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Vitamin D deficiency in Primary Hypothyroidism in the urban population of Visakhapatnam

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Abstract:
Background*: The aim of the present study is to know the prevalence of vitamin D deficiency in cases of primary hypothyroidism.*
Materials and Methods*: Total 195 patients were enrolled in the present study, out of which 17 were male patients and 178 were female patients . All patients were underwent investigations triiodothyronine(T3), tetraiodotyronine(T4), thyroid stimulating hormone(TSH), 25 OH (hydroxy) vitamin D and serum calcium.*
Results*: the mean age of presentation in the present study is 36 years. 179 out of 195 patients (92%) had either vitamin D deficiency or insufficiency and 16 out of 195 patients (8%) had normal levels of vitamin D. 107 patients out of 179 had vitamin D deficiency. Patients with vitamin D deficiency is again divided into severe,moderate and mild with 25 OH vitamin D levels less than 5 ng/ml, 5-10 ng/ml and 10-20 ng/ml respectively. 103 patients out of 195 patients(96%) had mild vitamin D deficiency in our study and 4 patients out of 195 (4%) had moderate vitamin D deficiency and none of the patients had severe vitamin D deficiency.*
Conclusion: *vitamin D deficiency is common in patients with primary hypothyroidism. All the patients had normal serum calcium levels. So,all patients with primary hypothyroidism must be evaluated for vitamin D deficiency with estimation of 25 OH vitamin D.*
Key Word*: vitamin D deficiency, primary hypothyroidism, 25 OH vitamin D, serum calcium.*

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I. Introduction

Vitamin D is a steroid hormone that is produced by skin and also by dietary sources.(1) However the major production of vitamin D is from exposure of skin to sunlight. Nowadays exposure to sunlight is minimized in both men and women because of limitation of their work in indoor activities. The primary action of Vitamin D is regulation of calcium and phosphorus homeostasis. Recent studies have shown that Vitamin D deficiency is associated with increased risk of Diabetes Mellitus , Infectious Diseases, Atherosclerosis and Autoimmune condition like Autoimmune Thyroiditis.(2) vitamin D deficiency is mainly due to decreased exposure to sunlight. There is also association between vitamin D deficiency and extraskeletal manifestations. Vitamin D activity is mediated through vitamin D receptors which further leads to activation of various genes. Since both Vitamin D and thyroid hormones act via steroid receptors, so any alteration in the level of Vitamin D is likely to increase problems associated with hypothyroidism.(3) There are approximately 42 million people in India who suffer from thyroid disorders. The present study was conducted with an aim to establish association between primary hypothyroidism and Vitamin D deficiency.

II. Material And Methods

This is a cross sectional study. The present study was conducted in the department of endocrinology, Andhra medical college, King George Hospital, Visakhapatnam, Andhra Pradesh. Patients were enrolled who presented to the outpatient department in the Department of Endocrinology at King George Hospital. The duration of the study is one year between january 2019 to december 2019.

Inclusion criteria:
1.The inclusion criteria of the present study were age above 18 years, new cases of hypothyroidism, old cases of hypothyroidism who are already on levothyroxine replacement therapy.

Exclusion criteria:
1.Exclusion criteria were pregnancy, thyroidectomy patients, thyrotoxicosis cases who underwent radioablation and developed hypothyroidism.

Procedure methodology

Total patients enrolled in the present study were 195. All the patients were underwent investigations necessary for the present study. Total T3, total T4 and TSH were assessed by chemiluminescence immunoassay. 25 OH vitamin D levels were also estimated by chemiluminescence immunoassay. Total calcium levels were assessed by o-cresolphthlein complex (OCPC) method. total T3 levels between 70-204 ng/dl , total T4 levels between 5.5-11 µgm/dl and TSH levels between 0.4 -4.2 µIU/ml were considered as normal according to our laboratory reference values. 25 OH vitamin D levels which less than 20 ng/ml were considred as vitamin D deficiency, levels between 20-30 ng/ml were considered as vitamin D insufficiency and levels between 30 -100 ng/ml were considered as normal. Patients were again divided into mild vitamin D deficiency, moderate vitamin D deficiency and severe vitamin D deficiency based on 25 OH vitamin D level 10-20 ng/ml, 5-10 ng/ml and less than 5 ng/ml respectively. Total calcium levels between 8.5 -10.1 mg/dl were considered as normal according to our laboratory reference value. 1,25 dihydroxy vitamin D levels were not measred in our study because the levels are usually normal until severe deficiency occurs. Thyroid peroxidase antibodies (TPO Ab) were could not be assessed for establishment of autoimmune thyroiditis due to economic constrains of the patients.

Statistical analysis

Baseline characteristics of the patients were shown as mean with standard deviation values using Microsoft excel software 2019 model. Independent Sample t test is used to compare the immune values of 25 hydroxy Vitamin-D in males versus females and also used for the mean serum calcium levels in males versus females using Microsoft excel software 2019 model. p value ≤ 0.05 is considered as significant.

III. Result

1.Baseline characteristics of patients:

The baseline characteristics of the all the patients were showed as mean value in table1. The average age of presentation in this study was 36 years. As primary hypothyroidism is common in females, in the present study females were more effected than males. Serum calcium levels were normal in all the patients in the present study. Mean vitamin D levels in the present study showing vitamin D deficiency in most of the patients.

Table 1: Baseline characteristics of all the patients

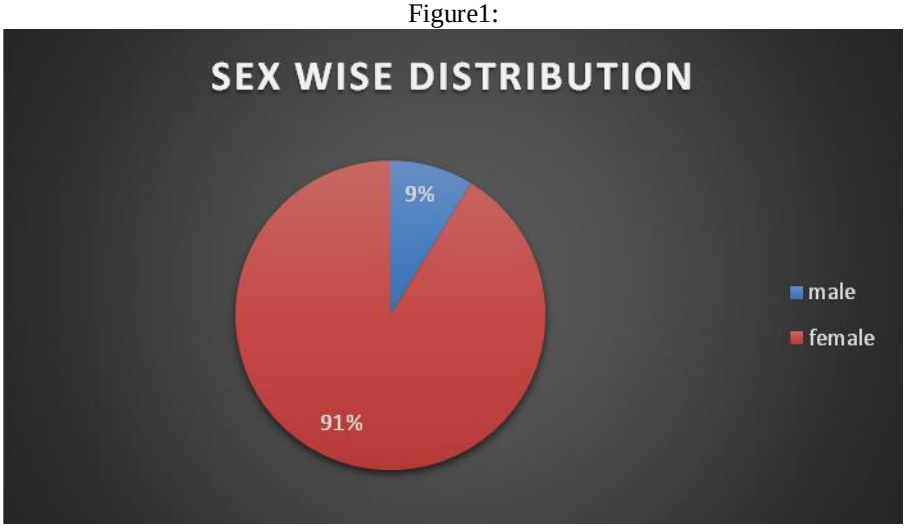
baseline characteristics	mean value	standard deviation
Age (years)	36.08	17
25 OH vitamin D level (ng/ml)	20.12	3.95
Serum Calcium (mg/dl)	9.53	0.21
T3 (ng/dl)	111.56	10.58
T4 (µgm/dl)	9.83	3.6
TSH (µIU/ml)	7.43	68.97

T3: triiodothyronine T4: tetraiodothyronine TSH:thyroid stimulating hormone

2.Sex wise distribution of cases:

Among 195 patients in the present study, 178 were female patients and 17 were male patients as shown in figure 1. Primary hypothyroidism was more common in female patients than male patients as autoimmune disorders are more common in female patients than male patients. Our study also showed female preponderance.

Figure1:



1. **Distribution of cases into three types based on vitamin D level**: Vitamin D deficiency group, vitamin D insufficiency group and normal vitamin D level group as represented in figure 2.

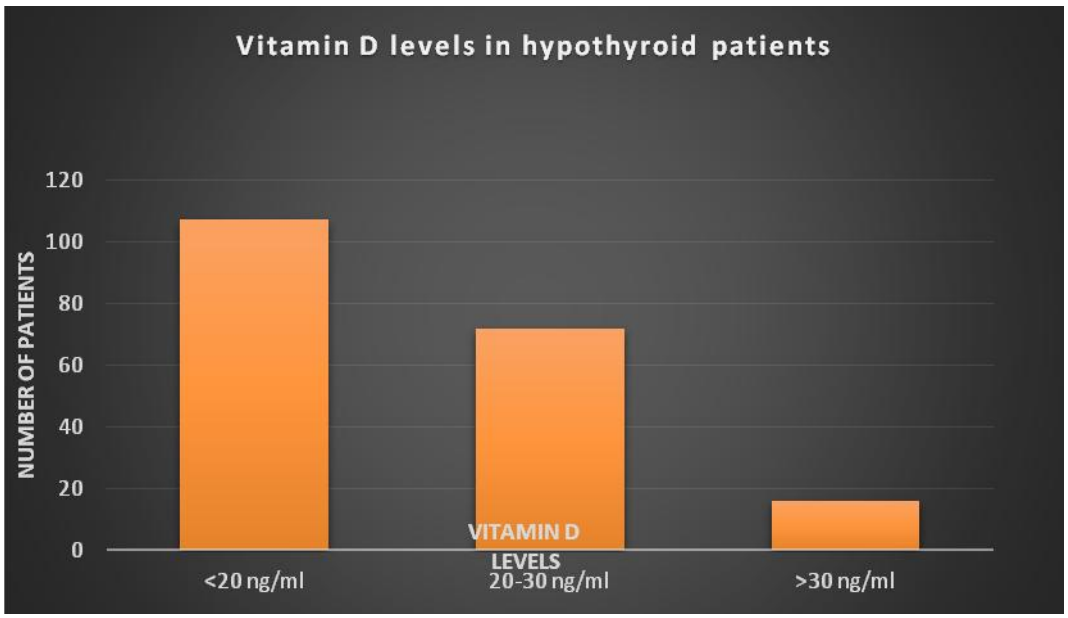


Figure 2:

Patients were divided into three groups based on vitamin D levels. 107 patients out of 195 (55%) had vitamin D deficiency, 72 patients out of 195 (37%) had vitamin D insufficiency and 16 patients out of 195 (8%) had normal levels of vitamin D. Totally 179 of 195 patients(92%) had either vitamin D insuffiency or deficiency in primary hypothyroid patients.

4. Severity of vitamin D deficiency categorized into three types: mild, moderate and severe based on 25 OH vitamin D level as represented in figure 3.

Figure 3:

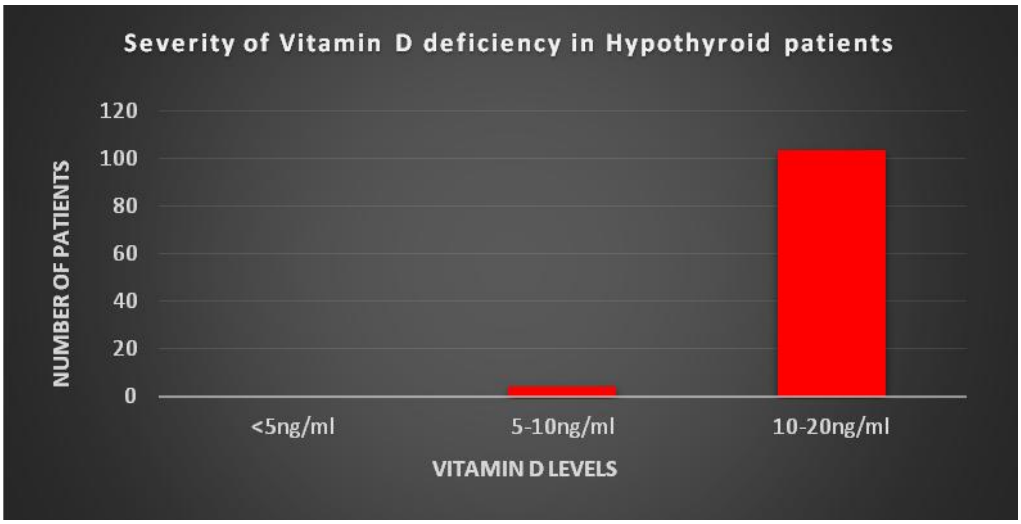


Figure 3:

Vitamin D deficiency is again divided into three types based on vitamin D levels into mild, moderate and severe with levels 10-20 ng/ml,5-10 ng/ml,and less than 5 ng/ml respectively. 103 patients out of 195 patients(96%) had mild vitamin D deficiency in our study and 4 patients out of 195 (4%) had moderate vitamin D deficiency and none of the patients had severe vitamin D deficiency.

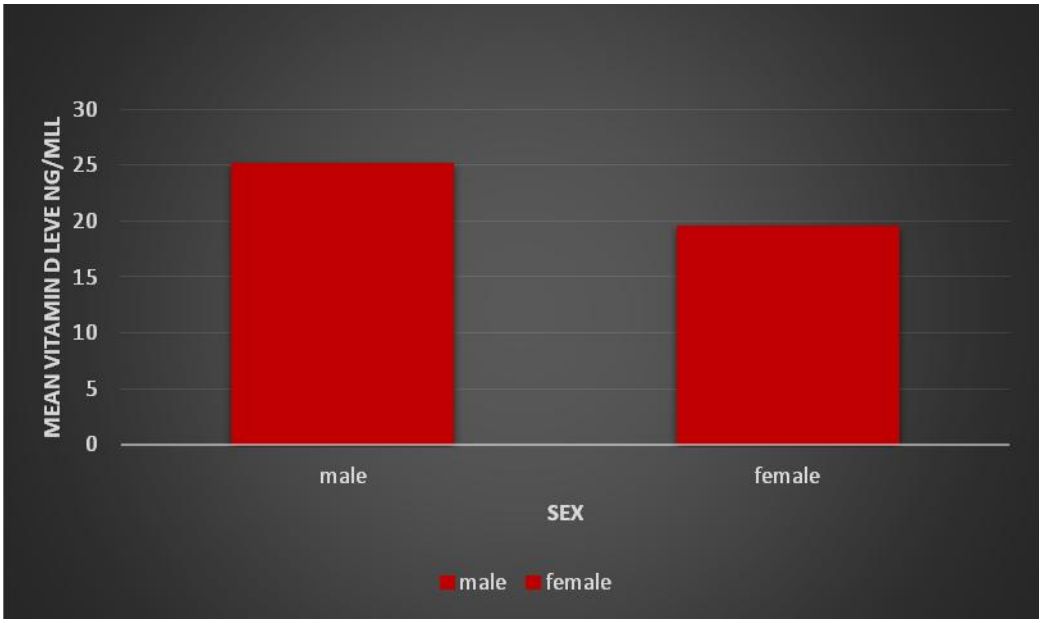
5.vitamin D deficiency or insufficiency in females: Vitamin D deficiency or insufficiency were observed in 166 out of 178 patients (93%) of patients in women and 12 out of 178 patients (7%) had normal levels of vitamin D levels.

6. vitamin D deficiency or insufficiency in males: Vitamin D deficiency or insufficiency were observed in 13 out of 17 male patients (76%) and 4 out of 17 patients (24%) had normal vitamin D levels.

7. serum calcium levels were normal in all the 195 patients whether the patient had vitamin D deficiency or insufficiency or normal vitamin D levels and including both male and female patients. Mean calcium levels in our study was 9.53 mg/dl.

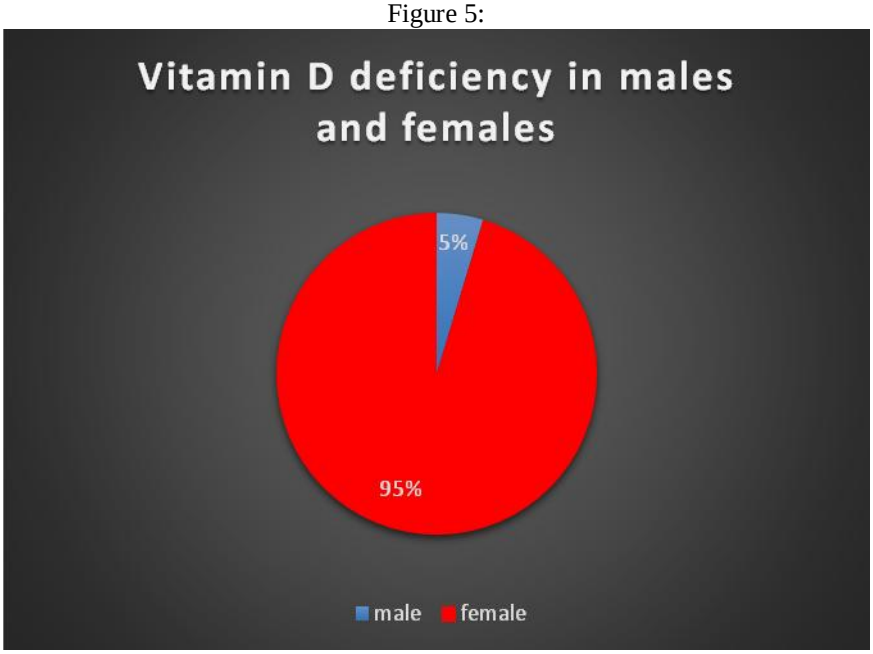
8. Mean 25 OH vitamin D levels in males were 25.21ng/ml and in females were 19.63 ng/ml as represented in figure 4. There was significant difference between the mean values of 25 OH vitamin D between males and females with a p value of 0.0048.

Figure 4: Mean 25 OH vitamin D Levels in Males and Females



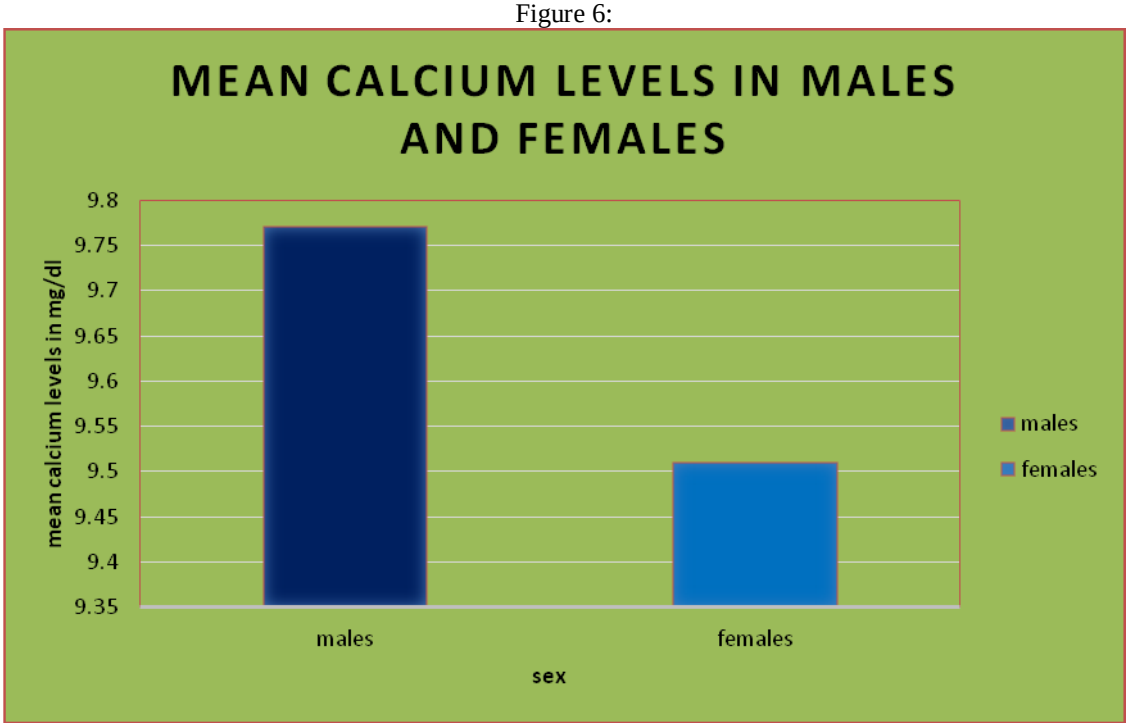
9. vitamin D deficiency was observed in 102 out of 178 (95%) female patients and 5 out of 17 (5%) male patients as represented in figure 5 .

Figure 5:



10. mean calcium levels in males were 9.77 mg/dl and mean calcium levels were 9.51 in females as represented in figure 6. There was significant difference between the two groups with a p value of 0.0229.

Figure 6:



IV. Discussion

Vitamin D deficiency is a global health problem with an estimate of over one billion people worldwide suffering from the deficiency(4). It has even been reported by the Ardawi Group, 30 to 50% of both children and adults had serum 25(OH)D levels which were under 30 ng/ml (5). Prevalence of vitamin D deficiency estimated in urban population was 62% in males and 75% in females, whereas the prevalence of Vitamin D deficiency was slightly lower in a rural area at 44% in males and 70% in females.(5). In South India, Harinarayan et al. in 2004 estimated Vitamin D deficiency in 69.3% of general population (58.6% in rural population and 85.6% in urban population).(6) In our study 55% had vitamin D deficiency which is in line with previous studies. Among the patients who had vitamin D deficiency in our study , 96% had mild vitamin D deficiency and 4% had moderate

vitamin D deficiency and none of the patients had severe vitamin D deficiency in our study. Mean 25 OH vitamin D levels lower in females compared to males in our study.

Serum concentration of 25(OH)D is the best indicator of vitamin D status. It reflects vitamin D produced cutaneously and that obtained from food and supplements and has a fairly long circulating half-life of 2-3 weeks. In contrast to 25(OH)D, circulating 1,25(OH)2D is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate . Levels of 1, 25(OH)2D do not typically decrease until vitamin D deficiency is severe. Therefore, in the present study we measured serum 25(OH)D rather than 1,25(OH)2D to ensure we are getting more accurate results. Vitamin D deficiency or insuffiency were observed in 92 % of patients in our study and 8% had normal levels of vitamin D. 55% had vitamin D deficiency and 37% had vitamin D insufficiency based on 25 OH vitamin D levels. Vitamin D deficiency again divided into three types based on 25 OH vitamin D levels and observed that none of the patients had severe vitamin D deficiency, 4% had moderate vitamin D deficiency and 96 % had mild vitamin D deficiency. Among the female patients 93% had either vitamin D deficiency or insufficiencyand 7% had normal vitamin D levels. Among the male patients 76% had either vitamin D deficiency or insufficiency and 24% had normal vitamin D levels. So vitamin D deficiency or insufficiency were more common in females compared to males in our study as hypothyroidism is more common in females compared to males.

Primary hypothyroidism is common in females than males with estimated prevalence of 0.3 % in overt hypothyroidism and 4.3% in subclinical hypothyroidism as per the wickham's survey conducted in United States of America. The average age of presentation in our study is 36 years. This could be related to common age of presentation of hypothyroidism. The prevalence of hypothyroidism is 0.9% in males compared to 4.8% in females with a ratio of 5.4. Similarly in our study 91% were women as compared to 9% men ,this could be because hypothyroidism is more common in females than males. In our study females were effected 10 times more than males.

Hashemipour et al (7) studied the prevalence of Vitamin D in Tehran and found non-significant differences between males and females without association between Vitamin D and sunlight exposure**.** In studies by Sedrani, (8**)** Al-Jurayyan et al, (9) Fida, (10) Naeem et al, (11) stated that vit D serum levels are significantly more decreased in females than males . In our study also vitamin D levels in females were significantly lower when compared to males. However, a study from Japan including 200 euthyrotic patients with Graves' disease found vitamin D deficiency in 40% of women and around 20% of men with a significant p value of less than 0.005.(12)

Pathogenesis of autoimmune thyroid disease (AITD) is multifactorial, combining genetic, immune, environmental, and hormonal influences like vitamin D.(13) In genetically predisposed individuals, the disruption of these neuroendocrine-immune interactions by environmental factors results in thyroid autoimmune dysfunction.(14)These interactions are able to shift the balance between type 1 T helper (Th1)-Th2 immune response, resulting in a Th1- cell-mediated autoimmune reaction with thyrocyte destruction and hypothyroidism in hashimotos thyroiditis , but to a hyperreactive Th2-mediated humoral response against TSH receptor with stimulatory antibodies leading to Grave's disease.(14) The mechanism underlying the link between vitamin D and autoimmunity is not completely understood but is probably associated with its anti-inflammatory and immunomodulatory functions.(15,16) The expression of the nuclear vitamin D receptor (VDR) and the vitamin-D-activating enzyme 1α-hydroxylase in most immune cells, including T cells, B cells, and antigen-presenting cells including macrophages and dendritic cells , highlighted the potential involvement of vitamin D in the immune system and in the pathogenesis of autoimmune diseases.(17,18)

Hypovitaminosis D has been correlated to the presence of metabolic syndrome, cardiovascular diseases, cancers, infections, neuromuscular disorders. (19). Interestingly, it has been shown recently that vitamin D has potent immunomodulatory effects and plays important roles in the pathogenesis of autoimmune diseases. As such, many researchers speculated that autoimmune disorders, including type I diabetes, autoimmune thyroiditis, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, could be related to vitamin D imbalance (20). Furthermore, vitamin D supplementation prevented the onset and/or development of several kinds of autoimmune diseases in humans and animal models. (21) These results suggested that vitamin D deficiency might cause the onset and/or development of several kinds of autoimmune diseases.

One of two mechanisms which may explain the low levels of vitamin D in patients with hypothyroidism. First, the low levels of vitamin D may be due to poor absorption of vitamin D from the intestine. Second, the body may not activate vitamin D properly. Importantly, both Vitamin D and thyroid hormone bind to similar receptors called steroid hormone receptors. A different gene in the Vitamin D receptor was shown to predispose people to autoimmune thyroid diseases including Graves' disease and Hashimoto's thyroiditis.

In previous decades, Vitamin D deficiency was considered virtually nonexistent in the Indian population as India lies in the tropical area.(22) But now a days various studies have revealed that 50-90% of the Indian population is deficient in Vitamin D due to inadequate dietary intake of vitamin D as well as lack of adequate exposure to sunlight.(23) In a study conducted by Nirensiongh et al (24) in North Indian population of Meerut, there were 53.94% subjects who were Vitamin D deficient. In a study conducted by Shilpa et al (25) there were 56% of the hypothyroid subjects in whom Vitamin D levels were below 20 ng/ml , there were only 10% subjects who had sufficient levels of Vitamin D. The present study showed 55% of the patients in our study had vitamin D deficiency with levels lower than 20 ng/ml and 8% had normal levels of vitamin D. So , our study results were similar to the previous studies.

The prevalence of vitamin D deficiency in adult population has been reported to be 9–70% with a higher prevalence in Asian countries.(26,27) some studies have reported the prevalence of vitamin D insufficiency in Hashimoto's disease (92%) was significantly higher than in healthy controls (63%).(28) Furthermore, Mackawy et al.(29) concluded that the patients with hypothyroidism suffered from hypovitaminosis D and there was a positive significant correlation between serum level of vitamin D with thyroid hormones and a negative significant correlation with TSH levels and suggested that the deficiency of serum levels of vitamin D was significantly associated with the degree and severity of hypothyroidism.

The calcium levels in the present study were normal in both males and females suggesting that vitamin D deficiency is not severe enough in patients with hypothyroidism in our study to cause hypocalcemia . Most of the patients in our study had either mild vitamin D deficiency or moderate vitamin D deficiency and none of the patients had severe vitamin D deficiency to cause hypocalcemia. However , the mean calcium levels in females were significantly lower than males with a p value of 0.0229.

Finally vitamin D deficiency is common in patients with primary hypothyroidism with normal calcium levels. Hence, encourage all patients with primary hypothyroidism about exposure to sunlight and diet rich in vitamin D for prevention of vitamin D deficiency in these patients.

V. Conclusion

The present study concluded that vitamin D deficiency is common in primary hypothyroidism patients. So every patient with primary hypothyroidism must be evaluated for vitamin D deficiency with mere estimation of 25 OH vitamin D levels. All patients with primary hypothyroidism must be exposed to sunlight every day to prevent vitamin D deficiency in these patients as this is the predominant source of vitamin D in the body and it is simple to follow.

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