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Research Article

INTERRELATIONSHIP OF VITAMIN D AND HOMA-IR IN HYPOTHYROID PATIENTS IN AN URBAN POPULATION

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ABSTRACT

Background: Increased risk of atherosclerosis and cardiovascular disorders in hypothyroidism are significantly attributable to insulin resistance and vitamin D deficiency. In the present study we tried to establish any interrelationship between Increased insulin resistance and decreased vitamin D levels in hypothyroid patients along with their dependence on the thyroid index parameters.

Methods: In a hospital based case control study including 54 hypothyroid cases and 100 controls, serum fT_4, TSH, 25 OH vitamin D and HOMA-IR were measured using ELISA. Data were analyzed for difference of mean values between case and control groups. Correlation and regression analyses were done to find out the strength of association and dependence of HOMA-IR and vitamin D with other study variables.

Results: Vitamin D was significantly reduced and HOMA-IR was significantly elevated in the case group. Although vitamin D and HOMA-IR showed significant negative and positive correlations respectively with TSH, they did not show any such significant dependence on TSH in the multiple linear regression analysis (β = -.197 and .087, P = .082 and .465 respectively). Vitamin D levels showed significant dependence on fT4 level and the HOMA-IR index (β = .293 and -.372, P = .021 and .004 respectively) while HOMA-IR index showed such dependence on the thyroxine level and vitamin D level (β = -.270 and -.404, P = .042 and .004 respectively).

Conclusion: A compromised status of both vitamin D homoeostasis and increased insulin resistance not only exist side by side in hypothyroid patients but they significantly potentiate each other in a linear manner.

INTRODUCTION

A high prevalence of diabetes mellitus in hypothyroidism has conferred upon a strong link between insulin resistance with thyroid hormone level [1, 2]. Hyperlipidemia and a low grade inflammatory status associated with hypothyroidism are significant confounding factors contributing to the increased insulin resistance observed in hypothyroid disorders as early as in their subclinical stages [3, 4]. On the other hand, some studies have reported no significant correlation between the TSH level and HOMA-IR among hypothyroid patients, thus leaving a lacuna for general agreement regarding the relationship of insulin resistance with hypothyroidism [5]. Due to several environmental influences and changes in working conditions, vitamin D deficiency has been increasing worldwide in up to 50 percent of the general population with a level less than 20 ng/ml[6]. Although, association of 25 (OH) D deficiencies with insulin resistance has been under the purview of recent research, but reports regarding any causative association is sparsely available among the Asian population. Among the few studies available, we got a Chinese study that reported an inverse association between 25(OH)D and insulin resistance in metabolic syndrome as well as in established type 2 diabetes mellitus [7, 8]. Among the Indian population a recent study undertaken by Bachali *et al* (2013) suggested a reduced vitamin D level in the diabetic group with significantly elevated insulin resistance[9]. However, an opposite linear relationship between the insulin resistance and vitamin D levels has been reported in the non obese non diabetics also indicating an inverse relationship between these two parameters irrespective of glycemic status and obesity [10].

A decrease in vitamin D level and increase in insulin resistance both have been found to be significantly associated with dyslipidemic changes[11], that merit an exploration of their interrelationship among the hypothyroid patients. A deficient vitamin D status has been reported suggesting a linear decrease in vitamin D levels with the severity of hypothyroidism[12]. Keeping these factors in mind we assumed the hypothesis that

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both vitamin D deficiency and insulin resistance are interlinked to each other in hypothyroid patients and their severity are directly dependent on the degree of hypothyroidism. Accordingly, we aimed to study the association of vitamin D deficiency with insulin resistance in our hypothyroid population and to find any potential dependence of these parameters on the thyroxine and TSH levels.

MATERIALS AND METHODS

The present study was undertaken as a case control, observational and hospital based study during the period of three months from June to August 2016. Cases were selected from the thyroid clinic of Department of Biochemistry by the method of convenience within the stipulated time period as mentioned above. Cases were diagnosed using the estimation of serum TSH and fT4. Patients having their TSH values crossing the upper reference limit and fT4 values below the lower reference limit as provided in the reagent kits were selected as hypothyroid cases. During the selection processes following inclusion and exclusion criteria were fulfilled:

Inclusion criteria

1. Patients diagnosed clinically and biochemically as primary hypothyroidism,
2. Both male and female patients were included with similar preference,
3. Patients belonging to the age group within 18 to 45 years were selected to avoid the effect of age induced decrease in vitamin D levels.
4. Patients belonging to same ethnicity and with similar socioeconomical background were selected.

Exclusion criteria

1. Patients having any secondary cause of hypothyroidism were excluded
2. Patients having any chronic illness, other than primary hypothyroidism were excluded.
3. Patients taking any vitamins or nutritional supplements were excluded.
4. Patients having any history of drug or substance addiction were excluded.

Ethical considerations

The study was undertaken strictly following the rules and regulations laid on by the Helsinki declaration revised 2000 and ICMR guidelines 2005 for human studies. Informed consents were obtained from all participants as par protocol. The study was approved by the institutional ethical committee for the human studies (vide CNMC/3, dt. 22. 06.16)

METHODOLOGY

Estimation of biochemical parameters

Hormone assays: TSH, fT4, Insulin and 25 OH vitamin D were assayed by ELISA obtained from ACCUBIND, USA and LABGILLS, USA. All ELISA assays were prevalidated with primarily standardized methods as per their literatures. In our laboratories the precision of these tests were monitored by assessment of coefficient of variation (CV) during the whole assay process and was found to be below 10 percent for all (6.6% for TSH, 6.2% for fT4, 7 % for vitamin D and 6.8% for insulin).

Calculation of the HOMA- IR: HOMA-IR was calculated using the HOMA calculator obtained from the website www.dtu.ox.ac.uk>homacalculator using the levels of fasting plasma glucose and insulin levels at the same point of time.

Statistical analysis: The data obtained were analyzed for difference of their mean values between the case and control groups for ascertaining the significance of difference of the study parameters between the healthy reference population and the hypothyroid patients. Bivariate correlation study was performed to assess the strength of relationship between the study parameters in the case group. It was followed by the multiple linear regression analysis to find out any dependence of vitamin D and HOMA-IR index on the thyroid function parameters. For all studies P value was considered to be significant if equal to or less than 0.05 for a 95% confidence interval. All statistical analyses were performed using the statistical package for social sciences (SPSS) version 20.0 for Windows.

RESULTS

Data obtained were tested for normal distribution by Smirnov Kolmogorov test and were found to follow a normal distribution pattern. Graphically, their distribution has been represented in Figure 1a and 1b using the Box plot.

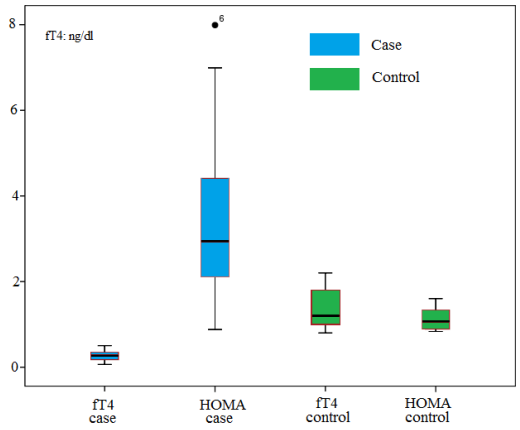

Fig 1a Box plot showing the pattern of distribution of fT4 and HOMA – IR values in the case and control groups

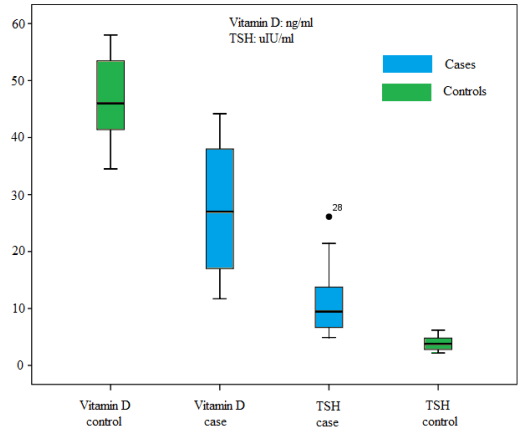

Fig 1b Box plot showing pattern of distribution of vitamin D and TSH in the case and control groups

Table 1 Group Statistics showing the significance of difference between the mean values of the study parameters

	Grouping	N	Mean	Std. Error Mean	P value
TSH	Case	54	10.7343	.71476	< 0.001*
(mIU/ml)	Control	100	4.1150	.12240	
fT4	Case	54	0.36	0.02	< 0.001*
(ng/dl)	Control	100	1.87	0.06	
VitD	Case	54	27.6165	1.46968	< 0.001*
(ng/ml)	Control	100	46.9288	.68150	
HOMA-IR	Case	54	3.3154	.22198	< 0.001*
	Control	100	1.1070	.02225	

*P value considered to be significant at P < 0.05 for 95% confidence interval.

The TSH and fT4 data in the Table 1 confirm the state of overt hypothyroid status in the case group. Vitamin D was significantly reduced in the case group while the insulin resistance indicator, HOMA-IR was significantly elevated. In the Table 2 the significance of relationships between these parameters were observed in the case group using the bivariate Pearson's correlation analysis.

Table 2 Bivariate correlation between the study variables among the case group

		TSH	fT4	HOMA	VITD
TSH	r	1	-.235	.304*	-.379**
	P value		.086	.025	.005
fT4	r	-.235	1	-.503**	.526**
	P value	.086		< .001	< .001
HOMA-IR	r	.304*	-.503**	1	-.579**
	P value	.025	< .001		< .001
VITD	r	-.379**	.526**	-.579**	1
	P value	.005	< .001	< .001	

*. Correlation is significant at the P < 0.05 level (2-tailed).
**. Correlation is significant at the P < 0.01 level (2-tailed).

r = Pearson's correlation coefficient.

In the bivariate correlation study insulin resistance was found to vary inversely with the thyroxine values and directly with its trophic regulator hormone TSH. Opposite trend is observed for vitamin D levels that show a positive association with the thyroxine levels and inverse association with the TSH values. All these correlations were statistically significant. So, we further progressed to analyze the dependence of vitamin D and insulin resistance on the study parameters taken together in the multiple linear regression study in the following Tables 3 and 4.

Table 3 Multiple linear regression analysis showing the dependence of Vitamin D on insulin resistance and thyroid function

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	32.647	5.588		5.842	< .001
	TSH	-.405	.229	-.197	-1.773	.082
	fT4	5.154	2.157	.293	2.390	.021*
	HOMA-IR	-2.463	.828	-.372	-2.975	.004*
a. Dependent Variable: 25 OH vitamin D						

*P value considered to be significant at the level of P < 0.05.

In the Table 3, vitamin D levels are found to be positively dependent significantly only on the thyroxine levels. Although the dependence is inverse with the TSH values, but unlike that observed in the bivariate correlation analysis, this negative dependence is not linearly significant when considered with other parameters. On the other hand, its dependence was significant in an inverse direction with the insulin resistance indicator, HOMA-IR in this multivariate analysis.

Table 4 Multiple linear regression analysis showing the dependence of insulin resistance on Vitamin D and thyroid function

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	5.751	.801		7.184	.000
	TSH	.027	.037	.087	.736	.465
	fT4	-.717	.344	-.270	-2.084	.042*
	Vitamin D	-.061	.021	-.404	-2.975	.004*
a. Dependent Variable: HOMA - IR						

*P value considered to be significant at the level of P < 0.05.

In a similar way, Table 4 shows that the insulin resistance index, the HOMA-IR, was significantly dependent only on the thyroxine level in a negative direction and vitamin D level. Although its regression coefficient B indicated a positive dependence on TSH values, but it was not statisticaly significant as compared to the other two in the multivariate analysis.

DISCUSSION

In the present study vitamin D and insulin resistance were found to be significantly lower and higher in the hypothyroid patients (Table 1). Lower levels of vitamin D have been already reported in the autoimmune thyroid disorders. Vitamin D mediates potent immunomodulating functions via its cognate receptors on a substantial number of immune cells and suppresses several interleukins (particularly IL 2) mediated autoimmune disorders including autoimmune hypothyroid disorders [13]. However, other than its link to the autoimmune thyroid disorders, vitamin D synthesis is also hampered in hypothyroid disorders. The keratinocytes of the basal dermal layer gets thinned out in thyroid hormone deficiency leading to reduced conversion of 7 dehydrocholesterol into active vitamin D[14]. As this effect mainly is dependent on the localized effect of the thyroxine hormone, a significant dependence of vitamin D level on serum thyroxine values in multiple linear regression study (Table 3) is rightly explained.

In the present study insulin resistance was found to be significantly higher among the hypothyroid group with a lowered vitamin D levels in them. Moreover, in the multiple linear regression analysis (Table 4) where the effects of all study parameters were considered together HOMA-IR was significantly dependent on the vitamin D levels in hypothyroid patients in an inverse direction. A wide distribution of vitamin D receptor on pancreatic beta cells, skeletal muscle and adipose tissues results in a significant effect of vitamin D on the insulin sensitivity and glucose metabolism [15, 16].The active form of vitamin D, calcitriol is supposed to mediate vitamin D function by stimulating the vitamin D response element in the vitamin D receptor gene complex. Vitamin D has been also found to stimulate the expression of insulin receptor enhancing the glucose tolerance [17-19]. An anti-inflammatory function of vitamin D helps to attenuate the cytokines like interleukin 4, 6, tumor necrosis factor alpha and the nuclear factor κβ (NF- κβ) which help to reduce the insulin resistance significantly [20-

22]. Furthermore, vitamin D can optimize the insulin sensitivity by maintaining a steady state of blood calcium level which has been corroborated by the findings that parathormone deficient states are linked to increased insulin resistance [1, 22]. These findings have been corroborated by several cross sectional studies that reported an inverse relationship between the vitamin D level and glucose tolerance[23, 24] that extended to the reports suggesting several mutant alleles of vitamin D receptors contributing to genetic risk factors for type 2 diabetes [25, 26].

In our study HOMA-IR has been found to be significantly positively correlated to the thyroxine levels indicating the direct effect of thyroxine hormone on the insulin sensitivity. This association has been strengthened by a significant dependence of the HOMA-IR on the fT4 levels in the multiple linear regression study (Table 4) that justifies the elevated insulin resistance in hypothyroidism. Increased insulin resistance is exhibited at both hepatic and peripheral level as early as the subclinical hypothyroid stage that is explicable by mainly the reduced uptake of GLUT 4 to the cell surface and a decrease in peripheral blood flow [2, 27]. Furthermore, the inverse relationship of the HOMA-IR with the TSH has been reported in some studies to enhance dyslipedemia in hypothyroid patients with elevated TSH level and increased insulin resistance. These findings have intense clinical implications regarding the high incidence of premature atherosclerosis and cardiovascular diseases in hypothyroidism [28] . In this context, our findings are particularly important regarding the fact that subnormal levels of vitamin D in hypothyroidism predispose our study population to the risk of hypercholesterolemia induced premature atherosclerosis and cardiovascular disease due to increased efflux of cholesterol from the cells [29].

In conclusion, our study reflects that a compromised status of both vitamin D homoeostasis and increased insulin resistance not only exist side by side in hypothyroid patients but they significantly potentiate each other in a linear manner. Hence, results of our study suggest that timely monitoring of these two parameters are needed to control the metabolic complications of hypothyroid disorders along with exogenous supplementation of the vitamin D in required dosage as needed. We propose that this will help to bring down the morbidities, particularly the cardiovascular and atherosclerotic disorders in this group of patients.

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