



Original Research Article

Elevated serum homocysteine as a potential marker for cardiovascular changes in overt hypothyroidism

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ABSTRACT

Overt hypothyroidism (HO) defined as high Thyroid Stimulating Hormone (TSH) levels with low levels of free thyroxine (FT4) and / or free triiodothyronine (FT3). Hypothyroidism is associated with an increased risk for atherosclerotic cardiovascular disease. Serum Homocysteine (Hcy) is an independent risk factor for atherosclerosis and cardiovascular diseases. Elevated plasma homocysteine levels have been reported in overt hypothyroidism.

Aim: To study levels of Hcy in relation to TSH, FT4 and FT3 levels in overt hypothyroid patients compared to control groups and correlation between Hcy and thyroid hormones.

Materials and Methods: This study included 50 female overt hypothyroid cases with age group between 18-50 years and 50 healthy females controls with same age group. Serum homocysteine was estimated by Homocysteine Enzyme Assay in Cobas Integra 400 plus. TSH, FT4 & FT3 estimated by CLIA method using Beckman coulter Access 2. Parameters of cases and controls are compared using unpaired 't' test and the association between parameters is assessed by using Pearson's correlation.

Results: There is a significant increase in Serum Hcy levels $19.24 \pm 7.15 \mu\text{mol/L}$ and TSH levels $30.91 \pm 10.21 \mu\text{IU/ml}$ respectively (p value <0.0001) and significant decrease in FT4 and FT3 levels (p <0.0001). Hcy was positively correlated with TSH and negatively correlated with FT4 and FT3.

Conclusion: Thus, from our study we can conclude that serum Hcy levels can be used as a marker, which points towards the possible risk factor for atherosclerosis and cardiovascular diseases in Overt hypothyroid patients.

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1. Introduction

Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones, which in turn results in a generalized slowing down of metabolic process.¹ Overt hypothyroidism (HO) defined as high TSH levels with low levels of FT4 and / or FT3.² Hypothyroidism is a common condition that is related to premature atherosclerosis and its clinical consequences such as myocardial infarction.³ The increased cardiovascular morbidity in hypothyroid patients has been related to elevated levels of Total cholesterol and Low density lipoproteins cholesterol, which are normalized after thyroid hormones replacements.⁴ Total

Homocysteine (tHcy) in plasma is an independent risk factor for cardiovascular disease.^{5,6} Homocysteine (Hcy) is a sulfhydryl-containing amino acid is synthesised during the conversion of methionine to cysteine.² Plasma Hcy levels is affected by several genetic, physiological and life style factors.⁷ Hyperhomocysteinemia induces endothelial injury, oxidative stress, smooth muscle hypertrophy and oxidation of LDL-Cholesterol and the process of atherosclerosis and cardiovascular diseases. Increased tHcy levels might be the result of two mechanisms either increased tHcy formation or decreased renal tHcy clearance due to direct effect of the thyroid hormones on the tHcy metabolism in the liver and clearance in the kidney. It may be explained as thyroid hormone deficiency decreases hepatic levels of enzymes involved in the remethylation

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pathway of tHcy to methionine, methylene tetrahydrofolate reductase (MTHFR) leading to hyperhomocysteinemia.⁸ The kidney most likely plays an important role in Hcy clearance and metabolism, as it does with other amino acids. In hypothyroidism systemic vascular resistance is increased and leads to reduced renal blood flow and low GFR (Glomerular filtration Rate). Thus it reduces its clearance and cause hyperhomocysteinemia.⁹

2. Materials and Methods

Female patients of age group between 18-50 years clinically suspected and biochemically confirmed overt hypothyroid cases were selected from Medicine & Endocrinology OPDs and Inpatients wards at ESIC Model Hospital, Rajajinagar, Bengaluru. Age and gender matched blood donating volunteers in Blood Bank of ESIC Model Hospital, Rajajinagar, Bengaluru served as control group. A study was carried out for a period of 18 months from January 2018-June 2019.

Criteria for selection of hypothyroidism was based on laboratory biochemical investigations. TSH $> 10 \mu\text{IU/ml}$; decreased FT4 $< 0.58 \text{ ng/dl}$. & normal or decreased FT3 $\leq 2.45 \text{ pg/ml}$.¹⁰⁻¹² From correlational study of previous literature, $r = 0.228$ we achieved 80% power of the study and 5% level of significance and we arrived to a sample size of 100 (50 cases and 50 controls). After taking informed consent, under aseptic precautions, about 5ml of venous blood was drawn from the selected subjects after overnight fasting of 10-12 hours.

2.1. Exclusion criteria

1. Cardiac diseases like Ischemic Heart diseases.
2. Renal diseases like Chronic Renal Failure.
3. Chronic diseases like Hypertension, Stroke, DVT.
4. Metabolic disorders like Homocysteinurias.
5. Treatment with drugs like Phenobarbitone, Phenytoin, Methotrexate, Propylthiouracil.

Methimazole, lithium etc, were excluded from study

3. Methods

TSH, FT4, FT3 is estimated using Chemiluminescence Immunoassay in automated Beckman Coulter Access 2 analyzer.¹⁰⁻¹² Normal range of TSH is $0.34-5.60 \mu\text{IU/ml}$, FT4 is $58-164 \text{ ng/dl}$ & FT3 is $2.45-4.25 \text{ pg/ml}$,

Homocysteine is estimated using Homocysteine enzymatic assay methodology from Cobas Integra 400 plus.¹³ Normal range is $5-15 \mu\text{mol/L}$.

3.1. Statistical analysis

All statistical analysis was performed using the prism pad software to indicate the significance between the mean values of hypothyroid patients and control group. Data were

given as Mean \pm SD, $p < 0.05$ were considered significant. Correlation was done using Pearson Correlation.

4. Results

In this study, the mean age in control group was found to be 27 ± 0.53 years and that of overt hypothyroid cases was 32.04 ± 0.82 years. As shown in Table 1, the mean TSH levels in control group was found to be $2.14 \pm 0.39 \mu\text{IU/ml}$ and that of overt hypothyroid cases was $30.91 \pm 10.21 \mu\text{IU/ml}$ ($p < 0.0001$) {Figure 1}. As shown in Table 1, the mean FT4 in control group was found to be $0.89 \pm 0.017 \text{ ng/dl}$ and that of overt hypothyroid cases was $0.59 \pm 0.23 \text{ ng/dl}$ ($p \text{ value} < 0.0001$). As shown in Table 1, the mean FT3 in control group was found to be $3.16 \pm 0.38 \text{ pg/ml}$ and that of overt hypothyroid cases was $2.84 \pm 0.39 \text{ pg/ml}$ ($p < 0.0001$). As shown in Table 2, the mean serum Homocysteine in control group was found to be $9.21 \pm 2.27 \mu\text{mol/L}$ and that of overt hypothyroid cases was $19.24 \pm 7.15 \mu\text{mol/L}$ ($p < 0.0001$) {Figure 2}. As shown in Table 3, there is statistically significant strong positive correlation between Hcy and TSH levels as shown in Figure 3 and negative correlation between Hcy and FT4, FT3 levels as shown in Figures 4 and 5.

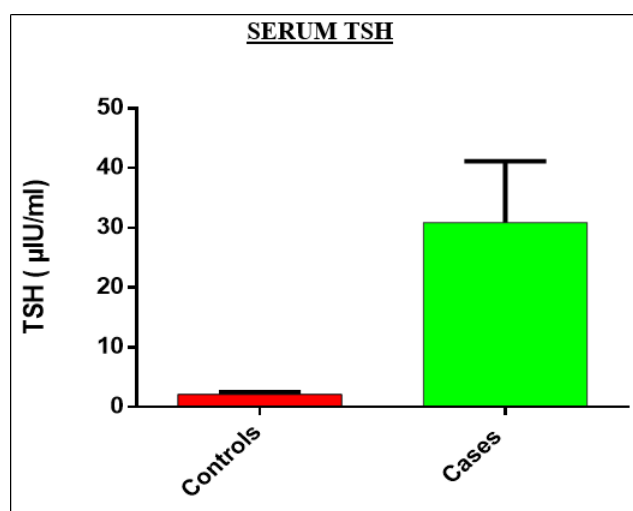


Fig. 1: Comparison of TSH within the two study

5. Discussion

In our study we found that serum Homocysteine is significantly increase in Overt Hypothyroid patients compared to Control groups $19.24 \pm 7.15 \mu\text{mol/L}$ vs $9.214 \pm 2.276 \mu\text{mol/L}$.

In our study there is statistically significant strong positive correlation between Hcy and TSH and negative correlation between Hcy and FT4, FT3.

Our study is in accordance with Molham Ali Al-Habori et al.,¹⁴ Aqsa Malik et al.,¹⁵ Saleh A Bamashmoos et al.,⁸

Table 1: Thyroid profile

TFT Hormones Mean ± SD	Controls	Cases	P value
TSH (μ IU/ ml)	2.146 \pm 0.3909	30.91 \pm 10.21	<0.0001
FT4 (ng/dl)	0.8988 \pm 0.01783	0.5992 \pm 0.2299	<0.0001
FT3 (pg/ml)	3.164 \pm 0.3842	2.84 \pm 0.3914	<0.0001

Table 2: Serum homocysteine

Biochemical Parameters Mean ± SD	Controls	Cases	P value
Homocysteine (μ mol/L)	9.214 \pm 2.276	19.24 \pm 7.158	<0.0001

Table 3: Correlation of serum homocysteine with thyroid profile

	r	Controls(n=50)		Hypothyroidism(n=50)			
		TSH	FT4	FT3	TSH	FT4	FT3
Homocysteine		-0.05227	-0.2018	-0.2462	0.7947	-0.7640	-0.5920
		0.7185	0.0848	0.1604	<0.0001***	<0.0001***	<0.0001***

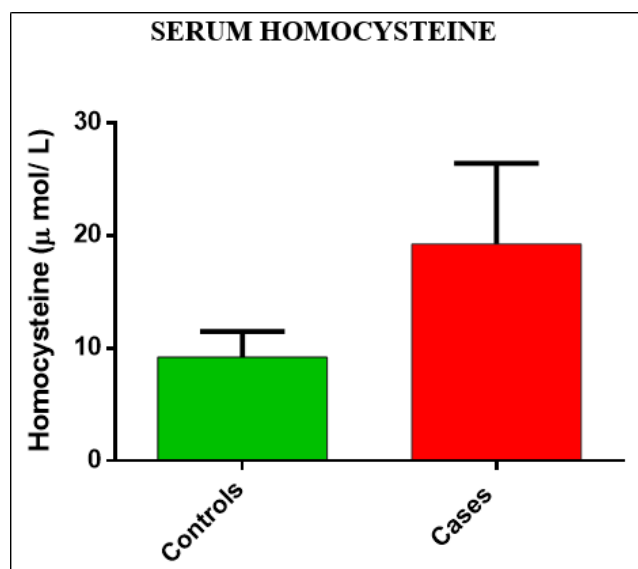


Fig. 2: Comparison of Serum Homocysteine within the two study groups

Yande Zhou et al.,² Rafael Luboshitzky et al.,¹⁶ Xuejie Dong et al.,¹⁷ Manju Chandankhede et al.¹⁸ Our study is not in accordance with Anjali R. Metgudmath et al.¹⁹

High plasma homocysteine concentration induces pathologic changes in the arterial wall and thus is strongly associated with an increased risk of atherosclerosis, later manifested as cardiovascular, cerebrovascular and peripheral vascular events. There are consistent reports that patients with hypothyroidism have elevated total Homocysteine in plasma.²⁰

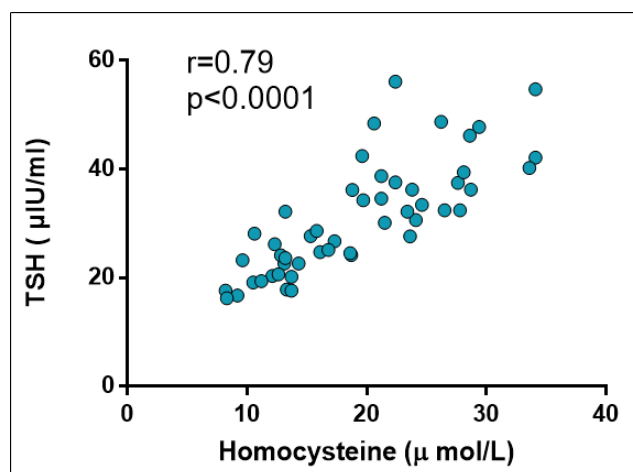


Fig. 3: Correlation of serum homocysteine and TSH in hypothyroid cases

In hyperhomocysteinemia, homocysteine stimulates protease endothelial cell activator of factor V and directly activates coagulation in the absence of thrombin.

Hyperhomocysteinemia favors binding of lipoprotein(a) to fibrin thus reduces plasminogen activation and inhibits fibrinolysis

Homocysteine thiolactone causes LDL cholesterol to aggregate and then are phagocytosed by vascular macrophages to form foam cells. Homocysteine thiolactone released from foam cells produces free radicals and causes endothelial cell damage.⁹

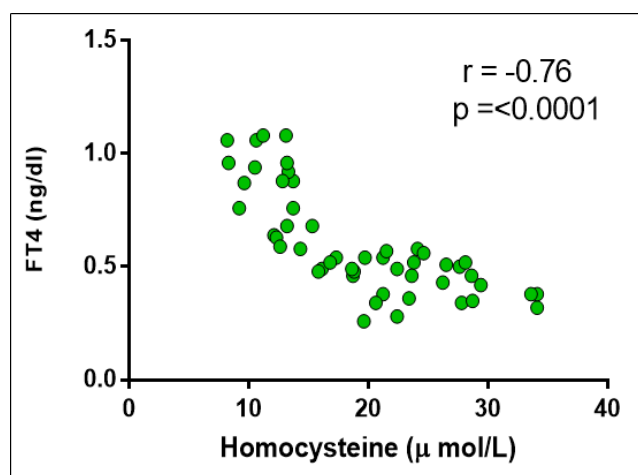


Fig. 4: Correlation of serum homocysteine and FT4 in hypothyroid cases

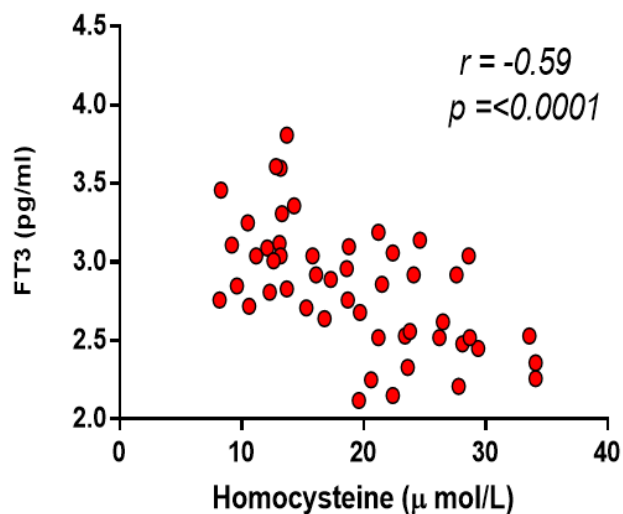


Fig. 5: Correlation of serum homocysteine and FT3 in hypothyroid cases

6. Conclusion

In our study there is a significant increase in levels of Serum Homocysteine in cases as compared to controls ($p = <0.0001$). Also there is a positive correlation between Serum Homocysteine and TSH levels. Hence, increased Homocysteine levels may contribute to a greater cardiovascular risk in Overt Hypothyroidism.

We can conclude from our study that patients suffering from Overt Hypothyroidism may be investigated for Serum homocysteine levels, which can be used as a possible marker for screening atherosclerosis and necessary treatment can be initiated at the earliest to prevent the progression of cardiovascular changes in these patients.

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8. Source of Funding

None.

9. Conflict of Interest

None.

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