ORIGINAL RESEARCH ARTICLE

A Study on Serum Vitamin D Levels among Subclinical Hypothyroid Adult Females From a Tertiary Health Care Institute – Case Control Study.

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Abstract: -

Introduction: Autoimmune thyroiditis is a organ specific disorder that causes diseases ranging from subclinical hypothyroidism to hyperthyroidism. Subclinical hypothyroidism is common entity encountered in practice. The cause for autoimmune thyroiditis is multifactorial and the one among them is hormonal influences. Recent evidences suggest that vitamin D deficiency have an important role in autoimmune diseases. In patients with Subclinical hypothyroidism they have few or no symptoms of thyroid dysfunction, so by nature it is a laboratory diagnosis. Aim: The aim of this study is to compare the relationship between vitamin D and subclinical hypothyroidism. Materials & Methods: It was conducted in Tamil Nadu Govt Multi Super Speciality Hospital, Chennai during the period of JAN-MAR 2019. The study participant includes 100 adult females aged 20 to 60 years with (mean age ±S.D : 47.52±11.19 and 49.04±13.62) for controls and cases respectively who underwent master health check up. Results: Cases had significantly lower vitamin D levels (18.15±8.61) than controls (25.81±10.85) level of significance (p<0.0001). Conclusion: Vitamin D deficiency is prevalent among subclinical hypothyroid adult females, supplementation with Vitamin D levels will have beneficial effects in adult females.

Keywords: Autoimmune Thyroiditis, Subclinical Hypothyroidism, Vitamin D deficiency, Prevalence.

Introduction:

Vitamin D deficiency is a global health problem, prevalent in India, despite being a tropical country and is being reported among all age groups barring genders, varying among different parts of the country. Besides its pivotal role in calcium homeostasis, bone and mineral metabolism, vitamin D endocrine system in now recognized to subserve a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth as well as immunomodulation. Serum 25-hydroxyvitamin D [25(OH) D] is the most reliable indicator of vitamin D adequacy of an individual [1].

Rural populations have better vitamin D status compared to urban population. The prevalence of sub-clinical 25(OH) D deficiency (hypovitaminosis D) may be over looked due to vague clinical presentation. There is now a vast body of evidence to suggest that vitamin D deficiency as a major factor in the pathology of at least 17 varieties of cancer as well as heart disease, stroke, hypertension, autoimmune diseases, diabetes, depression, chronic pain, osteoarthritis, osteoporosis, myopathies, birth defects, periodontal disease, and many more diseases [2].

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Several studies have found low levels of vitamin D among hypothyroid adults, there are a few studies which contradicts the same. So the study was aimed at estimating vitamin D levels among asymptomatic hypothyroid adult females, who remains as susceptible population at large in our society.

Materials & Methods:

Present study was case control observational study. The study was done after Ethical Commitee approval. It was conducted in Tamil Nadu Govt Multi Super Speciality Hospital, Chennai during the period of JAN-MAR 2019. The study participants were 100 adult females with ages ranged from 20 to 60 years with for controls and cases respectively, who underwent master health check up.

Inclusion Criterion:

The participants were divided into 2 groups

Group 1 : Cases – participants adult females aged 20-60 years with subclinical hypothyroidism (serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxin (T4) within the reference range.

Group 2 : Control – participants adult females aged 20-60 years with euthyroidism (normal thyroid status).

All the participants of the study are questioned at the baseline for a general medical history and specific history relating to thyroid disorder. They are also examined for a general medical examination.

Exclusion criteria:

Patients with Diabetes mellitus, renal disease, on hepatotoxic drugs, cholestatic disease, cardiac failure, anemia and any bleeding diathesis were not taken in this study.

Methodology:

Venous blood 5 ml collected by venepuncture under aseptic precautions in the fasting state. The collected blood is processed for serum separation and then sent for laboratory analysis.

Laboratory investigations include:

Routine investigation: Serum FT3, FT4, TSH (Thyroid stimulating hormone) and vitamin D levels using ECLIA (Electro Chemiluminescence Immunoassay) method in fully automated Immunoanalyser.

FT3- is performed by Electro-chemiluminescence immunoassay by Competition principle with a reference range : 3.1-6.8 pmol/L

FT4- is performed by Electro-chemiluminescence immunoassay by Two step competitive assay with a reference range 12-22 pmol/L

TSH-is performed by Electro-chemiluminescence immunoassay by sandwich principle with a reference range of 0.5-5.4μIU/ml

Vitamin D:Is performed by Electro-chemiluminescence with the sufficient range > 30 ng/ml, insufficient range 20-29ng/ml and deficiency <20ng/ml.

Observation & Results:

The study participants were 100 adult females with ages ranged from 20 to 60 years with (mean age ±S.D : 47.52±11.19 and 49.04±13.62) for controls and cases respectively, who underwent master health check up.

Table 1 : Comparison of mean of different parameters of cases and control

	Cases Mean±SD	Control Mean±SD	t-value	p-value
Vitamin D	18.15±8.61	25.81±10.85	3.90	P<0.0001 S
TSH	9.79±6.47	3.38±2.02	5.95	P<0.0001 S
FT4	16.37±2.82	17.59±2.93	2.11	P=0.03 S
FT3	4.86±0.60	4.97±0.49	1.02	P=0.30 NS

The mean vitamin D levels in cases group participants was 18.15±8.61 ng/ml as compared with control group participants i.e. 25.81±10.85 ng/ml. The mean vitamin D levels in cases group participants was lower as compared with control group. This mean difference of vitamin D levels in cases group and control group was found to be statistically significant (p<0.0001).

The mean TSH levels in cases group participants was 9.79±6.47 μIU/ml higher as compared with control group participants i.e. 3.38±2.02 μIU/ml. This mean difference of TSH levels in cases group and control group was found to be statistically significant (p<0.0001). The mean FT4 levels in cases group participants was 16.37±2.82 pmol/L lower as compared with control group participants i.e. 17.59±2.93 pmol/L. This mean difference of FT4 levels in cases group and control group was found to be statistically significant (p=0.03). The mean FT3 levels in cases group participants was 4.86±0.60pmol/L lower as compared with control group participants i.e. 4.97±0.49 pmol/L. This mean difference of FT3 levels in cases group and control group was found to be not statistically significant (p=0.30).

Discussion:

Vitamin D Deficiency:

Vitamin D deficiency has been documented across all age groups and both sexes from India and different parts of world [2-5]. In addition to the limited oral intake and age-related decline in its absorption, decreased exposure to sunlight is among the leading causes of Vitamin D insufficiency in women6. Vitamin D insufficiency has been implicated in increasing

prevalence of autoimmune diseases, including type I diabetes mellitus, rheumatoid arthritis and systemic lupus erythematosus. On the other hand, immune-mediated pathophysiology comprises the major etiology of hypothyroidism in iodine-replete areas. Moreover, aging is linked to the increased prevalence of subclinical forms of hypothyroidism [7]. Vitamin D levels have been found to be lower in patients with autoimmune thyroid disorders compared to the healthy volunteers in one study [8]. Yet, other studies have not yielded similar results [9].

Hypothyroid Disease :

Thyroid disorders are more common in women by 5–10 times [10], while their frequency increases with age [11]. Autoimmune thyroid diseases (AITD), including Hashimoto Thyroiditis and Graves Disease are the most common organ-specific autoimmune disorders. These AITDs are polygenic diseases resulting from a combination of genetic predisposition (thyroid-specific genes and immune-modulating genes) and environmental triggers (iodine, selenium, drugs, irradiation, smoking, infections, stress, etc.), characterized by lymphocytic infiltration into the thyroid gland and production of thyroid-specific autoantibodies. TSH is a physiologic indicator of thyroid function and its elevated level is particularly the most sensitive screening test for hypoactive thyroid function.

Role of Vitamin D in Thyroid Disease :

Vitamin D is an omnipotent regulator of the innate immunity, and inadequate serum levels of this vitamin have been linked to autoimmune reactions [12]. The pathogenesis of AITDs, like other autoimmune diseases, is multifactorial, combining genetic, immune, environmental and hormonal influences such as vitamin D.

Vitamin D suppresses interleukin (IL-12) production, which is a type-1 cytokine that polarizes T-helper lymphocytes. As a result of IL-12 suppression, there is a shift toward type-2 T-helper (TH2) responses that include expression of IL-4, IL-5, IL-6 and IL-10. TH2 response is a much stronger activator of B-cells leading to antibody secretion, particularly IgE responses in type-1 hypersensitivity reactions.Vitamin D exerts its effect by binding to vitamin D receptor , which is present on many cells of immune system and thereby regulating the activity of the immune cells. Individuals with genetic polymorphisms of these receptors are particularly prone to autoimmune thyroid disorders [13]. Metabolism of Vitamin D is also reciprocally regulated by thyroid hormones. Provitamin D3 is synthesized from 7-dehydrocholesterol and the enzymatic reaction takes place principally in keratinocytes located in the basal and spinous strata of the epidermis layer. On the other hand, thyroid hormone exerts important effects on skin. Histologic examination of the skin in hypothyroid patients has shown changes indicative of epidermal thinning and hyperkeratosis. There is a strong suggestion that the epidermal barrier function is probably impaired in hypothyroidism with a speculation that synthesis of Vitamin D is decreased in patients with overt hypothyroidism and high TSH[14].The biologically active form of vitamin D, a secosteroid hormone essential for bone and mineral homeostasis, has been shown to have immunoregulatory and anti-inflammatory properties. Most of the known biological effects of vitamin D are mediated through the vitamin D3 receptor (VDR), and can be regulated by the vitamin D-binding protein and the CYP27B1 hydroxylase[15]. The immune modulator properties of vitamin D are ascribed to its effect on cells of the innate and adaptive systems, including macrophages, dendritic cells, and T and B lymphocytes, all of which harbor VDRs. Dendritic cells are a primary target for the immunomodulatoric activity of vitamin D[16]. Allelic variations within the VDR gene have been implicated in mediating susceptibility to several endocrine autoimmune disorders[17]. Stefanicetal. reported an association between VDR-common haplotypic variants and Hashimoto's thyroiditis. In addition, several studies demonstrated genetic polymorphism of the vitamin D-binding protein among Polish and Japanese patients with AITDs, whereas the CYP27B1 hydroxylase polymorphism was found to predispose to Hashimoto's thyroiditis and Graves' disease in German subjects could not be confirmed in other studies.On the other hand, recent studies have demonstrated a role of vitamin D in Graves Disease (GD). First, Vitamin D related gene polymorphisms such as VDR gene and vitamin D binding protein gene are associated with GD. Second, Vitamin D deficiency modulates Graves' hyperthyroidism induced by thyrotropin receptor immunization in BALB/c mice. Third, Vitamin D analog inhibits inflammatory responses in human thyroid cells and T cells [18]. Also a study had been conducted in Netherlands showed that Vitamin D deficiency is not associated with early stages of thyroid autoimmunity[19].

Some studies, however, have failed to find an association between low vitamin D status and AITD or HT. Goswami et al., revealed no association of vitamin D deficiency (<25 nmol/L) and anti-TPO positivity, but only a weak inverse correlation between serum 25(OH)D and anti-TPO levels in 642 students, teachers, and staff from India

($r = 0.08$; $p = 0.04$). A total of 803 subjects from an AITD cohort from Amsterdam were investigated in a longitudinal study by Effraimidis et al., who showed that 25(OH)D levels were not lower in AIRD cases compared to controls, nor in subjects with a genetic

susceptibility for AITD or seroconverters with de novo occurrence of anti-TPO antibodies. The authors concluded that vitamin D deficiency is not associated with the early stages of thyroid autoimmunity [20]. This study shows that vitamin D deficiency is prevalent in subclinical hypothyroidism conducted on 100 adult females aged 20 to 60 years who underwent master health check up in a tertiary care hospital Tamil Nadu Govt.Multi Super Speciality Hospital. Cases had significantly lower vitamin D levels (18.15±8.61) than controls (25.81±10.85), level of significance ($p<0.0001$). Cases had significantly higher TSH levels (9.79±6.47) than controls (3.38±4.02).level of significance ($p<0.0001$). Thus vitamin D supplementation could have beneficial effects on both the future events related to thyroid diseases and Vitamin D deficiency.

Limitations:

The limitations of the study includes the small sample size, regression analysis lack which could well hide the impact of other factors in influencing the role of vitamin D in thyroid illness, lack of substantiating genetic and molecular associations for the study, to mention a few.

Conclusion:

The study concludes that Vitamin D deficiency is prevalent among subclinical hypothyroid adult females during routine health checkup. Though a bigger sample size would ascertain more meaningful association between the same, yet the study warrants a thorough search for Vitamin D deficiency among subclinical hypothyroids. An early Vitamin D supplementation could have beneficial effects on both the future events related to thyroid diseases and Vitamin D deficiency.

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