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Association of total plasma homocysteine levels in hypothyroid individuals

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Abstract

One of the major complication of hypothyroidism is atherosclerosis and cardiovascular disease. Hyperhomocysteinemia is an important and independent risk factor for atherosclerosis. Hypothyroidism decreases hepatic levels of enzymes which converts homocysteine to methionine that leads to increase in homocysteine level in the circulation of hypothyroid individuals. The aim of the study was to assess fasting total plasma homocysteine level in recently diagnosed hypothyroidism. The study included thirty recently diagnosed hypothyroid individuals, thirty treated hypothyroidism and thirty apparently healthy subjects with age and sex matched. The study group was selected after obtaining ethical committee clearance and consent from subjects attending outpatient department of Endocrinology, Madras Medical College, Chennai. Thyroid profile and homocysteine were measured in fasting blood samples. Total plasma homocysteine level was significantly more in recently diagnosed hypothyroidism compared to controls and treated hypothyroidism with p value 0.006. By this study we confirmed hyperhomocysteinemia in hypothyroidism which may lead to atherosclerosis. Hypothyroidism is one of the treatable cause for hyperhomocysteinemia. During treatment with thyroxine, hypothyroid patients should be monitored for total plasma homocysteine levels. In hypothyroidism, estimation of total plasma homocysteine level can be used as screening test to identify and monitor cardiovascular risk.

Keywords: Homocysteine, Hypothyroidism, Homocysteine & Cardiovascular Risk.

Introduction

Thyroid diseases are common worldwide. In India too, thyroid diseases are more prevalent and the most common among all the endocrine diseases.(1) In India 11% of the population are affected from hypothyroidism. Women were three times more prone for hypothyroidism than men.(2)

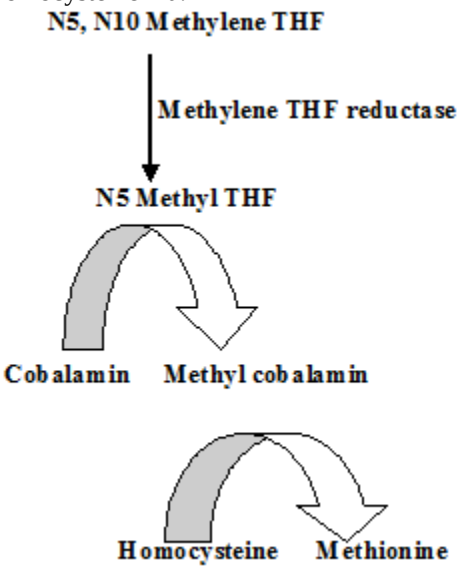
Homocysteine is a sulphur containing amino acid which is formed as an intermediate in the methionine metabolism and methionine is the only source of homocysteine in the human body.

Hyperhomocysteinemia is defined as the levels of homocysteine> 10 µmol/L. There are various causes for hyperhomocysteinemia. Hypothyroidism is one of the treatable cause for hyperhomocysteinemia. For each 1 µmol/L increase in homocysteine concentration there is a 1% increase in risk to develop cardiovascular events or death.(3)

Hyperhomocysteinemia is an important and independent risk factor for atherosclerosis. 60% of the patients affected by cardiovascular disease have hyperhomocysteinemia.(4) Many studies have reported mild hyperhomocysteinemia as an independent risk factor for venous and arterial occlusive disease.(5) For each 5 µmol/L increase in homocysteine there is a 33% risk of developing atherosclerosis.(6)

Hypothyroidism decreases the enzyme involved in remethylation pathway of homocysteine and thus leads to hyperhomocysteinemia.(7) Thyroid hormones stimulate flavokinase involved in the synthesis of flavin adenine mononucleotide and flavin adenine dinucleotide.(8,9)

In hypoyhroidism there is defective conversion of riboflavin to its 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.(10)



The kidney 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 reduce renal blood flow and low

GFR (Glomerular filtration Rate). Thus it reduces its clearance and cause hyperhomocysteinemia.[11]

Aim

To assess fasting total plasma homocysteine level in hypothyroid individuals.

Results

There was significant difference in total plasma homocysteine levels between three study groups with the p value 0.006. Total plasma homocysteine levels were significantly more in recently diagnosed hypothyroidism (11.64 ± 3.72) than controls (9.62 ± 1.65) and treated hypothyroidism (9.84 ± 1.97) with p value of 0.004 and 0.009 respectively.

Conclusion

Total plasma homocysteine is increased in hypothyroidism which may lead to atherosclerosis. Hypothyroid patients should be monitored for total plasma homocysteine levels and their estimation can be used as screening test to identify and monitor cardiovascular risk.

Materials and Method

This case control study was done after obtaining the approval from institutional ethical committee.

Group 1: 30 newly diagnosed hypothyroid individuals aged 15-45 years

Group 2: 30 treated hypothyroidism (3 months to one year duration) aged 15-45 years

Group 3: 30 Age and sex matched apparently healthy individuals

Exclusion criteria for both cases and controls:

1. Chronic smokers
2. Pregnancy & lactation
3. Diabetes mellitus
4. Renal disease
5. Liver disease
6. Megaloblasticanemia by peripheral smear and
7. Patients on other medication for a long time were excluded.

Fasting venous blood sample was collected in EDTA test tube with strict aseptic precautions.

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.

Results

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

Parameters	Controls	Treated Hypothyroidism	Recently Diagnosed Hypothyroidism	P Value
Age	28.57 ± 5.85	29.27 ± 6.3	30.57 ± 7.26	0.496NS
Sex Male	4 (13.3 %)	1 (3.3 %)	4 (13.3 %)	
Female	26 (86.7 %)	29 (96.7 %)	26 (86.7 %)	
Body Mass Index	21.14 ± 1.53	26.64 ± 5.04	26.8 ± 5.9	<0.001**
TSH (μIU/L)	2.26 ± 1.07	2.26 ± 1.3	45.4 ± 51.02	<0.001**
Homocysteine (μmol /L)	9.62 ± 1.65	9.84 ± 1.97	11.64 ± 3.72	0.006*

NS – Non significant

* - significant,** - Highly significant

Table 1 shows 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 0.006.

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

Parameters	Controls	Recently diagnosed hypothyroidism	p value
Age	28.57 ± 5.85	30.57 ± 7.26	0.244 NS
Sex Male	4 (13.3 %)	4 (13.3 %)	

Female	26 (86.7 %)	26 (86.7 %)	
Body Mass Index	21.14 ± 1.53	26.8 ± 5.9	< 0.001 **
TSH (μIU/L)	2.26 ± 1.07	45.4 ± 51.02	< 0.001 **
Homocysteine (μmol /L)	9.62 ± 1.65	11.64 ± 3.72	0.004 *

NS – Non significant
* - Significant
** - Highly significant

Table 2 shows 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 (11.64 ± 3.72) than controls (9.62 ± 1.65) with p value of 0.004.

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

Parameters	Recently Diagnosed Hypothyroidism	Treated Hypothyroidism	P Value
Age	30.57 ± 7.26	29.27 ± 6.3	0.448 NS
Sex Male	4 (13.3 %)	1 (3.3 %)	
Female	26 (86.7 %)	29 (96.7 %)	
Body Mass Index	26.8 ± 5.9	26.64 ± 5.04	0.919 NS
TSH (μIU/L)	45.4 ± 51.02	2.26 ± 1.3	< 0.001 **
Homocysteine (μmol /L)	11.64 ± 3.72	9.84 ± 1.97	0.009 *

NS – Non significant
* - Significant
** - Highly significant

Table 3 shows 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 0.009.

Table 4: Correlation of TSH with homocysteine and other parameters in study groups

	TSH
Body mass index Pearson Correlation	.028
Sig.(2-tailed)	.79
N	90
Homocysteine Pearson Correlation	.174
Sig.(2-tailed)	.10
N	90

Table 4 shows Pearson Correlation Coefficient. It was done on variables like Body mass index and Homocysteine with TSH in order to measure the strength of linear relationship between variables.

It is observed that as TSH increases, the concentration of homocysteine also increases. This is indicated by weak positive correlation with r = 0.174.

It is also observed that increase in TSH concentration has positive correlation with Body mass index.

Discussion

This study was conducted to measure homocysteine level in newly diagnosed hypothyroid individuals and to correlate them with treated and control groups.

ANOVA analysis showed that there was statistically significant difference in total plasma homocysteine level between the three study groups. Total plasma homocysteine level was high in newly diagnosed hypothyroidism compared to treated hypothyroidism and controls with p value of 0.006.

Post-Hoc test was used to show the difference of total plasma homocysteine level between the two study groups. Homocysteine was high in recently diagnosed hypothyroidism (11.64±3.72) compared to controls (9.62±1.65) with p value of 0.004. . Homocysteine was high in recently diagnosed hypothyroidism (11.64±3.72) when compared to treated hypothyroidism (9.84±1.97) with p value of 0.009.

From the above we confirmed that hypothyroidism is associated with hyperhomocysteinemia. The causes for hyperhomocysteinemia are:

- In hypothyroidism the activity of flavokinase is decreased which has an effect on the activity of flavoprotein enzyme methylene tetrahydrofolate reductase.
- This decreases the conversion of methylene tetrahydrofolate to methyl tetrahydrofolate which is one of the cofactor for the conversion of homocysteine to methionine, thus leading to increase in homocysteine level in hypothyroidism.

- While on treatment with thyroxine this enzyme activity is regained and homocysteineis converted back to methionine.
- The similar results were obtained by Bjorn G. Nedrebo et al,[12] Homocysteine level was high in recently diagnosed hypothyroidism and decreased in treated hypothyroidism. So early diagnosis and treatment of hypothyroidism may reduce homocysteine levels, which is one of the major cardiovascular risk factor.
- Prolonged exposure to high homocysteine is toxic because the levels of homocysteine exceeds the endothelial cell capacity to produce S-nitrosohomocysteine which has some effects of nitric oxide in smooth muscle relaxation.
- In hyperhomocysteinemia, homocysteine stimulates protease endothelial cell activator of factor V and directly activates coagulation in the absence of thrombin.
- Mild hyperhomocysteinemia favours binding of lipoprotein(a) to fibrin thus reduces plasminogen activation and inhibits fibrinolysis.
- Homocysteinethiolactone causes LDL cholesterol to aggregate and then phagocytosed by vascular macrophages to form foam cells. Homocysteinethiolactone released from foam cells which produces free radicals and causes endothelial cell damage.

3-9 months of treatment on thyroxine with appropriate dose decreases homocysteine level.[13]

Homocysteine has weak positive correlation with TSH(r = 0.174). This indicates that both TSH and homocysteine were in parallel rise in the study groups.

Conclusion

In this study we found that,

- Total plasma Homocysteine level was significantly increased in recently diagnosed hypothyroidism.
- Total plasma Homocysteine level was near normal in treated hypothyroidism.
- Total plasma Homocysteine level was normal in control groups.
- In this study we found that hypothyroidism is associated with hyperhomocysteinemia which causes premature atherosclerosis.
- Measurement of total plasma homocysteine level for screening cardiovascular risk factor and to avoid untoward complications in hypothyroidism cases is necessary.
- Patients with unexplained hyperhomocysteinemia should be screened for thyroid status.[14]

Limitations of the study

- Because of the financial limits, Vitamin B12 and Folic acid were not measured in the study groups to rule out its deficiency and Megaloblastic anemia.

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