyroidism (P value 0.001)[15]. Furthermore, a study in India by Lohokare R, *et al* (2016) discovered that hypothyroid individuals had significantly lower serum levels of Vitamin D 25 (OH) than euthyroid patients (P value 0.001)[25]. Kim reported in the Korean population by 2016 that Vitamin D deficiency is more prevalent in auto-immune Hashimoto's thyroiditis presenting with overt hypothyroidism than sub-clinical hypothyroid variants[26]. In the present study, Thyroid-stimulating Hormone (TSH) levels correlate negatively with Vitamin D levels. Similar studies have shown that a reciprocal relationship exists between serum TSH and Vitamin D levels in hypothyroid subjects[26,27].

According to a study done by Talaei A, *et al* in Iran by 2018 where 12 weeks supplement of 50,000 IU Vitamin D was given to one group and one group received placebo, the supplemented group had significant decrease in the TSH levels. They also found the prevalence of Vitamin D deficiency to be high in hypothyroid patients. They, thus, suggested a significant relationship between Vitamin-D deficiency and hypothyroidism[28].

We observed a lower level of serum calcium in patients suffering from overt hypothyroidism (9.01 ± 0.62) when compared with sub-clinical hypothyroidism (9.21±0.62), but it was not statistically insignificant (P value = 0.235). In contrast to our findings, a study by Mackawy, *et al* in Saudi Arabia discovered that serum calcium levels recorded a significant decrease in hypothyroid patients when compared to controls[8]. In India, a study by Sinha R, *et al* in 2019 observed that hypothyroid people had significantly lower blood calcium levels than the control group[23]. Disturbance in calcium homeostasis is frequently observed with dysfunction in the thyroid gland[29]. Thyroxine, which normally controls blood calcium levels through cellular calcium release, is reduced in hypothyroidism. As a result, there is less thyroxine in the circulation, which leads to less thyroxin entrance into cells and hence less extracellular calcium release[30].

These findings point towards the role of Vitamin D as a potential modifiable risk factor for hypothyroidism. The effect of Vitamin D is mediated through its binding to the Vitamin D Receptor (VDR) and activation of VDR-responsive genes. VDR is found in several cell types, including the thyroid gland[29]. So, probably, Vitamin D plays a role in maintaining an euthyroid state by interacting with its receptor in the thyroid gland. Similar findings were reported in other studies as well[8,25].

This study indicates that patients with hypothyroidism suffer from low serum levels of Vitamin D and calcium and these levels are associated with the degree and severity of hypothyroidism. Screening of newly diagnosed hypothyroid patients for 25-OH Vitamin D and serum calcium levels and supplementation of Vitamin D at an early stage of diagnosis are strongly recommended.

Limitations :

Our study population of 100 samples is comparatively small and the study can be extended to a larger population. The levels of phosphorous, parathyroid hormone and thyroid antibodies were not investigated. No genetic workup was done. The

current study was conducted as a hospital-based study due to a lack of resources. As this was a cross-sectional study, the association was found to lack a temporal association between hypothyroidism and the level of Vitamin D. Due to resource constraints, certain important variables related to Vitamin D, such as indoor versus outdoor physical activity, seasonal changes and geographical coordinates, could not be ascertained, which could have led to some biases. In addition, it was not possible to identify whether or not Vitamin D levels were affected by pathological disorders such as non-alcoholic fatty liver disease.

Conclusion

In this study, clinical or overt hypothyroidism was associated with considerably lower serum Vitamin D levels than sub-clinical hypothyroidism. This study indicates that patients with hypothyroidism suffer from low serum levels of Vitamin D, which correlate with TSH. These findings may suggest a potential role for 25-OH Vitamin D in the development of hypothyroidism. This study recommends that patients with hypothyroid disorders be regularly checked for levels of Vitamin D and serum calcium. There may be a rationale for the recommendation of Vitamin D and calcium supplementation for hypothyroid patients. Ongoing and future long-term randomized control trials are required to determine the role of Vitamin D in the pathogenesis of hypothyroidism.

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