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NOTE

Plasma Homocysteine Levels in Hyperthyroid Patients

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Abstract. Hyperhomocysteinemia is a risk factor for premature atherosclerotic vascular diseases. It is known that plasma homocysteine levels are higher in hypothyroid patients compared to healthy subjects. The aim of our study was to assess plasma total homocysteine concentrations in hyperthyroid patients before and after treatment when euthyroid status was reached and compare them with control group. Thirteen hyperthyroid patients (age, 42.9 ± 15.6 year) and eleven healthy subjects (age, 39.9 ± 12.5 year) were involved in the study. Plasma levels of homocysteine and serum cholesterol, triglyceride, HDL cholesterol, urea, creatinine, vitamin B12, folate were measured before and after treatment. LDL cholesterol and creatinine clearences were calculated. Pretreatment homocycteine levels of the hyperthyroid patients were significantly lower than healthy controls (11.5 ± 3.6 μmol/L vs. 15.1 ± 4.5 μmol/L, respectively, $p<0.05$). Posttreatment homocysteine levels were significantly higher than pretreatment levels (13.9 ± 6.3 μmol/L vs. 11.5 ± 3.6 μmol/L, respectively, $p<0.05$) and posttreatment creatinine clearance were lower than pretreatment level (103.5 ± 12.7 ml/min vs. 114.2 ± 9.3 ml/min, respectively, $p<0.01$). Lower homocysteine levels in hyperthyroidism can be partially explained with the changes in creatinine clearance.

Key words: Homocysteine, Folate, Hyperthyroidism

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HOMOCYSTEINE is a sulphur-containing amino acid which in humans can only be derived from the metabolism of the essential amino acid methionine. Vitamin B12 is an essential cofactor for methionine synthase. Homocysteine is metabolized by one of the two pathways: remethylation and trans-sulphuration [1, 2]. Hyperhomocysteinemia is an independent risk factor for atherosclerosis and atherothrombosis [3–7]. Although the molecular mechanism by which homocysteine or a related metabolite promotes atherothrombosis is unknown, the epidemiologic evidence of the association of hyperhomocysteinemia with atherothrombotic vascular disease is convincing [1]. Thyroid status has a profound influence on a variety of biochemical processes, some of which may have secondary effects on homocysteine metabolism. Hypothyroidism has been reported to cause mild hyperhomocysteinemia. The increase in homocysteine concentrations during hypothyroidism may be explained by changes in folate status and also by modifications in the enzymes involved in homocysteine metabolism, distribution or clearance and/ or by concurrent changes in renal function [8]. The aim of this study was to assess plasma total homocysteine concentrations in recently diagnosed hyperthyroid patients before and after treatment.

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Materials and Methods

Thirteen patients with toxic diffuse goitre (3 male, 10 female; mean age 42.9 ± 15.6 yr) were enrolled in this study. These patients had normal vitamin B12 and folate levels and elevated serum free T3 (FT3), free T4 (FT4) levels, and had low thyrotropin (TSH) levels. Patients with any major organ or systemic disease were excluded from the study. Control group consisted of 11 euthyroid healthy subjects (2 male, 9 female; mean age 39.9 ± 12.5 yr). None of the patients and

control group was on a special diet or used nutritional suplements ; they did not use any medication known to interfere with thyroid hormone or homocysteine metabolism. All patients and control group were non-smokers. After detailed physical examination body mass indexes (BMI) were measured and blood was withdrawn after 12 hour of overnight fasting, at 08.30 a.m., for serum TSH, FT_3, FT_4, total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C), VLDL-cholesterol (VLDL-C), creatinine, urea, folate, vitamin B12, and homocysteine. All patients were given antithyroid drug therapy. Hyperthyroid patients treated with methimazole or propylthiouracil visited the clinic once a month for adjustment of the doses of both drugs. BMI, thyroid functions, lipid tests including TC, TG HDL-C, VLDL-C and vitamin B12, folate, creatinine, homocysteine levels of the patients were measured again at least three months (minimum three, maximum five months) after achieving euthyroid state.

Serum creatinine was measured by an automated enzymatic method and creatinine clearance (C_{cr}) was calculated using the Cockcroft and Gault formula: C_{cr} (ml/min) = [140–age(year)]×weight (kg)/[0.81×creatinine (μmol/l)]. For women this value was multiplied by 0.85. Since measurement of creatinine clearance requires the collection of urine over a 24-hour period, which is inconvenient for patients and often leads to inaccurate collections we preferred the Cockcroft and Gault formula. This formula has been shown to have a significant correlation to GFR in the literature [2, 9].

Plasma FT_3, FT_4 and TSH were measured by chemiluminescent method.

Serum TC ,TG and, HDL-C were determined enzymatically. LDL-C was calculated with the Friedewald formula (LDL-C=TC–(HDL-C+TG/5).

Plasma folate and plasma vitamin B12 were measured by radioassay.

Total homocysteine concentrations were determined in EDTA plasma by high performance liquid chromatography.

The local ethics committee approved this study, and all the subjects gave their written informed consent.

Statistical analyses were performed using paired sample t test and independent samples t test with the statistical package for social sciences software (SPSS, version 9.0). Obtained data are presented as means ± standard deviation. A probability value less than 0.05 is accepted as statistically significant. Correlation analyses were performed according to Pearson and Spearman.

Results

The main characteristics of the patient and the control group are summarized in Table 1. Age and BMI values of the patients and the control group were similar (42.9 ± 15.6 yr. vs. 39.9 ± 12.5 yr; 22.2 ± 1.8 kg/m^2 vs. 22.4 ± 2.6 kg/m^2, respectively). Serum TC (147.1 ± 29.5 mg/dl vs. 192.1 ± 21.3 mg/dl, $p<0.001$, respectively), TG (108.6 ± 55.8 mg/dl vs. 205.5 ± 52.8 mg/dl, $p<0.001$, respectively) and LDL-C (79.6 ± 18.9 mg/dl vs. 100.3 ± 11.1 mg/dl, $p<0.01$, respectively) concentrations were significantly lower in hyperthyroid patients than the healthy subjects. While there were no differences in serum vitamin B12 levels between hyperthyroid patients and control subjects, folate levels of the hyperthyroid patients were significantly higher than control group (9.4 ± 3.4 nmol/L vs. 7.2 ± 1.0 nmol/L, $p<0.05$, respectively).

Creatinine clearance of the hyperthyroid patients was significantly higher than healthy subjects (114.2 ± 9.3 ml/min vs. 105.1 ± 11.5 ml/min, $p<0.05$, respectively). Plasma total homocysteine concentrations of the hyperthyroid patients were significantly lower than the healthy control (11.5 ± 3.6 μmol/L vs. 15.1 ± 4.5 μmol/L, $p<0.05$, respectively).

Pretreatment and posttreatment values of the patients are given in Table 2. Whereas pretreatment and posttreatment BMI, TC, TG, LDL-C concentrations were similar, HDL-C concentrations increased significantly after euthyroid state was achieved (40.7 ± 11.4 mg/dl vs. 44.7 ± 14.2 mg/dl, $p<0.05$, respectively). There were no significant differences in serum vitamin B12 and folate levels before and after antithyroid therapy. Serum total homocysteine levels increased and creatinine clearance decreased significantly after antithyroid therapy (11.5 ± 3.6 μmol/L vs. 13.9 ± 6.3 μmol/L, $p<0.05$, 114.2 ± 9.3 ml/min vs. 103.5 ± 12.7 ml/min, $p<0.01$ respectively).

There were no significant correlations between the parameters in correlation analysis.

Discussion

There are consistent reports demonstrating that thy-

Table 1. Baseline clinical and laboratory characteristics of the patients and the control groups.

	Patients (n = 13)	Controls (n = 11)	p	Reference range
Male/female	3/10	2/9		
Age (year)	42.9 ± 15.6	39.9 ± 12.5	NS	
BMI (kg/m^2)	22.2 ± 1.8	22.4 ± 2.6	NS	
TC (mg/dl)	147.1 ± 29.5	192.1 ± 21.3	<0.001	<200
TG (mg/dl)	108.6 ± 55.8	205.5 ± 52.8	<0.001	35–135
HDL-C (mg/dl)	40.7 ± 11.4	48.2 ± 7.7	NS	30–85
LDL-C (mg/dl)	79.6 ± 18.9	100.3 ± 11.1	<0.01	<130
C_{cr} (ml/min)	114.2 ± 9.3	105.1 ± 11.5	<0.05	100–120
VIT B12 (pmol/L)	193.4 ± 51.1	209.4 ± 36.3	NS	180–810
Folate (nmol/L)	9.4 ± 3.4	7.2 ± 1.0	<0.05	6–36
TSH (μIU/ml)	0.004 ± 0.0	2.1 ± 0.9	<0.001	0.40–4.01
FT3 (pg/ml)	8.2 ± 3.2	2.8 ± 0.6	<0.001	2.0–4.9
FT4 (ng/dl)	3.0 ± 1.2	1.4 ± 0.2	<0.01	0.7–1.63
Homocysteine (μmol/L)	11.5 ± 3.6	15.1 ± 4.5	<0.05	6–16

NS: Statistically not significant

Table 2. Pretreatment and post treatment laboratory characteristics of the hyperthyroid patients

	Pretreatment	Posttreatment	p	Reference range
BMI (kg/m^2)	22.2 ± 1.8	22.3 ± 1.9	NS	
TC (mg/dl)	147.1 ± 29.5	168.8 ± 48.2	NS	<200
TG (mg/dl)	108.6 ± 55.8	98.0 ± 54.5	NS	35–135
HDL-C (mg/dl)	40.7 ± 11.4	44.7 ± 14.2	<0.05	30–85
LDL-C (mg/dl)	79.6 ± 18.9	85.2 ± 21.0	NS	<130
C_{cr} (ml/min)	114.2 ± 9.3	103.5 ± 12.7	<0.01	100–120
VIT B12 (pmol/L)	193.4 ± 51.1	177.1 ± 67.6	NS	180–810
Folate (nmol/L)	9.4 ± 3.4	9.9 ± 4.1	NS	6–36
TSH (μIU/ml)	0.004 ± 0.0	0.8 ± 0.5	<0.001	0.40–4.01
FT3 (pg/ml)	8.2 ± 3.2	2.9 ± 1.5	<0.001	2.0–4.9
FT4 (ng/dl)	3.0 ± 1.2	1.3 ± 0.5	<0.001	0.7–1.63
Homocysteine (μmol/L)	11.5 ± 3.6	13.9 ± 6.3	<0.05	6–16

NS: Statistically not significant

roid status is an important determinant of the plasma concentration of total homocysteine, which has been established as an independent risk factor of vascular occlusive disease [6–8] Hypothyroidism is associated with high homocysteine levels. The apparent close relation between the plasma homocysteine and thyroid hormone levels indicates a hormone effect on homocysteine metabolism, distribution, or clearence. A similar argument can be made for the creatinine and cholesterol responses [8–14].

Lien *et al.* observed a close relation between plasma total homocysteine and serum creatinine in iatrogenic hypothyroidism [8]. They found a progressive and parallel increase in total homocysteine, serum creatinine, and serum cholesterol during hypothyroidism and those values returned to the original levels within 4–6 weeks after reinitiating T4 therapy. Both the homocysteine and creatinine responses were explained by the hypodynamic circulation in hypothyroidism [8].

Thyroid hormones are cardiotonic agents, which increase cardiac output while lowering systemic vascular resistance, resulting in increased renal blood flow [8, 15]. This in turn may increase the glomerular filtration rate, which is related to serum creatinine, but also closely associated with plasma homocysteine [8, 13, 16]. Thyroid hormones also act by modulating gene expression and influencing a multitude of enzyme systems. Many enzymes involved in the pathways of homocysteine metabolism may be affected. From experimental studies it is known that not only activities

of enzymes that participate in folate metabolism such as methylene tetrahydrofolate-reductase but also activities of methionine synthase and cystathionine β-synthase are influenced by thyroid hormone. Probably thyroid hormone-induced alterations in these enzymatic activities contribute homocysteine levels [2, 3].

Nedrebo *et al.* found that plasma total homocysteine, serum folate, total cholesterol, HDL-cholesterol and creatinine levels were significantly higher in patients with hypothyroidism than in patients with hyperthyroidism [6]. In hyperthyroid patients, total homocysteine, creatinine, and cholesterol increased during treatment. Serum folate decreased significantly, whereas there was no significant change in cobalamin. During treatment of both patient groups, plasma homocysteine showed a strong covariation with serum cholesterol and creatinine whereas there was no relation to serum folate and cobalamin. From those observations, they explained that changes in renal function rather than vitamin status might account for variation in plasma total homocysteine [6].

Both animal and human studies have demonstrated that hypothyroidism is associated with low and hyperthyroidism with high glomerular filtration rate, which in turn is closely related to plasma total homocysteine [6, 13, 17]. Renal homocysteine excretion is negligible, but homocysteine metabolism in the kidneys may play a major role in homocysteine clearance [6, 11].

Ford *et al.* demonstrated elevated serum folate levels in hyperthyroidism and low levels in hypothyroidism. Folate response was related to direct effect of thyroid hormones on folate metabolizing enzymes, including methylenetetrahydrofolate reductase [8, 10, 18]. Barbe *et al.* found lower serum folate in the hypothyroid compared with the hyperthyroid state, and they observed the usual inverse relationship between serum folate an homocysteine [7, 19]. From this observation they inferred that the changes in homocysteine may be explained by altered folate status or a modification of the activity of folate metabolizing enzymes [7, 19].

Hypothyroidism is associated with high cholesterol and lipoprotein levels, which are normalized after thyroid hormone replacement [8]. The covariation between homocysteine and serum cholesterol was equally strong [7]. A positive correlation between homocysteine level and total or low-density lipoprotein cholesterol level has been demonstrated in a few reports. A biochemical explanation for the association between plasma homocysteine and serum cholesterol level has not been identified [8].

We observed lower plasma total homocysteine and serum TC, TG levels and higher creatinine clearance in hyperthyroid patients than euthyroid healthy subjects. Folate levels were found significantly higher in hyperthyroid subjects, whereas vitamin B12 levels were similar. After antithyroid drug therapy, homocysteine levels increased and creatinine clearance decreased significantly. HDL-C levels increased significantly when euthyroid status was achieved. In conclusion, increased glomerular filtration rate in hyperthyroidism is linked to increased renal homocysteine clearance.

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