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ASSESSMENT OF BIOCHEMICAL RISK FACTORS OF CARDIO METABOLIC SYNDROME IN PATIENTS OF HYPOTHYROIDISM

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ABSTRACT

Introduction: Hypothyroidism is the second most prevalent endocrinal disorder in India. Most of existing data supports that thyroid disease is associated with increased cardiovascular risk which is mainly attributed to hemodynamic alteration as well as to a high risk of atherosclerosis, dylipidemia and insulin resistance.

Aim: To investigate relationship between thyroid function and biochemical risk factors of cardiovascular diseases.

Material and Methods: The present study was a cross-sectional, prospective. The study population was comprised of a total of ninety (90) participants (30 new cases of overt hypothyroidism, 30 new cases of subclinical hypothyroidism and 30 age and gender matched controls).

Estimation of serum Thyroid profile and Insulin (fT_3, fT_4 and TSH) was done by CLIA while Glucose and Lipid profile were estimated by biochemistry autoanalyzer. Insulin Resistance was calculated by HOMA IR score.

Statistical Analysis: Data obtained was statistically analyzed by using student "t" test.

Results: We found statistically significant rise in the levels of serum cholesterol triglycerides VLDL and LDL in the cases of overt hypothyroidism than controls. HDL levels are low in overt hypothyroidism. We also found statistically significant rise in the levels of blood glucose, serum insulin and HOMA IR score in cases of overt hypothyroidism than controls.

Conclusion: Overt Hypothyroidism is at the risk of developing cardiovascular diseases and type II DM.

Key Words: Hypothyroidism, Cardiovascular diseases, Type II DM

INTRODUCTION

The thyroid gland synthesizes and releases two iodoamino acid hormones: 3,5,3'-triiodothyronine (T_3) and 3,5,3',5' thyroxine (T_4). Thyroxine (T_4). More than 99% of the circulating T_3 and T_4 is protein bound. (1)

The biologically active component of T_4 and T_3 in plasma is the free fraction (fT_3 and fT_4 respectively); that are not bound to proteins. Assay of free thyroid hormone levels is done routinely to avoid problems in interpretation of thyroid hormone levels caused by fluctuations in binding proteins.(2,3) Thyroid hormones may be considered the accelerator pedal of metabolism.(4,5,6)

Thyroid disorders are among the commonest endocrine disorders worldwide. It has been estimated that about 42 million people in India suffer from thyroid diseases.(7) Hypothyroidism is the second most prevalent endocrinal disorder in India.

'Hypothyroidism' is the reduced production of thyroid hormone.(8) It is a clinical entity resulting from the deficiency of thyroid hormones or more rarely from its impaired activity at tissue levels.(9)

Hypothyroidism is classified as Primary, Secondary and Tertiary by its association with the indicated organ dysfunction. (10)

According to symptoms and clinical features; it is further sub classified into:

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i. Subclinical Hypothyroidism (SCH):

It is defined as biochemical evidence of thyroid hormone deficiency i.e. elevated serum Thyroid Stimulating Hormone (TSH) level with a normal serum free Thyroxine concentration[11] in patients who have few or no apparent clinical features of hypothyroidism.

Subclinical hypothyroidism can progress to Overt Hypothyroidism.[12]

ii. Overt Hypothyroidism(OH):

It is defined as an elevated serum Thyroid Stimulating Hormone (TSH) concentration and reduced free thyroid hormones with symptoms and clinical features of hypothyroidism. It is also referred as Clinical Hypothyroidism.[13]

Most of existing data supports that thyroid disease is also associated with increased cardiovascular risk which is mainly attributed to hemodynamic alteration as well as to a high risk of atherosclerosis. [14-15] Dyslipidemia induces insulin resistance, oxidative stress, via vicious cycle. It has been also observed that Insulin resistance, hypertension, inflammation, oxidative stress and coagulation defect are also promoted by thyroid disease, independently of dyslipidemia.[15,16]

AIM AND OBJECTIVES:

Assessment of biochemical risk factors of cardiovascular diseases in patients with hypothyroidism

MATERIAL AND METHODS:

The present study was a cross-sectional, prospective study. It was conducted in the department of biochemistry; of university medical college with a tertiary care hospital. The duration was November 2011- June 2013.The study protocol was approved by Institutional Ethics Committee.

The study group of a total of ninety (90) participants was divided into three groups:

1. Group A: Control- Euthyroid: Thirty (30) age and gender matched normal; healthy euthyroid individuals.
2. Group B: Subclinical hypothyroidism (SCH): Thirty (30) clinically diagnosed, new cases of subclinical hypothyroidism on the basis of clinical examination and their fT_3, fT_4 and TSH levels.
3. Group C: Overt hypothyroidism (OH): Thirty (30) clinically diagnosed, new cases of overt hypothyroidism on the basis of clinical examination and their fT_3, fT_4 and TSH levels.

Exclusion Criteria for cases and controls:

Participants suffering from DM, CVDs, Renal, Liver diseases, Malignancy, other systemic disease that alters thyroid status or participants taking thyroid hormone supplementation, β-blockers, Multivitamins, Steroids, alcohol and smokers.

All participants after their written informed consent underwent detailed physical and clinical examination.

METHODS

About 2 ml of fasting serum and plasma samples were subjected towards estimation of following parameters:

Sr. No.	Parameter	Method
1	Thyroid profile (fT_3, fT_4 and TSH)	Chemiluminiscence immunoassay (CLIA) [17]
2	Serum Lipid profile	Automated Biochemistry analyser
	i. Serum Total Cholesterol (CHO)	Cholesterol Oxidase-peroxidase (CHOD-PAP) method [18]
	ii. Serum Triglycerides (TG)	Glycerol phosphate oxidase method [19]
	iii. Serum High Density Lipoprotein Cholesterol(HDL) –direct	Enzymatic method [20]
	iv. Serum Low Density Lipoprotein Cholesterol (LDL)	Calculated by Friedewald's equation [21]
	v. Serum Very Low Density Lipoprotein Cholesterol (VLDL)	
3	Blood Glucose	Glucose –Oxidase Peroxidase (GOD-POD) [22]
4	Serum Insulin	Chemiluminiscence immunoassay [17] (CLIA)

Insulin Resistance (IR) calculated by Homeostasis model for assessment of Insulin Resistance HOMA-IR score [23].

Statistical Analysis: Microsoft Excel 2007 was used to calculate Z Test for finding the statistical significance between the means of Serum lipid profile, Blood glucose, Serum Insulin and HOMA-IR score in all the three groups.

RESULTS

Table 1A, B: Comparison of Thyroid Profile in Groups

Group	freeT3 (fT3) Pg/ml Mean ± SD	freeT4 (fT4) ng/dl Mean ± SD	TSH μIU/ml Mean ± SD
Group A:Euthyroid	3.08.±0.80	1.82±0.42	1.60±0.89
Group B:Subclinical hypothyroid	2.73±0.81	1.60±0.53	11.72±7.66
Z-value	1.72	1.76	7.18
p-value	0.08	0.07	< 0.001
Group	freeT3 (fT3) Pg/ml Mean ± SD	freeT4 (fT4) ng/dl Mean ± SD	TSH μIU/ml Mean ± SD
Group A:Euthyroid	2.65±0.82	1.82±0.42	1.60±0.89
Group C:Overt hypothyroid	0.76±0.62	0.38±0.28	65.23± 22.00
Z-value	17.9	14.69	15.8
p-value	< 0.0001	< 0.0001	< 0.0001

Table 2 A,B: Comparison of Blood Glucose between the groups

Group	Blood Glucose: mg/dl (Mean ± SD)
Group A: Euthyroid	89.1 ± 2.7
Group B: Subclinical hypothyroid	95.3 ± 1.56
Z-value	1.13
p-value	0.27*

Group	Blood Glucose: mg/dl (Mean ± SD)
Group A: Euthyroid	89.1 ± 2.7
Group C: Overt hypothyroid	115.36± 10.78
Z-value	2.19
p-value	<0.001*

Table 3A,B: Comparison of Insulin levels in groups

Group	Insulin(nmol/ml) Mean±SD
Group A:Euthyroid	4.6± 1.34
Group B:Subclinical hypothyroid	6.9± 0.98
Z-value	1.09
P-value	0.35

Group	Insulin(nmol/ml) Mean±SD
Group A:Euthyroid	4.6± 1.34
Group C:Overt hypothyroid	36.67±11.56
Z-value	5.7
P-value	< 0.0001

Table 4 A,B: Comparison of HOMA –IR score in groups

Group	HOMA –IR score Mean±SD
Group A:Euthyroid	1.04 ±0.98
Group B:Subclinical hypothyroid	2.02 ± 0.86
Z-value	1.05
P-value	0.09

Group	HOMA –IR score Mean±SD
Group A:Euthyroid	1.04 ±0.98
Group C:Overt hypothyroid	11.03 ± 2.31
Z-value	5.39
P-value	< 0.0001

Table 5 A,B: Comparison of serum Lipid profile in all groups

Group	CHO	TG	HDL	VLDL	LDL
Group A: Euthyroid	170.11 ± 40.26783	106.63 ± 42.03569	46.44 ± 12.11	21.32 ± 8.40	148.78± 34.08045
Group B: Subclinical hypothyroid	180.06 ± 43.21173	133.64± 79.60838	43.27 ± 12.846	25.83± 16.38	154.22± 40.48
z value	0.92	1.62	1.22	0.22	0.56
p value	0.35	0.10	0.45	0.17	0.57

Group	CHO	TG	HDL	VLDL	LDL
Group A:Euthyroid	170.11 ±	106.63 ±	46.44 ± 12.11	21.32 ± 8.40	148.78±
Group C:Overt hypothyroid	211.30± 40.22	155.03 ± 96.39	32.5 ± 8.74	31.00 ± 19.22	170.9± 33.37
z value	3.96	2.52	5.07	3.92	2.47
p value	<0.0001	<0.01	<0.001	<0.001	<0.05

DISCUSSION

Table 1 A,B shows thyroid profile in groups. We observed that there was no statistically significant difference in the levels of fT3 and fT4 in subclinical hypothyroid group as compared with euthyroid group. However, the levels of TSH were significantly increased in subclinical hypothyroid group as compared with euthyroid group.

Vanderpump MP et al. (1995)[24] and Surks MI et al. (2004)[25] stated that subclinical hypothyroidism is a state of biochemical hypothyroidism rather than clinical hypothyroidism.

We noted that the levels of fT3 and fT4 had been significantly decreased while levels of TSH were significantly increased in subclinical and overt hypothyroid group as compared to euthyroid group.

Table 2 A,B shows the levels of Blood Glucose in all the groups. We found statistically highly significantly rise in Blood Glucose level in the overt hypothyroid group (115.36 ± 10.78) as compared with euthyroid (89.1 ±2.7) and subclinical hypothyroid (95.3 ±1.56).

Table 3 A,B shows high levels of Serum Insulin in all the groups. We found that statistically significant rise in Serum Insulin overt hypothyroid group (36.67 ± 11.56) as compared with euthyroid (4.60 ±1.34) and subclinical hypothyroid (6.90 ±0.98).

Table 4 A,B shows the levels HOMA-IR Score in all the groups. We found statistically highly significant rise in HOMA-IR Score in overt hypothyroid group (11.03 ±2.31) as compared with euthyroid (1.04 ± 0.98) and subclinical hypothyroid (2.02 ±0.86).

Table 5 A,B shows the Lipid Profile in groups. We found significant dyslipidemia in overt hypothyroid group. There was significant increase in Total Cholesterol (211.30 ±40.22), Triglyceride (155.30±96.39) LDL(170.9 ±33.37) and VLDL (31.00±19.22) levels as compared in subclinical hypothyroid group where it was Total Cholesterol (180.06±43.21), Triglycerides (133.64±79.60), LDL (154.22±40.48), VLDL (25.83±16.38) and in euthyroid group it was Total Cholesterol (170.11±40.26), Triglycerides (106.63±42.03), LDL (148.78 ±34.08), VLDL (21.32±8.40).

There was also statistically significant decrease in HDL levels in overt hypothyroid group HDL (32.5±8.74) as compared with subclinical hypothyroid group (43.27±12.84) and euthyroid group (46.44 ± 12.11).

We calculated the correlation of biochemical risk factors of cardiovascular diseases with TSH levels. There is statistically significant positive correlation between TSH levels and BGL (r=0.41, p=< 0.0001), Insulin (r=0.50 p=< 0.0001), HOMA- IR (r=0.51 p=< 0.0001),Total Cholesterol (r=0.39, p=0.0001),TG(r=0.20, p=0.04) levels.

We also found statistically significant negative correlation between TSH levels and HDL levels. (r= - 0.33, p=< 0.001) However we could not find any significant correlation between TSH levels and LDL levels. (r=0.20, p =0.96).

Therefore it can be clearly seen from our results that there is dyslipidemia and insulin resistance associated with overt hypothyroidism, however the same was not observed in subclinical hypothyroid group. The levels of TSH `showed a strong positive correlation with biochemical markers of cardiovascular diseases in our study.

Togini et al [26] observed increase in total cholesterol, LDL, TG levels and decrease in HDL levels in overt hypothyroid group.

XuC et al[27] observed that even after adjusting the confounding factors such as age, sex, smoking status, fasting plasma glucose levels and thyroid hormones , a significant positive impact of TSH on the serum total cholesterol (TC) level was revealed (r = 0.095, p = 0.035).

Similarly Benetti-Pinto CL et al[28] also observed no change in BGL, Insulin, HOMA IR, cholesterol, TG, HDL levels in sub clinically hypothyroids females. However they reported significantly elevated LDL levels.

Garduno-Garcia Jde J et al [29] concluded that though subclinical hypothyroidism was not associated with derangements in the markers of metabolic syndrome (as per National Cholesterol Education Programme ATP III Criteria). Despite the low thyroid function in hypothyroidism can predispose to cardio- metabolic syndrome.

Uzunlula et al [30] and Shantha et al [31] also could not found any significant difference in lipid profile in euthyroid and sub clinical hypothyroid patients.

Purvi Purohit [32] noted increase in serum insulin level and HOMA-IR score in hypothyroidism as well as hyperthyroidism. However, increased TSH level were positively correlated with IR. Their study concluded that there was presence of triad of metabolic syndrome in hypothyroid subjects. (i.e hypertension, dyslipidemia increased fasting plasma glucose).

Khan et al [33] reported significant correlation TG and HDL level with HOMA-IR values in human subjects with Insulin Resistance syndrome.

Chen G et al[34] could not found difference in Glucose, insulin HOMA-IR level in hypothyroid patient compared to euthyroid patients.

Thyroid hormone increases LDL receptor expression, increases Cholesterol Ester Transport Protein (CETP) concentrations and increases hepatic lipase (HL) concentrations. Thyroid hormone also increases hepatic cholesterol synthesis by inducing hydroxyl methylglutaryl coenzyme A (HMG CoA) reductase and decreases intestinal cholesterol absorption[35, 36]. Overall effect of this leads to increased cholesterol synthesis and decreased degradation.

It is known that T_3 and insulin have synergetic role in Glucose homeostasis, since hormone possess similar action site in regulation of Glucose metabolism at both cellular and molecular level [37,38,39].

It could therefore be hypothesized that reduced intracellular content of T_3 could lead to impaired insulin stimulated Glucose disposal. Interestingly even subtle decreases in level of thyroid hormone within the pathological range have been shown to correlate inversely with HOMA-index.

Insulin resistance and metabolic syndrome are important cardiovascular risk factor, even in non-diabetic individuals [40]. It has been found that individuals with Insulin resistance and raised TSH have higher LDL concentration while in those with normal insulin sensitivity, TSH level do not affect LDL [41].

CONCLUSIONS

- Overt hypothyroidism is associated with significant dyslipidemia.
- There is no derangement in this biochemical risk factor of cardiovascular disease in subclinical hypothyroidism.
- Thyroid stimulating hormone (TSH) showed significant positive correlation with total cholesterol, triglyceride, BGL, Insulin and HOMA- IR score and negative correlation with HDL level. Therefore estimation of TSH level can serve as prognostic marker of future cardio-vascular risk.

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