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Role of vitamin D in conversion of free T4 to T3: A hospital based cross sectional study

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Abstract

Introduction and Objective: Few speculations are made regarding the conversion of T4 to T3 using vitamin D. Studies show that thyroid hormone inhibits 25 (OH) D l alpha hydroxylase and the latter also suppresses TSH secretion and exerts direct effects on thyroid cells such as inhibition of iodine uptake. Polymorphisms in the vitamin D receptor gene have been associated with autoimmune thyroid disease. There is a complex interplay between thyroid hormones and vitamin D which needs further clarification.

Material and Method:A retrograde study of 50 cases was done in the biochemistry lab of Subharti Medical College whose vitamin D and thyroid profile was requested together. Thyroid profile was estimated by Vidas automatic analyzer and vitamin D was estimated using Robonik elisa reader using DRG kits.

Results: There was a significant positive correlation of 25 OH-vitamin D with fT3 levels ($r=0.22$, $p<0.5$) as well as fT4 levels ($r=0.41$, $p<0.05$) and significant negative correlation with TSH ($r= 0.15$, $p<0.5$).

Conclusion: There is definitely a direct relationship of vitamin D levels, with thyroid hormones which is confirmed by the indirect relation with TSH levels as per this preliminary study.

Keyword – Vitamin D, fT3, fT4, TSH

Introduction

Hypothyroidism, which is rempant in present scenario especially in women, is mainly autoimmune in nature. Studies have reported the impact of vitamin D deficiency on autoimmune thyroid disease [1,2]. It has been shown in animal studies that vitamin D directly affects the thyroid gland through immune mediated processes and also influences thyroid follicular cells [3].

It was previously reported that higher vitamin D status was associated with low circulating thyroid stimulating hormone (TSH) only among younger individuals and not in adults [4]. Later, high vitamin D status has been associated with low TSH by several studies [5,6]. A recent study found that free T3 level is inversely associated with circulating 25 (OH) vitamin D [7].

Furthermore, while vitamin D deficiency has been implicated in several autoimmune thyroid diseases, no association was elicited between the antibodies measured in the present study and vitamin D, confirming a recent study among Dutch natives about the lack of correlation of low vitamin D levels and the early stages of thyroid auto-immunity [8]. Similarly, polymorphisms of Vitmain D l alpha-hydroxylase (CYP l alpha) gene has been found to be associated with type 1 diabetes mellitus, Grave's

disease and Hashimota's thyroidits among Caucasian pedigrees [9,10]. In the context, it should be taken into account that TSH may have direct and independent effects on bone metabolism regardless of thyroid hormones [11,12]. Vitamin D and calcium serum levels had negative correlation when compared to TSH level [13]. Prevalence of vitamin D insufficiency in Hashimoto's cases (92%) was significantly higher than that observed in healthy controls [14,15]. Reports say that a lack of vitamin D contributed to the possibility of low thyroid hormones [16]. Other articles [17] have demonstrated that patients with Graves's disease also have low levels of Vitamin D. Importantly, both vitamin D and thyroid hormone bind to similar receptor called steroid hormone receptors. A different gene in the Vitamin D receptor was shown to predispose people to autoimmune thyroid disease including Grave's disease and Hashimoto's thyroiditis. Vitamin D inhibits the production of Th1 polarizing cytokine (IL-12), thereby indirectly shifting the polarization of T cells from a Th1 toward a Th2 phenotype [18]. In addition, recent numerous studies have shown the relation of vitamin D and various autoimmune diseases. Vitamin D receptor (VDR) gene polymorphisms and vitamin D status are associated with different autoimmune diseases [19,20]. Furthermore, vitamin D supplementation prevented the onset and/or development of several kinds of autoimmune disease in humans and animal models [18]. These results suggested that vitamin D deficiency might cause the onset and/or development of several kinds of autoimmune diseases. Recent studies have demonstrated a role of vitamin D in Graves Disease (GD). Vitamin D analog inhibits inflammatory responses in human thyroid cells and T cells [21,22]. On the other hand, study had been conducted in Netherlands showed that Vitamin D deficiency is not associated with early stages of thyroid autoimmunity [8].

Lower vitamin D levels have been found in rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and autoimmune thyroid diseases (i.e. Hashimoto's thyroiditis and Graves' disease). Low vitamin D status is associated with increased TRAb titer in GD, suggesting a possible link between vitamin D status and increased thyroid autoimmunity in GD patients [23].

A Significant association was found for serum 25 (OH) D and FT3 and serum 1,25 (OH) D and FT3. Thyroid hormones, exert their actions by binding to thyroid hormone receptors. Polymorphisms in the [vitamin D receptor] gene have been associated with autoimmune thyroid disease. The reason for the close relationship between FT3 and vitamin D remains speculative [24].

Material and Methods

A total of 94 consenting adult [52 control (6 males; 46 females), 42 cases (3 males, 39 females)] were included in this cross-sectional study. All subjects were recruited at the Endocrinology unit of Chatrapati Shivaji Subharti Hospital of Subharti Medical College. Adults aged 20-50, who were known cases of subclinical hypothyroid dysfunction based on previous clinical assessment (elevated TSH with normal FT4 levels), medications taken and laboratory tests with no complication were included.

Control subjects were those who tested negative for subclinical hypothyroid dysfunction with no history of thyroid medications. Pregnant women as well as children were excluded from the study. Written and informed consent were secured prior to inclusion. Ethical approval was obtained from the Institutional ethical committee.

Blood measurements

Blood was withdrawn after an overnight fast (>10 hours) in plain vials. TSH, fT3 and fT4 were estimated by Vidas fully automated analyzer from Biomerieux France using kit method. 25 (OH) D were measured by specific ELISA

(by Robonik, India) in accordance with the instructions provided by the manufacturer (DRG diagnostics, Germany). 25 (OH) vitamin D has been the preferred metabolite for the measurement of vitamin D status instead of 1, 25 (OH) D, and remains the basis for the diagnosis of vitamin D deficiency [7].

Data analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.5 (Chicago, IL, USA). Linear regression analysis was performed for TSH, fT3 and fT4. Data were presented as mean ± standard deviation. For group comparisons (control versus cases), independent T-test was applied. Significance was set at $p < 0.05$.

Results

Table 1 shows the general characteristics of both cases and controls. There was no significant difference in the mean age of both groups. Mean fT3, fT4 values were similar in both cases and controls. Table 2 shows the coefficients of Vitamin D versus the different thyroid tests. There is inverse and significant association between FT3 and circulating 25 (OH) vitamin D ($R = -0.22$; $p = 0.01$). TSH was not significantly associated with 25 (OH) vitamin D.

Table 1 showing different parameters of cases and control

	Cases	Control
Mean Age (in yrs)	41.54 ± 12.24	42.06 ±12.67
Vit D (in ng/mL)	23.16 ± 18.79	23.31 ± 19.1
TSH (in μIU/L)	3.19 ± 2.45	3.18 ± 2.47
fT3 (in pmol/L)	4.44 ± 0.88	4.44 ± 0.91
fT4 (in nmol/L)	14.21 ± 4.65	14.06 ± 4.49

Table 2 shows correlation between vitamin D and thyroid parameters

	Correlation	r value	p value
Vit D vs TSH	Negative	0.15	< 0.5
Vit D vs fT3	Positive	0.22	<0.5
Vit D vs fT4	Positive	0.41	<0.05

Discussion

Smith et al [6] also found that exogenous vitamin D administration significantly suppressed pituitary thyrotropin TSH secretion in the basal state. This study also found that serum TSH levels of middle-aged and elderly women were higher than those of same-age men, and this result was consistent with those of previous reports [27,28]. This result may indicate that TSH secretion is regulated by sex hormones, genetic susceptibility, or environmental factors, which may also mediate the relationship between vitamin D status and serum TSH levels.

According to study done by Zhang et al [23] the prevalence of vitamin D insufficiency was 9.29% in males and 97.22% in females, and the prevalence of vitamin D deficiency was 55.61% in males and 69.64% in females. Vitamin D status was not associated with positive thyroid autoantibodies after controlling for age, gender, body mass index, and smoking status. Higher 25 (OH) D levels were associated with lower TSH levels after controlling for age, FT4 and FT3 levels, thyroid volume, the presence of thyroid nodule(s), and smoking status in males. Higher vitamin D status in middle-aged and elderly males was associated with low circulating TSH levels independent of thyroid hormone.

According to study done by A1 Johani et al [7] circulating triglycerides were significantly higher in cases than the controls. FT3 was inversely associated with circulating 25

(OH) vitamin D. One striking and unexpected finding in there study was the significant higher mean 25 (OH) vitamin D levels among patients with subclinical hypothyroid dysfunction than controls despite the presence of established risk factors for vitamin D deficiency including obesity and hypetriglyceridemia. Also, the inverse association of FT3 to circulating levels of 25 (OH) D should be interpreted with caution. It was previously reported that higher vitamin D status was associated with low TSH only among younger individuals and not in adults [4].

Results of Mackawy AMH et al [13] indicated that patients with hypothyroidism suffered from hypovitaminosis D with hypocalcaemia that was significantly associated with the degree and severity of hypothyroidism. Serum 25 (OH) vit D was significantly lower in hypothyroid patients than in controls. Its level was insignificantly decreased in females than male patients. Moreover, serum calcium levels recorded a significant decreased in hypothyroid patients when compared to controls.

Conclusion

There is definitely a direct relationship of vitamin D levels, with thyroid hormones which is confirmed by the indirect relation with TSH levels as per this preliminary study.

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