



Original Research Article

Assessment of interrelationship between vitamin D status, thyroid stimulating hormone levels, insulin resistance and secretion in patients with subclinical hypothyroidism

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TSH: Thyroid Stimulating Hormone

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25-Hydroxycholecalciferol

ECLIA: Electro Chemiluminisence immuno assay

ABSTRACT

Objective: To study the relationship between thyroid stimulating hormone levels, 25 hydroxycholecalciferol (Vitamin D₃) and Insulin resistance and secretion in subclinical hypothyroidism

Materials and Methods: The study population was divided into two groups, Group I include 40 subjects diagnosed with subclinical hypothyroidism and Group II includes 40 ages matched healthy euthyroid control group. Serum Thyroid stimulation hormone, Vitamin D₃ (25-Hydroxycholecalciferol) were analyzed by Electrochemiluminisence immune assay. Insulin resistance and insulin secretion were calculated from fasting glucose and fasting insulin by Homeostasis model assessment HOMA IR and HOMA B.

Results: In subclinical hypothyroidism Serum Thyroid stimulation hormone levels and Insulin resistance were elevated ($p < 0.001$) significantly compared to euthyroids ($p < 0.001$). Serum Vitamin D₃ (25-Hydroxycholecalciferol) and insulin secretion (HOMA B) ($p < 0.05$) were decreased significantly compared to euthyroids. Vitamin D₃ (25-Hydroxycholecalciferol) is negatively correlated with TSH and Insulin resistance ($P < 0.001$). TSH is positively correlated with insulin resistance ($P < 0.001$).

Conclusion: Subclinical hypothyroidism is associated with a decreased vitamin D and insulin secretion and increased insulin resistance. This prompts us to question whether prevalence of vitamin D deficiency in Subclinical hypothyroidism, predisposes to early development of diabetes especially where both diabetes and hypothyroidism are highly prevalent. Both Insulin resistance and Vitamin D₃ deficiency in subclinical hypothyroidism together lead to early development of insulin resistance disorders, metabolic syndrome and cardiovascular diseases.

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1. Introduction

Thyroid dysfunction, diabetes mellitus and vitamin D deficiency are widely prevalent around the globe and in India. According to international diabetes federation, the number of diabetes patients expected to increase from 415 million to 642 million by 2040, India having 69.1 million patients among them.¹ Similarly, studies have shown that

around 42 million people in India suffer with thyroid diseases.² Subclinical hypothyroidism is the most prevalent thyroid disorder affecting 3-15% of adult population,³ eventually a substantial number of patients with Subclinical hypothyroidism develop into overt hypothyroidism at a rate of 4.3 to 8% with a high predisposition among adult population.⁴⁻⁶ On the other hand vitamin D deficiency is increasing world wide ranging from 80–90% still becomes the most underdiagnosed and untreated nutritional deficiency in the world.^{7,8} Vitamin D deficiency is drawing

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much attention in its association with various diseases including cancer, cardiovascular diseases, autoimmune diseases, endocrine and metabolic diseases.^{9,10} Vitamin D function as an immunomodulator, its deficiency may affect autoimmune thyroid disease. Subclinical hypothyroidism associated with increased TSH and normal T3 and T4, most commonly is an early stage of hypothyroidism may be caused due to chronic autoimmune thyroiditis, which eventually develop to overt hypothyroidism each year at a rate of 4.3–8%.⁴⁻⁶

Vitamin D deficiency, hypothyroidism and diabetes mellitus are widely prevalent in India and across the world, In the present work we tried to study the association between Subclinical hypothyroidism, vitamin D deficiency and insulin resistance, whether they had any significant impact in the early predisposition of diabetes mellitus and overhypothyroidism.

2. Materials and Methods

Across-sectional study was carried in two groups

2.1. Inclusion criteria

In the group I, 40 clinically diagnosed patients of subclinical hypothyroidism, presenting with normal T3, T4 and increased TSH levels were included. In Group II, 40 apparently healthy euthyroid individuals were included. Inform consent was obtained from all the patients.

2.2. Exclusion criteria

Patients suffering from chronic or systemic illness that alter thyroid functional tests were excluded from the study. Alcoholics, chronic smokers & patients already on treatment for hypothyroidism were also excluded from the study. None of the patients are on vitamin D supplements.

The study was performed in Department of Biochemistry. Shadan Institute of Medical Sciences, Teaching Hospital and Research Centre, Hyderabad.

2.3. Collection of the blood sample

Under aseptic conditions, Fasting blood sample (5 ml) was drawn from antecubital veins of all the subjects. 4 ml of the blood sample was transferred into plain vacutainer was allowed to clot for 30 minutes and then centrifuged at 2000 rpm for 15 minutes for clear separation of serum. 1ml fasting blood samples are collected in fluoride vacutainers for glucose estimation. Serum was taken for the analysis of T3, T4 and Thyroid stimulating hormone, Insulin, Vitamin D (25 hydroxy cholecalciferol).

Insulin, T3, T4, Thyroid stimulating hormone and Vitamin D (25 hydroxycholecalciferol) were measured by Electro Chemiluminisence Immune Assay (E CLIA) method, in Cobase 411 auto analyser and glucose by glucose

oxidase and peroxides (GOD-POD) method. HOMA IR and HOMA B were calculated from fasting sugar and fasting insulin levels. $\text{HOMA IR} = \text{fasting insulin } (\mu\text{IU/ml}) \times \text{fasting glucose (mmol/L)} / 22.5$ and $\text{HOMA B} = 20 \times \text{fasting insulin } (\mu\text{IU/ml}) - 3.5 / \text{fasting glucose (mmol/L)}$.¹¹⁻¹³

3. Results

On Pearson correlation of the parameters between the health control group and sub clinical hypothyroidism we found significant (<0.001) increase in serum TSH and HOMA IR and significant (<0.001) decrease in Vitamin D₃ (25 hydroxy cholecalciferol) in subclinical hypothyroidism compared to the normal healthy control group. There is significant (< 0.05) decrease in HOMA B in subclinical hypothyroidism.

In subclinical hypothyroidism, Vitamin D₃ (25 hydroxy cholecalciferol) is negatively correlated with thyroid stimulating hormone and HOMA IR. Indicating increase in both HOMA IR (insulin resistance) and TSH levels in vitamin D deficiency. Similarly, we found significant positive correlation between TSH and HOMA IR. Results indicating both subclinical hypothyroid and vitamin D deficiency independently contribute the development of insulin resistance.

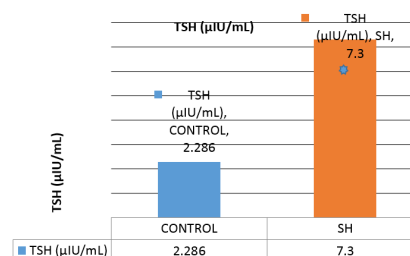


Fig. 1: Significant increase in TSH in subclinical hypothyroid. ($P < 0.001$)

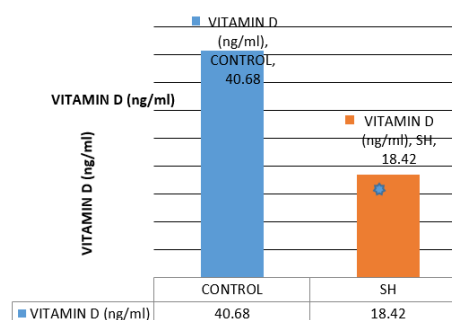
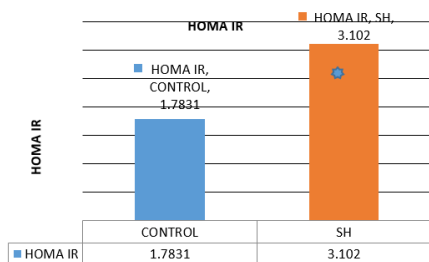
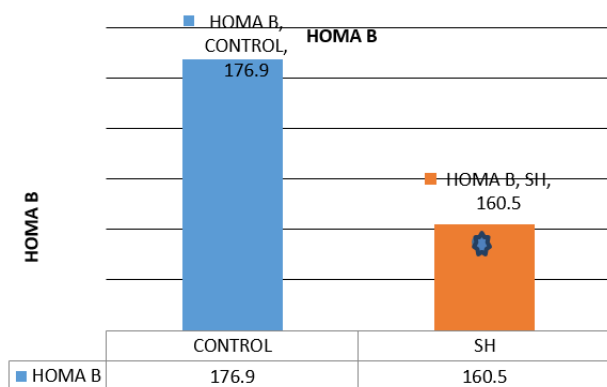


Fig. 2: Significant decrease in vitamin D in subclinical hypothyroid. ($P < 0.001$)

Table 1: Comparison of results between two groups

Parameter	Control	Subclinical hypothyroidism	Significance (p<0.05)
NUMBER	40	40	
AGE in years	39±6	37±8	
SEX(m/f)	20/20	16/24	
TSH(μIU/mL)	2.286 ± 1.3852	7.3+ 0.65	<0.001
Vitamin D ₃ (μIU/mL)	40.68 ± 11.60	18.42 ± 4.11	<0.001
HOMA IR	1.7831± .632	3.102±1.050	<0.001
HOMA B	176.90 ±76.209	150± 56.209	<0.05

**Fig. 3:** Significant increase in HOMA IR in subclinical hypothyroid.(P<0.001)**Fig. 4:** Significant decrease in HOMA B in subclinical hypothyroid.(P<0.05)

4. Discussion

4.1. Thyroid and insulin resistance

Thyroid hormones play an important role in carbohydrate metabolism by stimulating hepatic gluconeogenesis, glycogenolysis and upregulating the expression of glucose transporters (GLUT-4) and phosphoglycerate kinase. Thus facilitating glucose uptake and utilisation in peripheral tissues, acting synergistically to insulin.¹⁴⁻¹⁷

Studies found high prevalence of thyroid diseases in patients with diabetes indicating possible interrelationship between thyroid status and insulin resistance. In our study we tried to observe insulin resistance in subclinical hypothyroidism. In comparison to diverse studies indicating significant impact of thyroid hormones on insulin resistance

and secretion, in our study we tried to observe insulin resistance and secretion in subclinical hypothyroidism. Our search in the literature found some of the studies showing the interrelationship between thyroid hormones and its affecton insulin resistance, In a study by E. Maratou et al¹⁸ on the levels of GLUT 3 and GLUT 4 glucose transporters on the monocyte plasmamembrane observed decreased insulin stimulated glucose transport in monocytes from patients with subclinical hypothyroidism and overt hypothyroidism due to impaired translocation of GLUT-4 glucose transporters on the plasma membrane. They suggested that if these findings in monocytes reflect respective changes in peripheral tissues, it can lead to impairment in insulin-stimulated rates of glucose disposal in muscle and adipose tissue in patients with HO and SHO, which is accounted for by impaired translocation of GLUT4 transporters on the cell surface. AL Sayed et al¹⁹ and Tuzcu A et al²⁰ in their studies on subclinical hypothyroidism found only significant increase in insulin levels, but no significant change was found in insulin resistance. Lekakis et al²¹ stated that flow mediated endothelial vasodilation is impaired in hypothyroid which leads to insulin resistance. In another study by Kim et al²² from their study stated that thyroid hormones and insulin have synergistic role in glucose homeostasis at both cellular and molecular level. They hypothesised that reduced intracellular content of thyroid hormones, impairs insulin stimulated glucose uptake, hence mild decrease in thyroid hormones in subclinical hypothyroidism inversely correlated with insulin resistance. Teixeirass et al²³ from their invitro studies reveal that triiodothyronine(T3) rapidly increases glucose uptake in L6 GLUT4 muscle cells without increasing the surface GLUT4, GLUT1 and GLUT3, they proposed that rapid action of triiodothyronine(T3) is due to activation of GLUT4 transporters at the cell surface. Some other studies indicated that even a small increase in plasma TSH levels with in normal range can affect insulin secretion and may cause insulin resistance, in contrast to this in another study²⁴ on euthyroids, we found significant positive correlation between TSH and insulin secretion but no significant change was found in insulin resistance within normal range of TSH. In our study HOMA-IR was significantly higher in SCH when compared with euthyroid. A positive correlation was observed for TSH

with HOMA IR, similar to studies by Abdel-Gayoum AA²⁵ where subclinical hypothyroidism associated with increasing insulin resistance, positively correlating with TSH.

4.2. Thyroid and Vitamin D

Recent studies have shown that, In addition to the maintenance of homeostasis of bone and mineral metabolism, Vitamin D, deficiency has been associated in the pathogenesis of many diseases like cancer, diabetes, heart diseases, infections and hypothyroidism.^{26,27} In the skin 7 dehydrocholesterol get converted to cholecalciferol, which get hydroxylated in the liver to 25 hydroxycholecalciferol, which has a long half-life of 15 days. 25 hydroxycholecalciferol gets hydroxylated in the kidneys forming functional vitamin D3 calcitriol (1,25 dihydroxy cholecalciferol). Calcitriol has a short half-life of 15 days and its levels in the blood are regulated by Parathormone, calcium and phosphorous.^{28,29} Calcitriol levels do not usually decrease until severe vitamin D deficiency.^{30,31} Therefore serum concentrations of 25 hydroxycholecalciferol are considered as a good indicator of vitamin D status in the body. Hence in the present study we measured 25 hydroxycholecalciferol. Though some studies have shown the association between hypothyroid and vitamin D deficiency, scanty literature is available correlating whether vitamin D deficiency leads to hypothyroidism or hypothyroidism itself a causative factor for the development of vitamin D deficiency.

In the present study we observed that vitamin D had a role to play in subclinical hypothyroidism. In this study, the subclinical hypothyroid patients had significantly lower levels of serum 25 hydroxycholecalciferol as compared to controls ($p < 0.001$). We found a negative correlation of serum 25 hydroxycholecalciferol levels with TSH in subclinical hypothyroid patients on Pearson's correlation analysis ($r = -0.35$, $p < 0.001$), our results similar to other studies has good correlation with Thyroid stimulation hormone and vitamin D. Similar to our study, Byran Richards³² from their experimental study on the thyroid gland found that deficiency of the vitamin D was a causative factor for low thyroid hormones, Friedman T.C³³ from his study found that a different vitamin D receptor predisposes to autoimmune diseases including hashimotos thyroiditis and graves disease. Shilpa et al³⁴ study on Indian population found significant relationship between hypothyroidism and vitamin D, Afsaneh et al³⁵ in their study on hypothyroid patients with vitamin D deficiency found improvement in thyroid function after vitamin D supplementation, indicating possible role of vitamin D in thyroid function. In addition, in hypothyroid patients decreased levels of the vitamin D might be due to poor absorption of the vitamin D from intestines or impairment in the activation of the vitamin D.

Conversely, few studies have focused on the effect of hypothyroidism on the synthesis of the vitamin D in the body, leading to vitamin D deficiency. Vitamin D Metabolism intum is regulated by the thyroid hormones. In keratinocytes located in the basal and spinous strata of the epidermis layer 7-dehydrocholesterol is converted to Provitamin D3.³⁶ Thyroid hormone exerts important effects on skin. In a study by Safer JD³⁷ in hypothyroid patients found changes indicative of epidermal thinning and hyperkeratosis on histologic examination of the skin. Suggesting, probable impaired epidermal barrier function in hypothyroidism, speculating decreased synthesis of vitamin D.

In comparison to earlier studies indicating high prevalence of vitamin D deficiency, as a contributing factor for the development of hypothyroidism, Safer JD³⁷ from their study indicates prevalence of hypothyroidism itself can lead to vitamin D deficiency.

4.3. Vitamin D and insulin resistance

Benetti E et al in their study in mice found negative correlation between the vitamin D and insulin resistance.³⁸ Anastassios G, in their study found vitamin D supplementation in type1 and type 2 diabetes improved insulin sensitivity associated with decreased blood glucose and HbA1c levels, further suggesting higher concentration of the vitamin D are associated with subsequent decrease in cardiovascular diseases, type 2 diabetes mellitus and metabolic syndrome.³⁹

Maestro B et al⁴⁰ in their study, when treated human promonocytic cells with 1,25

Dihydroxycholecalciferol for 24 hours, found transcriptional activation of human insulin receptor gene associated with improved insulin sensitivity, indicating the possible role of vitamin D on insulin resistance. Influence of the vitamin D on glucose homeostasis can be explained by the presence of specific vitamin D receptors on pancreatic beta cells and also the expression of 1 α -hydroxylase in the pancreatic beta cells, indicating extra renal synthesis of vitamin D in the pancreas. It was even found the presence of the vitamin D receptors in the skeletal muscle, which activates insulin receptor gene and upregulates the expression of insulin receptors leading to insulin mediated uptake of glucose.⁴¹⁻⁴⁷

There is compelling evidence between the vitamin D and its effect on insulin sensitivity and secretion in animal and invitro studies. Studies^{48,49} in mice with mutation in vitamin D receptor found with increased insulin resistance and impaired insulin secretion. Vitamin D receptor is expressed in both adipose tissue and human skeletal muscle, which are the main sites of peripheral insulin sensitivity. It was found that with increase in age there was significant decrease in the expression of vitamin D receptor associated with increase in insulin resistance.⁵⁰

Vitamin D deficiency may also result in the elevation of PTH,⁵¹ which in turn elevates intracellular calcium which may inhibit insulin target cells from sensing the brisk intracellular calcium fluxes necessary for insulin action.⁵²⁻⁵⁵ Even Increased intracellular calcium enhances calmodulin binding to IRS-1, which interferes with insulin stimulated tyrosine phosphorylation and PI3-kinase activation leading to increased insulin resistance.⁵⁶⁻⁵⁸ In contrast Kamycheraetal⁵⁹ did not find any significant difference in insulin action in secondary hyperparathyroidism compared with the control group. In another study by Prasanjitetal,⁶⁰ on adipocytes cultured from murine adipocytes cultured from murine 3T3LI fibroblast cell line, when treated with high glucose in the presence and absence of 1,25 dihydroxycholecalciferol, found significant upregulation of GLUT 4 protein expression, translocation to cell surface and increase in glucose uptake, Indicating by which vitamin D can upregulate GLUT4 and increase glucose uptake.

5. Conclusion

1. We found that significant decrease in the vitamin D, independently affecting insulin sensitivity and secretion can lead to the early predisposition of insulin resistance associated disorders diabetes mellitus and metabolic syndrome.
2. Subclinical hypothyroidism initial phase of hypothyroidism, if untreated might have a significant influence on insulin resistance and secretion that might potentiate the insulin resistance and pathogenesis of diabetes mellitus.
3. If untreated Hypovitaminosis D and subclinical hypothyroidism together can become a potential factor that might potentiate the pathogenesis of diseases associated with insulin resistance, including diabetes mellitus, cardiovascular diseases and metabolic syndrome.

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7. Source of funding

None.

8. Conflict of interest

None.

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