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Original Research

An Association of total plasma homocysteine levels in hypothyroid patients

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ABSTRACT:
Introduction: This meta-analysis was to elucidate plasma Hcy levels in patients with hypothyroidism, and to evaluate the effect of L-T4 therapy on plasma Hcy levels in patients with hypothyroidism. **Materials and Methods:** Thyroid profile- Total T3 and Total T4 was measured by Competitive Enzyme Linked Immunosorbent Assay, and TSH by Non-competitive Sandwich ELISA.Total plasma Homocysteine was measured by Competitive Enzyme linked Immunosorbent Assay by using Axis-shield Homocysteine EIA kit. A statistical analysis was done by using ANOVA to compare TSH, Homocysteine levels between three groups. Correlation of TSH with Homocysteine was done by using Pearson Correlation Coefficient. SHO is characterized by a serum TSH above the upper reference limit in combination with a normal FT4. **Results:** Highly significant difference was observed between the study groups in Body mass index and TSH with the p value < 0.001. There was significant difference in total plasma homocysteine level between study groups with the p value 0.005. **Conclusion:** We identified an association between hyperhomocysteinemia and FT4 in a group of euthyroid type 2 diabetes patients for the first time.
Keywords: plasma homocysteine, hypothyroid, Thyroid profile.

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INTRODUCTION:

Hypothyroidism is associated with high cholesterol and lipoprotein levels, which are normalized after thyroid hor- mone replacement.[1-3] The atherogenic lipid profile in particular, but also other abnormalities[4-6], have been suggested to be responsible for the increased cardiovascular morbidity in hypothyroid patients.[1-3] Total homocysteine (tHcy) in plasma has recently been proposed as an independent risk factor for occlusive cardio- vascular disease.[7-8] The plasma level is affected by several life-style and physiological factors and is elevated under conditions of impaired folate and cobalamin status and in renal failure.[7]We recently reported that plasma tHcy is influenced by thyroid status. Hypothyroid patients had higher plasma tHcy levels than healthy controls and hyperthyroid patients, but a tendency toward low tHcy in hyperthyroidism did not reach statistical significance.[9] The heterogeneity of the study population with respect to age, vitamin status, and severity of disease[9] probably reduced the power of this cross-sectional investigation. In the present work we further investigated the effect of thyroid status on alterations in plasma tHcy levels. Hyperhomocysteinemia is an important and independent risk factor for atherosclerosis. 60% of the patients affected by cardiovascular disease have hyperhomocysteinemia.[10] Many studies have reported mild hyperhomocysteinemia as an independent risk factor for venous and arterial occlusive disease.[11] For each 5 µmol/L increase in homocysteine there is a 33% risk of developing atherosclerosis.[12] Hypothyroidism decreases the enzyme involved in remethylation

pathway of homocysteine and thus leads to hyperhomocysteinemia. Thyroid hormones stimulate flavokinase involved in the synthesis of flavin adenine mononucleotide and flavin adenine dinucleotide.[14,15] In hypothyroidism there is defective conversion of riboflavin toits FAD co-enzyme. Methylene tetrahydrofolate reductase is the flavoprotein enzyme that converts methylene THF (Tetrahydrofolate) to methyl THF. The methyl THF is necessary for methylation of vitamin B12 and further conversion of homocysteine to methionine. MTHFR (Methylene tetrahydrofolate Reductase) activity is decreased in hypothyroid individuals which leads to hyperhomocysteinemia.[16] As the major treatment of hypothy- roidism, levothyroxine (L-T4) replacement has been used for a long time. The effect of L-T4 treatment on plasma homocysteine status in patients with hypothyroidism has not yet reached a consensus.[17-19] Considering all those conflicting studies, meta- analysis may be an appropriate way to summa- rize available data to provide more strong evi- dences than the individual study. This meta- analysis was to elucidate plasma Hcy levels in patients with hypothyroidism, and to evaluate the effect of L-T4 therapy on plasma Hcy levels in patients with hypothyroidism.

MATERIALS AND METHOD:

Thyroid profile- Total T3 and Total T4 was measured by Competitive Enzyme Linked Immunosorbent Assay, and TSH by Non-competitive Sandwich ELISA. Total plasma Homocysteine was measured by Competitive Enzyme linked Immunosorbent Assay by using Axis-shield Homocysteine EIA kit.A statistical analysis was done by using ANOVA to compare TSH, Homocysteine levels between three groups. Correlation of TSH with Homocysteine was done by using Pearson Correlation Coefficient. SHO is characterized by a serum TSH above the upper reference limit in combination with a normal FT4. This designation is only applicable when thyroid function has been stable for weeks or more, the hypothalamic-pituitary-thyroid axis is normal, and there is no recent or ongoing severe illness. An elevated TSH, usually above 10 mIU/L, in combination with a subnormal FT4 characterizes overt HO. Exclusion criteria were patients with cardiovascular disease, hypertension, diabetes mellitus or impaired glucose tolerance, renal diseases or other endocrine diseases. Therefore, 73 patients were excluded. The final study cohort included 190 patients of those initially enrolled, which included 78 patients with HO and 102 patients with SHO. All patients did not received any treatment. T4 supplementation was stopped for 5–6 weeks and was resumed 2 days after 131I scintigraphy, with a dose escalation over 2–3 weeks. All patients gave their informed consent to participate in the study. Fasting blood samples were drawn immediately before discontinuing supplementation (designated time point− 6 weeks) and thereafter at 2-week intervals (−4 and −2 weeks) until scintigraphy was carried out (time zero). This period, from −6 to 0 weeks, is referred to as phase I. After resumption of T4 supplementation, fasting blood samples were drawn at 2-week intervals (2, 4, 6, and 8 to 10 weeks) for up to 10 weeks. The period from 0 to 10 weeks is referred to as phase II. We did not obtain complete blood sampling from all patients.

RESULTS:

Total plasma homocysteine levels were significantly more in recently diagnosed hypothyroidism (12.61 ± 4.70) than controls (10.60 ± 2.61) and treated hypothyroidism (10.80 ± 2.95) with p value of 0.004and 0.009 respectively. Baseline characteristics and biochemical parameters of the controls, treated hypothyroidism and recently diagnosed hypothyroidism cases. No significant difference were found in the distribution of age and sex among the study groups. This shows that the study is age and sex matched. Highly significant difference was observed between the study groups in Body mass index and TSH with the p value < 0.001. There was significant difference in total plasma homocysteine level between study groups with the p value 0.005. [Table 1].

Table 1: Characteristics of Controls, treated hypothyroidism and recently diagnosed hypothyroidism

Parameters	Controls	Treated Hypothyroidism	Recently Diagnosed Hypothyroidism	P Value
Age	29.51 ± 6.80	30.22 ± 7.1	31.56 ± 8.22	0.496NS
Sex Male	6 (17.1 %)	2 (5.7 %)	5 (14.2 %)	
Female	29 (82.8 %)	34 (97.1 %)	29 (82.8 %)	
Body Mass Index	22.11 ± 2.51	27.61 ± 6.03	27.5 ± 6.8	<0.001**
TSH (μIU/L)	3.21 ± 2.04	3.20 ± 2.5	46.1 ± 52.01	<0.001**
Homocysteine (μmol /L)	10.60 ± 2.61	10.80 ± 2.95	12.61 ± 4.70	0.005*

The comparison of characteristics between controls and recently diagnosed hypothyroidism. The two groups showed significantly different in body mass index and TSH with the p value 0.001. Total plasma homocysteine levels were significantly more in recently diagnosed hypothyroidism (12.61 ± 4.70) than controls (10.60 ± 2.61) with p value of 0.005. [Table 2].

Table 2: Comparison of characteristics between controls and recently diagnosed hypothyroidism

Parameters	Controls	Recently diagnosed hypothyroidism	p value
Age	29.51 ± 6.80	31.56 ± 8.22	0.244 NS
Sex Male	6 (17.1 %)	5 (14.2 %)	
Female	29 (82.8 %)	29 (82.8 %)	
Body Mass Index	22.11 ± 2.51	27.5 ± 6.8	< 0.001 **
TSH (μIU/L)	3.21 ± 2.04	46.1 ± 52.01	< 0.001 **
Homocysteine (μmol /L)	10.60 ± 2.61	12.61 ± 4.70	0.005 *

Comparison of characteristics between recently diagnosed hypothyroidism and treated hypothyroidism. Total plasma Homocysteine levels were significantly increased in recently diagnosed hypothyroidism compared to treated hypothyroidism with p value of 0.008. [Table 3].

Table 3: Comparison of characteristics between recently diagnosed hypothyroidism and treated hypothyroidism

Parameters	Recently Diagnosed Hypothyroidism	Treated Hypothyroidism	P Value
Age	31.56 ± 8.22	30.22 ± 7.1	0.449 NS
Sex Male	5 (14.2 %)	2 (5.7 %)	
Female	29 (82.8 %)	34 (97.1 %)	
Body Mass Index	27.5 ± 6.8	27.61 ± 6.03	0.920 NS
TSH (μIU/L)	46.1 ± 52.01	3.20 ± 2.5	< 0.001 **
Homocysteine (μmol /L)	12.61 ± 4.70	10.80 ± 2.95	0.008 *

DISCUSSION:

The longitudinal design ensures high statistical power, because the inter individual variations are minimized. The data are somewhat weakened by incomplete sample series due to logistic problems. The main finding is a gradual increase in plasma tHcy during development of the hypothyroid state and a return of the tHcy level when T_4 supplementation was resumed. Notably, the increase and decrease take place over weeks. A similar time course was observed for serum creatinine and total cholesterol. The kinetics of these changes might reflect the turnover rate of T_4, which has a half-life of about 7 days in humans.[20] This is supported by comparing tHcy and thyroid hormone kinetics during The results of the present study are in accordance with the recent observation that plasma tHcy is high in hypothyroid patients and tends to be low in hyperthyroid patients.[9] The apparent close relation between the plasma tHcy and thyroid hormone levels during phases I and II indicates a hormone effect on homocysteine metabolism, distribution, or clearance. A similar argument can be made for the creatinine and cholesterol responses. Hyperhomo- cysteinemia induces endothelial injury, oxidative stress, oxidation of LDL-cholesterol and smooth muscle hypertrophy.[20,21] Toxic effect of Hcy and its spontaneous oxidation product, homocysteic acid, have the ability to activate N-methyl-D-aspartic acid (NMDA) re- ceptors, then increase intracellular levels of calcium ion and reactive oxygen species.[22,23] An alternative explanation for the concurrent elevation of plasma tHcy and serum creatinine during iatrogenic hypothyroidism is the formation of homocysteine in conjunction with creatine-creatinine synthesis, which is related to muscle mass.[24] However, creatinine formation was not increased in hypothyroid patients in one study.[25] Furthermore, significant changes in muscle mass during the short study pe- riod are unlikely. Taken together, these data give no support to the idea[9] that increased tHcy during hypothyroidism is due to enhanced homocysteine production. We observed a moderate transient decline in both serum and RBC folate during discontinuation of T_4 supplementation. This is in agreement with the finding published previ- ously by us[9] and others[28], demonstrating elevated serum folate in hyperthyroidism and low levels in hypothyroidism. The folate response could be related to direct effect of thyroid hormones on folate-metabolizing enzymes, including methylene tetrahydrofolate reductase.[26] Folate sta- tus has been established as a major determinant of tHcy level.[27] However, in the present study the changes in vitamin levels are minor and show only weak, nonsignificant, correlations with tHcy. This suggests that impaired folate status is not responsible for the transient hyperhomocysteinemia during discontinuation of T_4 supplementation.

CONCLUSION:

In conclusion, we identified an association between hyperhomocysteinemia and FT4 in a group of euthyroid type 2 diabetes patients for the first time. A longitudinal

study is needed to assess the effects of the variation in thyroid hormone levels within the euthyroid range in the development of hyperhomocysteinaemia.

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