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Scientific Evidence on Interrelationship Between Vitamin D and Vitamin B12 in Euthyroid Subjects

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KEYWORDS

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ABSTRACT:

Introduction: Vitamin B12 acts as the coenzyme of homocysteine methyl transferase which converts homocysteine (Hcy) to methionine and thyroxine regulates the activity of this enzyme. Vitamin D modulates the gene expression of enzymes involved in Hcy metabolism. Vitamin D receptors are present on thyrotropes that secrete TSH speculating the link between vitamin D and thyroid gland activity.

Objective: The study aims to explore the correlation between vitamin D and B12 with thyroid hormones in euthyroid status.

Methods: 100 euthyroid subjects aged between 20-60 years, with normal thyroid hormones and TSH, were classified into two groups based on vitamin B12 levels. Group I consisted of 50 patients whose vitamin B12 level was less than 200 pg/ml (B12 deficient group) and Group II included 50 patients whose vitamin B12 level was more than 200 pg/ml (B12 sufficient group). Thyroid profile, total vitamin D, vitamin B12 and folic acid were determined in the fasting serum samples by ECLIA in Cobas 6000 autoanalyzer.

Results: There was an apparent decrease in mean serum TSH, T3 and T4 levels in vitamin B12 deficient group compared to sufficient group. A significantly higher vitamin D was observed in vitamin B12 sufficient group than the deficient group ($p = 0.001$). Vitamin D and B12 showed positive correlation with serum T3, T4 and TSH. The correlation between TSH and vitamin B12 ($r = 0.31$, $p = 0.01$), vitamin D ($r = 0.435$, $p = 0.001$) were significant. Further, the correlation between vitamin D and B12 ($r = 0.42$, $p = 0.005$), was also statistically significant.

Conclusions: Vitamin B12 deficiency is linked to vitamin D deficiency which in turn may be associated with alteration of thyroid profile even in euthyroid status. The study establishes a link between vitamin B12 and vitamin D in euthyroid subjects.

1. Introduction

In India the large proportion of the population are vegetarians and prevalence of vitamin B12 (Vit B12) is common. If prevalence in the general population is around 4%, in autoimmune hypothyroidism it goes up to 12% [1]. Several reports suggest inadequate intake and decreased absorption due to slow bowel movement as the causes of vitamin deficiency in hypothyroidism. Further, B12 deficient and hypothyroid patients share common symptoms like fatigue, weakness, numbness and tingling [2]. Vitamin B12 acts as the coenzyme of homocysteine methyl transferase which converts homocysteine (Hcy) to methionine and thyroxine regulates the activity of this enzyme [3]. Vitamin D is thought to modulate the gene expression of enzymes involved in Hcy metabolism [4]. Moreover, in rats, vitamin D receptors are present on thyrotropes that secrete TSH speculating the link between vitamin D and thyroid gland activity [5]. Therefore, we hypothesize that vitamin B12 deficiency is linked to vitamin D deficiency which in turn may be associated with alteration of thyroid profile even in euthyroid status.

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2. Objectives

The present study examines the interrelationship between vitamin D and B12 with thyroid hormones in euthyroid status.

3. Methods

This prospective cross-sectional study was conducted after obtaining the approval from Institutional Ethics Committee (IEC KMC MLR11/2019/345). Written consent was obtained from all the subjects enrolled for the study. The study population included 100 euthyroid subjects aged between 20-60 years with normal serum thyroid hormones and TSH levels were recruited for the study. Individuals with a history of thyroid dysfunction or who were on antithyroid drug /L thyroxine treatment or vitamin supplements were also excluded from the study. The study population was classified into 2 groups based on the serum vitamin B12 levels. Group I consisted of 50 patients whose vitamin B12 level was less than 200 pg/ml (B12 deficient group) and Group II included 50 patients whose vitamin B12 level was more than 200 pg/ml (B12 sufficient group). Fasting blood samples were collected in a plain vacutainer, and serum separated was used for biochemical analysis. TSH, T3, T4, total vitamin D, vitamin B12 and folate were estimated by ECLIA in Cobas 6000 autoanalyzer [6-8]. SPSS software version 20 was used for statistical analysis. Data was analyzed by Mann Whitney test and the correlation between vitamin B12 and other variables was tested by Pearson's coefficient. $p < 0.05$ was considered significant.

4. Results

There was an apparent decrease in mean serum TSH, T3 and T4 levels in the vitamin B12 deficient group (Group I) compared to sufficient group (Group II). The mean vitamin B12 value was 4 times greater in Group II than Group I. A significantly higher levels of vitamin D was observed in Group II compared to Group I (p=0.001). Although folate was decreased in Vitamin B12 deficient group, compared to sufficient group the decrease was not statistically significant (Table 1). All the vitamins showed a positive correlation with serum T3, T4 and TSH.

Further, the correlation between TSH versus vitamin B12(r= -0.221, p= 0.042) and TSH versus vitamin D (r= -0.435, p= 0.001) was significant in entire euthyroid subjects. Furthermore, the correlation between vitamin D and vitamin B12 (r=0.42, p=0.005), was also statistically significant.

Table 1: Comparison of thyroid profile and vitamins between SCH and euthyroid adults (Mean ± SD)

	Group I **Vit B12 <200pg/ml** **n=50**	**Group II** **Vit B12 >200 pg/ml** **n = 50**	**p-value**
T3 (ng/ml)	1.05 ± 0.19	1.09 ± 0.24	NS
T4 (µg/dl)	7.31 ± 1.53	7.82 ± 1.54	NS
TSH (µIU/ml)	2.53 ± 1.39	2.8 ± 2.08	NS
Folate (ng/ml)	8.44 ± 2.96	9.16 ± 2.96	NS
Vitamin D (ng/ml)	13.71 ± 8.19	21.64 ± 10.	0.001
Vitamin B12 (pg/ml)	129 ± 37	498 ± 151	0.001

n = number of patients, NS – not significant

Table 2: Correlation of vitamin B12 with thyroid profile in euthyroid subjects

	Vitamin B12	
	r	**p**
T3	0.181	NS
T4	0.025	NS
TSH	-0.221	0.042
Vit D	0.42	0.005
Folate	0.016	NS

NS – not significant

Table 3: Correlation of vitamin D with thyroid profile in euthyroid subjects

	Vitamin D	
	r	**p**
T3	0.138	NS
T4	0.095	NS
TSH	-0.435	<0.001
Vit B12	0.42	0.005
Folate	0.019	NS

NS – not significant

5. Discussion

Analysis of the result revealed that serum TSH, T3 and T4 decreased with a decline in vitamin B12 in euthyroid patients. A previous study on Saudi hypothyroid patients with multiple sclerosis also reported a similar interrelationship between vitamin B12 and thyroid

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profile [9]. The dietary vitamin B12 binds to intrinsic factor in the stomach and gets absorbed in the ileum which is a calcium dependent process and vitamin D is a vital regulator of calcium homeostasis[10].One of the earlier studies hypothesizes that vitamin B12 deficiency may be secondary to deficiency of vitamin D. The presence of calcitriol receptors in the stomach leads to the speculation that this vitamin may regulate gene coding for intrinsic factor [11]. Vitamin D deficiency may pose a risk for B12 absorption through a reduction in the secretion of intrinsic factor [12]. This is justified by our results where euthyroid subjects with low vitamin D were mostly in the vitamin B12 deficient group. Vitamin D prevents gastric inflammation and maintains the mucosa by suppressing HCl secretion and renders protection against H pylori infection [13]. Vitamin D is known to regulate the genes responsible for the maintenance of epithelial integrity of GIT. Individuals with sufficient vitamin B12 exhibited marginally higher TSH, T3, T4, folate and vitamin D compared to the vitamin B12 deficient group [14]. Prevalence of cobalamine deficiency was high in autoimmune disorders like hypothyroidism, and type I diabetes mellitus [15]. Moreover, autoimmune atrophic gastritis, characterized by antibodies against intrinsic factor, was frequently found in association with Hashimoto's thyroiditis and with type I diabetes mellitus [16]. Furthermore, autoimmune hypothyroidism was a common comorbidity in type I diabetic patients [17]. Moreover, low serum thyroid hormones can aggravate vitamin B12 deficiency due to reduced intestinal motility leading to malabsorption and dyserythropoiesis [18]. A positive correlation was seen between vitamin B12 and thyroid hormones in the current study. This is in agreement with earlier study which reported a significant positive correlation observed between vitamin B12 and free T3, free T4 in healthy pregnant women and pregnant women with subclinical hypothyroidism [19]. Earlier studies demonstrated reduced serum TSH in rats fed with a vitamin D deficient diet, justifying the role of vitamin D in modulating the pituitary thyroid axis [20]. Vitamin D is considered as an immune molecule that inhibits inflammatory cytokines like IL6 and TGF beta and has an important role in decreasing inflammation of the thyroid gland [20]. Methyl cobalamine acts as a cofactor for methylation of homocysteine to methionine and its deficiency leads to homocysteinemia. Methyl tetrahydrofolate in turn helps in the regeneration of methyl cobalamine. Moreover, the expression of gene coding for homocysteine methyl transferase is modulated by thyroid hormones and vitamin D. Thus a positive correlation between vitamin B12 with TSH and vitamin D seen in the current study can be explained by a reaction catalyzed by homocysteine methyl transferase. In the present study vitamin B12 deficient individuals had significantly lower vitamin D. Further, we observed a significant positive correlation between vitamin B12 and vitamin D. Furthermore, the correlation between TSH and the vitamins was also statistically significant.

Euthyroid subjects with elevated vit B12 showed a lower prevalence of metabolic syndrome, a disorder that is associated with hyperhomocysteinemia [21]. This corroborates our conclusion that vitamin D, vitamin B12 and TSH act in association with each other even in euthyroid status.

The outcome of the study suggests that hypovitaminosis D may impair vitamin B12 absorption, with a consequent decline in serum TSH that may lead to the pathogenesis or progression of thyroid diseases. Since vitamin D deficiency is highly prevalent worldwide, its negative effect on the absorption of other vitamins may pose additional risks to public health.

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