Egyptian Journal of Surgery Vol. (23), No. (1), Jan., 2004

STUDY OF THE ALTERATIONS OF TOTAL PLASMA HOMOCYSTEINE LEVELS AND ATHEROGENIC LIPID PROFILE IN HYPOTHYROIDISM

By

Mohamed Abd Ellatif[1], Mosaad Soliman[2] and Mohamed Y. Abdel Aziz[3]

Departments of Medical Biochemistry[1], and General Surgery[2], and General Medicine [3], Faculty of Medicine, Mansoura University, Mansoura, Egypt

Hypothyroidism is associated with increased cardiovascular morbidity, which cannot be fully explained by the atherogenic lipid profile observed in these patients. Elevation of total plasma concentrations of homocystein (t-Hcy) is an important and independent risk factor for cardiovascular disease. Because hypothyroidism decreases hepatic levels of enzymes involved in the remethylation pathway of homocystein, we prospectively evaluated fasting t-Hcy in hypothyroid patients before and after recovery of euthyroidism. In the current study we examined 40 patients with peripheral hypothyroidism [12 with autoimmune thyroiditis, 10 with Graves' disease, (treated surgically or carbimazole), 2 with toxic multinodular goiter (treated surgically), 12 surgically resected goiter, and 4 with idiopathic hypothyroidism] in comparison with those of 25 hyperthyroid patients and 25 euthyroid control subjects with the same age and sex attending the outpatient and the inpatient departments of general surgery, Mansoura University Hospital. In all cases, a detailed medical history was obtained and a thorough physical examination was performed with emphasis on the presence of symptoms / signs indicative of underlying thyroid disorders. In addition to plasma lipid parameters, thyrotropin (TSH), T3, T4 and t-Hcy levels were measured in a fasting blood samples. Fasting t-Hcy levels were higher in patients with hypothyroidism in comparison with those of hyperthyroid patients and euthyroid control subjects. Plasma t-Hcy in hypothyroidism was significantly correlated with high TSH and lipoprotein (a) levels (r = 0.306, P = <0.01 & r = 0.476, P = <0.001, respectively). The restoration of euthyroid state with levothyroxine therap (75 ug/day) was followed by a significant improvement of plasma lipid profile. Also, thyroid hormone replacement significantly decreased fasting t-Hcy. We confirmed the observation of hyperhomocysteinemia in hypothyroidism, which together with the elevated plasma lipoprotein (a) may contribute to an accelerated atherogenesis in these patients. As hypothyroidism may be a treatable cause of hyperhomocysteinemia, and as fasting t-Hcy is associated with a significant increased relative risk of coronary artery disease, measurement of t-Hcy to screen this dynamic association of cardiovascular risk factors during hypothyroidism may be of interest.

INTRODUCTION

Overt thyroid disturbances, characterized by symptoms and/or clinical signs with abnormal serum levels of thyroid hormones, are generally associated with perturbations in the lipid profile [(1).]

Primary hypothyroidism is a graded phenomenon with different levels of severity, showing a wide inter individual range of clinical and biochemical presentation [(2).] The earliest form of hypothyroidism, called subclinical hypothyroidism (SCH) or mild thyroid failure is defined by an increased serum TSH level in the presence of normal concentrations of circulating thyroid hormones.

Overt hypothyroidism may result in accelerated atherosclerosis and coronary heart disease (CHD) presumably because of the associated hypertension, hypercholesterolemia, and hyperhomocysteinemia. Because of the evidence linking raised lipoprotein (a) [Lp(a)] concentrations with the development of atherosclerosis, attention has been focused on plasma Lp(a) levels in thyroid diseases[(3).]

An elevated total plasma homocystiene (t-Hcy) level has recently received greater attention as an important and easily modifiable risk factor for atherosclerotic and thromboembolic diseases such as cerebrovascular disease, coronary artery disease and venous thrombosis [(4).]

Homocystiene is metabolized by one of two pathways; remethylation and transsulfuration. Thus, hyperhomocystienemia may be due to deficiency of enzymes of the remethylation pathway that recycles homocystiene to methionine, or of enzymes of the transsulfuration pathway (cystathionine β-synthetase) [5].

Moderately elevated plasma homocysteine concentration is readily correctable by folic acid, betaine, or vitamin B12 supplementation. However, several investigations have indicated that the theory of vitamin B12 deprivation provides only a partial explanation for the observed abnormalities of the sulfur-containing amino acids [6,7].

Laraqui et al [8] reported a positive correlation between the levels of homocysteine and those of Lp(a), and that the hyperhomocysteinemia and/or increased plasma level of lipoprotein Lp(a) are risk factors for coronary heart disease.

Lipid abnormalities associated with thyroid disturbances remain controversial[1]. The increased risk of coronary heart disease assumed to be associated with hypothyroidism is not linked with the presence of pattern β LDL, but rather with concomitant metabolic abnormalities[9]. Hypothyroidism is associated with increased cardiovascular morbidity, which cannot be fully explained by the atherogenic lipid profile observed in these patients [10,11].

Aim of the study:

The study was designed to evaluate the alterations of plasma t-Hcy levels and plasma lipid profile in hypothyroidism. Also, this study was conducted to evaluate the effect of thyroid hormone replacement and restoration of the euthyroide state on these parameters.

Study populations:

Forty patients suffering from hypothyroidism, 35 women and 5 men, with a mean age of 44.7±9.5 years were studied prospectively. The underlying thyroid disorders leading to hypothyroidism were autoimmune thyroiditis (n = 12), Graves' disease (n = 10; treated with surgery or, carbimazole), toxic multinodular goiter (n = 2; treated surgically), surgically resected goiter (n = 12), and idiopathic hypothyroidism (n = 4). Also, twenty-five hyperthyroid patients (21 women and 4 men, with mean age of 43.7 ±7.8 years), in addition to twenty-five euthyroid (20 women and 5 men with mean age of 43.2±6.0 years) were enrolled in this study. All the study populations were selected from those attending the outpatient and the inpatient departments of general surgery, Mansoura University Hospital.

All subjects were in good health, all women were premenopausal with regular menses, and none was pregnant. Patients treated with medications known to interfere with t-Hcy metabolism, particularly estrogen-containing medications, or associated diseases states that might influence t-Hcy levels were excluded from the study. Obese subjects, smokers, and those with primary or secondary dyslipidemia, diabetes mellitus, renal and hepatic failure, or other systemic diseases were excluded from the study. Other exclusion criteria were: coronary heart disease, pituitary/hypothalamic disorders, or other nonthyroidal illnesses; thyroid hormone medication up to 3 months before enrollment; lipid-lowering agents within 6 months before enrollment; and obvious or suspected poor compliance.

In all cases a detailed medical history was obtained, and a thorough physical examination was performed. Special emphasis was given to the presence of symptoms/findings indicative of an underlying thyroid disease or any other disease causing dyslipidemia.

Additionally, the patients with hypothyroidism were reinvestigated after an euthyroid state was achieved by the administration of levothyroxine (L-T4) (75 μg daily) for three months, and normalization of plasma TSH.

Biochemical measurements:

After an overnight fast, venous blood samples were drawn and immediately put into heparinized tubes. As synthesis of homocysteine would take place in red blood cells after sampling, it was very important that centrifugation and separation of plasma from the blood cells to take place within 1 hour. The samples were kept on ice until separation [12]. Plasma was separated and divided into aliquots which were stored at -20^{o}C till assayed for: total homocystein (t-Hcy) and thyroid functions (T3, T4 and TSH). Also, assayed for plasma lipid profile including: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low- density lipoprotein cholesterol (LDL-c), and lipoprotein (a) [Lp(a)] concentrations.

Assay of total homocystein: Plasma t-Hcy levels were measured by an enzyme immunoassay for the determination of t-Hcy in plasma [13]. Protein – bound homocysteine was reduced to free homocysteine and enzymatically converted to S-adenosyl-L-homocysteine (SAH), by the use of SAH hydrolase and excess adenosine, in a separate procedure prior to the immunoassay [14]. The enzyme is specific for the L-form of homocysteine , which is the only form present in the blood. This was performed by the use of Axis® Homocysteine EIA kits supplied by Bio Rad Diagnostics Group, Axis Biochemicals, Oslo, Norway.

LP (a) was assayed by immunoprecipitin analysis

according to Gries et al [15]. The reagents were obtained ready for use from Incstar corp. USA.

- Plasma levels of total cholesterol [16], HDL cholesterol [17] and triglycerides [18] were estimated by kits of Bio-Meriuex Lab-France.

- Plasma LDL cholesterol was calculated according to Friedewald et al [19].

- Plasma T3 [20], and T4 [21] were determined by ELISA method using the kits from Diagnostic System Laboratories Inc., Webster, Texas, USA.

- Plasma TSH was assayed [22] by ELISA method using Immunotech kit, Marseille, France.

Statistical analysis:

Descriptive data are expressed as mean ± SD. Baseline characteristics of the hypothyroid subjects were compared with the hyperthyroid and control subjects by use of Mann-Whitney U test. The simple Pearson's correlation coefficient was used to evaluate the correlation between 2 variables. Baseline characteristics and response before and after thyroid hormone replacement were compared by use of Wilcoxon signed rank test. These tests were run on an IBM compatible personal computer using the Statistical Package of Social Scientists (SPSS) program for windows version 7.5 (SPSS Inc., Chicago, IL. USA). P value was considered significant if less than 0.05.

RESULTS

Table (1) summarizes laboratory data of hypothyroid and hyperthyroid patients as well as control subjects. Fasting t-Hcy levels were higher in patients with hypothyroidism versus hyperthyroid and control subjects (P = <0.01), while there was a non significant difference between hyperthyroid and control subjects. The increased t-Hcy in hypothyroidism was significantly correlated with high TSH and Lp (a) levels (r = 0.306, P = <0.01 & r = 0.476, P = <0.001, respectively) (Table 3).

The L-thyroxine dose in the treatment of hypothyroid group (75 µg daily) was adapted at 6-wk intervals to decrease the TSH concentration to the euthyroid reference range. Fasting plasma t-Hcy significantly decreased from 15.4 ± 7.5 to 9.6 ± 4.8 µmol/L (P = < 0.01), after recovery of euthyroidism in the group of hypothyroid patients table (2). These patients were rendered biochemically euthyroid, simultaneously with a marked improvement in plasma lipid profile, including a significant decrease of total cholesterol, LDL cholesterol, and Lp(a) levels (table 2)

Thyroid hormones:

TSH levels were significantly higher in hypothyroid patients than hyperthyroid patients and control subjects (P < 0.0001), whereas serum T3 and T4 levels, were significantlylower(P=0.001)table(1)
.After therapy, plasma TSH levels at the end of the study had returned within the normal range 3.98 ± 0.92 uIU/L in the L-thyroxine treated hypothyroid patients and were significantly lower than before treatment (P < 0.0001). Plasma T3 and T4 levels rose significantly in the L-T4-treated group (P = <0.05 and <0.001) respectively vs. before treatment (Table 2).

Plasma lipid profile:

Hypothyroid patients showed significantly higher plasma TC (P= < 0.001), LDL-c (P = 0.001). Significant positive relationships were found between plasma t-Hcy and both TC (r = 0.38; P = <0.01), and LDL-c (r = 0.63; P = <0.001) levels (Table 3). Elevated Lp (a) levels (>30 mg/dl) were significantly more frequent in hypothyroid patients vs. hyperthyroid patients and control subjects (P =< 0.001) (Table 1).

Significant positive relationships were found between plasma Lp(a) and each of TSH, TC, and HDL-c (r = 0.576, P = <0.001; r = 0.77, P = <0.001; r = 0.83 and P = <0.001) respectively (Table 3). After recovery of stable euthyroidism, L-T4-treated patients showed a significant decrease in plasma TC and LDL-c concentrations (P = 0.015 and 0.004 respectively) table (2). Also, Lp (a) levels were significantly lowered after the treatment of hypothyroid condition (P = 0.031). Moreover, HDL-c and triglycerides levels showed a non significant change (Table 2).

Table (1): ***Comparison of plasma t-Hcy levels and other laboratory data in hypothyroid and hyperthyroid patients as well as control subjects.***

Variable	*Group (1) Hypothyroidism (n=40)*	*Group (2) Hyperthyroid (n= 25)*	*Group (3) Control (n=25)*	*P Value* 1 vs. 2	1 vs. 3	2 vs.3
t-Hcy(µmol/L)	15.4 ±7.5	7.4 ± 2.9	7.9 ± 2.8	<0.01	<0.01	NS
T3 (ng/ml)	0.5 ± 0.29	2.92 ± 0.51	1.13 ± 0.21	<0.001	<0.001	<0.001
T4 (ug/dl)	2.74 ± 0.71	15.51± 1.58	7.1± 1.03	<0.001	<0.001	<0.001
TSH (uIU /L)	22.15 ± 3.28	0.30 ± 0.08	1.7 ± 0.6	<0.0001	<0.0001	<0.001
T.C (mg/dl)	291.0 ± 41.6	160.8 ± 14.9	169.3 ± 12.86	<0.001	<0.001	NS
HDL-c(mg/dl)	33.1± 6.7	41.7 ± 5.4	40.5 ± 4.8	<0.01	<0.01	NS
LDL-c (md/dl)	221.6 ± 41.1	123.1± 8.4	122.4 ± 9.09	<0.001	<0.001	NS
T.G (mg/dl)	176.0 ± 48.0	110.7± 16.4	115.0 ± 15.35	<0.01	<0.01	NS
Lp(a) (mg/dl)	39.8 ± 7.9	24.4 ± 6.7	23.5 ± 7.01	<0.001	<0.001	NS

Data are mean± SD
NS = Non significant.

Table (2): ***Plasma t-Hcy, lipid profile and thyroid functions, before and after treatment of hypothyroidism.***

Parameter	*Before treatment*	*After treatment*	*P*
t-Hcy (µmol/L)	15.4 ±7.5	9.6 ± 4.8	<0.01
TSH (uIU/L)	22.15 ± 3.28	3.98±0.92	<0.0001
T_3 (ng/ml)	0.5 ± 0.29	0.84± 0.13	<0.05
T_4 (µg/dl)	2.74 ± 0.71	7.38± 1.7	<0.001
T.C (mg/dl)	291.0 ± 41.6	234.0± 36.0	0.015
HDL-c (mg/dl)	33.1 ± 6.7	35.0 ± 5.1	NS
LDL-c (mg/dl)	221.6 ± 41.1	165.6 ± 32.5	0.004
T.G (mg/dl)	176.0 ± 48.0	160.0 ± 29.1	NS
Lp(a) (mg/dl)	39.8 ± 7.9	29.7 ± 6.3	0.031

Data are mean± SD
NS = Non significant.

Table (3): ***Pearson's correlation between t-Hcy and Lp (a) with the different variables in hypothyroid patients group (n = 40).***

Variable		*TSH*	*T_3*	*T_4*	*T.C*	*HDL-c*	*LDL-c*	*T.G*
t-Hcy	r =	0.306	- 0.59	-0.60	-0.38	-0.167	0.63	0.251
	P =	<0.01	<0.001	<0.001	<0.01	NS	<0.001	<0.05
Lp(a)	r =	0.576	-0.548	-0.174	0.83	-0.76	0.77	0.62
	P =	<0.001	<0.001	NS	<0.001	<0.001	<0.001	<0.001

DISCUSSION

Hyperhomocysteinaemia is a risk factor for premature atherosclerotic vascular disease and venous thrombosis [23]. It is thought to predispose to atherosclerosis by several mechanisms, including stimulation of LDL oxidation and endothelial dysfunction [24]. It is at least as important as cholesterol, lipoprotein abnormalities and hypertension and should be part of risk assessment, especially those at high risk[4] Hyperhomocysteinemia is regarded as a public health problem of increasing importance likely to contribute to vascular disorders and premature mortality[6].

We observed that t-Hcy level was statistically higher in hypothyroidism in comparison to hyperthyroid and healthy controls. On univariate analysis, fasting t-Hcy is positively related to TSH. The finding of high fasting t-Hcy in patients with hypoyhyroidism is in agreement with a retrospective report [24]. A strong inverse relationship between homocysteine and thyroid hormones confirms the effect of thyroid hormones on homocysteine metabolism [25]. Elevated plasma homocysteine levels were described in a preliminary report on primary hypothyroidism [26]. However, certain investigators have suggested that subjects with hypothyroidism have an increased risk for coronary artery disease, which may be related to atherogenic changes in lipid profile [24]. Moderately elevated total plasma homocysteine levels have been reported in patients with overt hypothyroidism, a condition that is associated with an increased risk for cardiovascular disease [27].

Hyperhomocysteinemia may arise from the shrinking of endogenous nitrogen pools as a result of decreased protein intake or stress-induced increased losses. Raised total homocysteine may result from the attempt of the malnourished and/or stressed body to preserve methionine homeostasis [7,8].

Catargi et al [24] reported that there are negative correlations between plasma homocysteine and serum folate and vitamin B12 concentrations. This may also be important because the enzyme 5,10-methylene tetrahydrofolate reductase (MTHFR) is responsible for the formation of 5-methyltetrahydrofolate, which functions as methyl donor during remethylation of homocysteine to methionine. Several experimental studies have shown that hypothyroidism affects folate metabolism and the enzymes involved in the remethylation of homocysteine and particularly MTHFR. Thus, the decrease of hepatic level of MTHFR may be relevant to the relation that we observed between t-Hcy and TSH. To test this hypothesis, Catargi and coworkers [24] performed a methionine challenge test, they found that recovery of euthyroidism normalized fasting t-Hcy and reduced postload elevated levels of t-Hcy, which confirmed the causal relationship between hyperhomocysteinemia and hypothyroidism. This might be because in situations of excess methionine the transsulfuration pathway is favored by upregulation of cystathionine β-synthase and downregulation of the remethylation pathway.

Recently, Shibata, et al [28] examined thyroidectomized chickens in terms of plasma lipid concentration and protein expression within the liver. An increase in phospholipid, triglyceride, and total cholesterol levels within the blood plasma of thyroidectomized chickens was observed, clearly reflecting increased lipid synthesis within the liver. Over expression of some proteins was observed in thyroidectomized chicken livers. The amino acid sequence of this protein showed a high degree of homology with the betaine-homocysteine S-methyltransferase (BHMT) of mammalian species. In the liver, after thyroidectomy, the synthesis of hepatic BHMT had already been enhanced. Generally, BHMT catalyzes the transfer of a methyl group from betaine to L-homocysteine. In addition, it seems that this enzyme is also closely related to lipid metabolism in the liver. Moreover, hypothyroidism may be directly or indirectly related to overexpression of BHMT [28].

The t-Hcy level of hyperthyroid patients did not differ significantly from that of the controls. Nedrebo,et al[29] reported that serum creatinine was higher in hypothyroid patients and lower in hyperthyroid patients than in controls, whereas serum folate was higher in hyperthyroid patients compared with the two other groups. Also, Diekman,et al[23] reported that the lower folate levels and creatinine clearance in hypo-thyroidism, and a higher creatinine clearance in hyperthyroidism only partially explain the changes in t-Hcy.

Elevated levels of homocysteine in hypothyroidism significantly decreased after correction[25].Thyroid hormones cause marked reduction in enzymes involved in the alternative transsulfuration pathway of homocysteine and particularly in betaine homocysteine transferase, which may balance the changes in MTHFR[24], providing another explanation for the restoration by thyroid replacement. So, Toft & Toft [30] recommend TSH screening of patients with unexplained hyperhomocysteinaemia.

In overt hypothyroidism the relationship between dyslipidemia and atherosclerosis is well established [3,25]. Further mechanisms are suggested to be involved in the association between thyroid failure and cardiovascular disease. These include a hypercoagulable state [31] and endothelial effects of thyroid hormones [32].

Because of the evidence linking raised Lp(a) concentrations with the development of atherosclerosis, attention has focused on serum Lp(a) levels in thyroid diseases[3]. This lipoprotein is synthesized mainly in the liver and consists of LDL particle bound to an apoprotein that is

structurally similar to plasminogen.

In this study Lp (a) levels were significantly higher in hypothyroid cases than in hyperthyroid and control subjects. A significant correlation between Lp(a) and LDL-c was observed. In this regard, hypothyroidism may be of particular interest, not only because several experimental studies have shown that hypothyroidism may decrease hepatic levels of enzymes involved in the remethylation pathway, but also because hypothyroidism may be associated with atherogenic lipid abnormalities, and particularly with elevated LDL[33]. It is possible that hypercholesterolemia due to other causes may be exaggerated when hypothyroidism supervenes. Thus, a high level of suspicion of clinical or even subclinical hypothyroidism as a cause of hyperlipidemia is mandatory in the lipid clinic [24]. This viewpoint is strengthened by the fact that the development of hypothyroidism is insidious and significant hypercholesterolemia may develop before the clinical features of hypothyroidism are apparent. In some patients with hypothyroidism, inadequate response to hypolipidemic drugs was evident, which may also be a clue pointing towards the diagnosis of an underlying disease, such as thyroid dysfunction [34]. Thus, in the era of widespread cholesterol screening, a growing number of patients with minimal thyroid failure may present with hypercholesterolemia rather than the more traditional features of hypothyroidism.

Thyroid disorders are known to influence lipoprotein metabolism. The study performed by Tsimihodimos et al [34] clearly showed that thyroid function abnormalities are not rare in patients attending a lipid clinic. In patients with hypothyroidism, there is often an increase in the serum cholesterol concentrations due to the raised levels of serum low-density lipoproteins (LDL) and intermediate-density lipoproteins (IDL). Less consistently, there is hypertriglyceridemia associated with an increase in VLDL and occasionally fasting chylomicronemia [24]. Recent data have also shown that serum Lp(a) levels are modulated by thyroid hormones with Lp(a) levels being elevated in hypothyroidism and decreased in hyperthyroidism[3,35]. In severe hyperthyroidism, a decrease of total cholesterol, LDL cholesterol and apoprotein B concentrations are generally observed. These biological parameters are normalized when appropriate antithyroid treatment is given. In profound hypothyroidism, on the contrary, elevated levels of total and LDL cholesterol (LDL-c) levels are observed, which decrease after hormonal replacement. In both cases, the changes in serum levels of HDL cholesterol (HDL-c), triglycerides and Lp (a) are less systematic, both before and after treatment[1].

The decision to treat patients with mild thyroid failure is based on the fact that some symptoms may be reversed by hormone supplementation and that therapy prevents progression to the overt stage of hypothyroidism. Furthermore, L-thyroxine (L-T4) therapy is indicated in special clinical conditions, such as goiter, thyroidectomy, depression, infertility, and endocrine ophthalmopathy [2]. L-T4 treatment is generally considered in two prospects: 1- to prevent progression to overt hypothyroidism and 2- to reduce symptoms of thyroid hormone deficiency [3].

The potential favorable influence of levothyroxine treatment on Lp (a) levels in patients with hypothyroidism should be emphasized. In our study, increased Lp (a) levels were evident in patients with hypothyroidism. The significant reduction in total and LDL-c as well as in Lp(a) levels, that were observed in our hypothyroid patients after L-thyroxine treatment, is in close agreement with previously published data [2,35]. A mean decrease in serum LDL-c, as documented in L-thyroxine-treated patients, corresponds to an important risk reduction [2]. Tzotzas, et al [35] reported that in overt hypothyroidism, Lp(a) levels and most of the lipoproteins were elevated before treatment and decreased significantly during L-thyroxine treatment. Also, Meier and coworkers [2] designed their study to show that physiological L-thyroxine replacement in patients with hypothyroidism has a beneficial effect on LDL-c levels and clinical symptoms of hypothyroidism. Regarding our findings of a definite improvement in the plasma lipoprotein profile, we advocate replacement therapy in patients with mild thyroid failure and hypercholesterolemia, in particular in the presence of other cardiovascular risk factors. Also, our data are in accordance with 2 recent meta-analyses that calculated a beneficial effect of L-thyroxine on serum cholesterol concentrations [36,37]. In a quantitative review of 13 intervention trials Danese and coworkers [37] reported similar reductions of total cholesterol and LDL-c levels. Also, Bicikova et al [25] reported that correction of thyroid function led to normalization of elevated levels of total cholesterol and triglycerides in hypothyroidism, along with a significant increase in HDL-c. Thus, the results from the present study are in agreement with those of several intervention trials. Obviously, inherently elevated Lp (a) levels may conspire with the raised LDL-c of untreated hypothyroidism to enhance cardiovascular risk [3]. However, overdose with unphysiological (not TSH-controlled) T4 treatment can produce overt or mainly subclinical hyperthyroidism with TSH suppression [2].

So, the increase in both plasma t-Hcy, Lp(a) and plasma cholesterol may confer increased cardiovascular risk in hypothyroid patients [10]. Hyperhomocysteinemia and hypercholesterolemia could help to explain the increased risk for arteriosclerotic coronary artery disease in hypothyroidism [38].

CONCLUSIONS:

We confirmed the observation of hyperhomocysteinemia in hypothyroidism, which together

with the elevated plasma lipoprotein (a) may contribute to an accelerated atherogenesis in these patients. As hypothyroidism may be a treatable cause of hyperhomocysteinemia, and as fasting t-Hcy is associated with a significant increased relative risk of coronary artery disease, measurement of t-Hcy to screen this dynamic association of cardiovascular risk factors during hypothyroidism may be of interest.

REFERENCES

1. Deschampheleire M, Luyckx FH, Scheen AJ. (1999): Thyroid disorders and dyslipidemias. [Article in French] Rev Med Liege; 54(9):746-50.

2. Meier C , Staub J, Roth C , Guglielmetti M , Kunz M , Miserez A. R., Drewe J , Huber P , Herzog R, and Müller B.(2001): TSH-Controlled L-Thyroxine Therapy Reduces Cholesterol Levels and Clinical Symptoms in Subclinical Hypothyroidism: A Double Blind, Placebo-Controlled Trial (Basel Thyroid Study). The Journal of Clinical Endocrinology & Metabolism Vol. 86, No. 10 4860-4866

3. Caraccio N, Ferrannini E, Monzani F. (2002): Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab; 87(4):1533-8

4. Sarkar PK, Lambert LA. (2001): Aetiology and treatment of hyperhomocysteinaemia causing ischaemic stroke.Int J Clin Pract; 55(4):262-8

5. Duell PB, Malinow R. (1997): Homocysteine: An important risk factor for atherosclerotic vascular disease. Curr Opin Lipidology; 8:28-34.

6. Ingenbleek Y, Hardillier E, Jung L. (2002): Subclinical protein malnutrition is a determinant of hyperhomocysteinemia. Nutrition; 18(1):40-6

7. Salles-Montaudon N, Parrot F, Balas D, Bouzigon E, Rainfray M, Emeriau JP. (2003): Prevalence and mechanisms of hyperhomocysteinemia in elderly hospitalized patients. J Nutr Health Aging; 7(2):111-6

8. Laraqui A, Bennouar N, Meggouh F, Allami A, Kadiri NE, Benkouka F, Azeddoug H, Haitem NE, Benomar A, Fellat S, Benomar M.(2002): Homocysteine, lipoprotein (a): risk factors for coronary heart disease. Ann Biol Clin (Paris); 60(5):549-57.

9. Roscini AR, Lupattelli G, Siepi D, Pagliaricci S, Pirro M, Mannarino E. (1999): Low-density lipoprotein size in primary hypothyroidism. Effects of hormone replacement therapy. Ann Nutr Metab; 43(6):374-9.

10. Lien EA, Nedrebo BG, Varhaug JE, Nygard O, Aakvaag A, Ueland PM. (2000): Plasma total homocysteine levels during short-term iatrogenic hypothyroidism. J Clin Endocrinol Metab; 85(3):1049-53

11. Luboshitzky R, Aviv A, Herer P, Lavie L. (2002): Risk factors for cardiovascular disease in women with subclinical hypothyroidism. Thyroid; 12(5):421-5

12. Ubbink JB, Vermaak WJH, Van der Merwe A, Becker PJ (1992): The effect of blood sample aging and food consumption on plasma total homocysteine levels. Clinica Chemica Acta; 207:119-128.

13. Frantzen F., Faaren Al., Alfheim I., and Nordhei AK. (1998): an enzyme conversion immunoassay for determining total homocysteine in plasma or serum. Clin. Chem; 44: 311-316.

14. Ueland PM., Refsum H., Stabler SP., Malinow R., Andersson A., Allen RH. (1993): Total homocysteine in plasma or serum: Methods and clinical applications. Clin. Chem; 39:1764-1779.

15. Gries A., Nimpf J., Nimpf M., Wurm H., and Kostner GM. (1987): Free and apo-B associated LP (a) - specific protein in human serum. Clinica Chemica Acta. 164: 93-100.

16. Allian CC, Poll LS, Richmond W and Fu PC (1974): Enzymatic determination of total serum cholesterol. Clin. Chem.20:470 – 475.

17. Warnick GR., Benderson J., and Albers JJ. (1982): Dextran sulphate-Mg +2 precipetation procedure for quantitation of high density lipoproteincholesterol. Clin.Chem; 28:1379-87.

18. Wahlefeld AW. (1974): Triglycerides determination after enzymatic hydrolysis. In:Bergmyere H.W.(ed.)Methods of enzymatic analysis . Academic Press, New York .P.18.

19. Friedewald W.T.,Levy R.I.and Frdrickson D.S. (1972): Estemation of concentration of LDLcholesterolcholesterol in plasma . Clin.Chem; 18:499-502.

20. Sterling L. (1975): Diagnosis and treatment of thyroid disease. Cleveland CRC Press. P.19-51.

21. Liewendahl K. (1990): Assessment of thyroid status by laboratory methods: development and prospectives. Scand J Clin Invest. 50 (suppl 201): 83-92.

22. Woodhead JS., Weeks I. (1995): Circulating thyrotropin as an index of thyroid function. Ann. C lin. Biochem. 22:455-459.

23. Diekman MJ, Van der Put NM, Blom HJ, Tijssen JG, Wiersinga WM. (2001): Determinants of changes in plasma homocysteine in hyperthyroidism and hypothyroidism. Clin Endocrinol (Oxf); 54(2):197-204

24. Catargi B; Parrot-Roulaud F; Cochet C; Ducassou D; Roger P; and Tabarin A; (1999): Homocysteine, hypothyroidism, and effect of thyroid hormone replacement. Thyroid.Vol.9 Number 12: 1163-1174.

25. Bicikova M, Hampl R, Hill M, Stanicka S, Tallova J, Vondra K. (2003): Steroids, sex hormone-binding globulin, homocysteine, selected hormones and markers of lipid and carbohydrate metabolism in patients with severe hypothyroidism and their

changes following thyroid hormone supplementation. Clin Chem Lab Med; 41(3):284-92

26. Hussein WI, Green R, Jacobsen DW, Faiman C. (1999): Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism. Ann Intern Med. 7; 131(5):348-351.

27. Deicher R, Vierhapper H. (2002): Homocysteine: a risk factor for cardiovascular disease in subclinical hypothyroidism? Thyroid; 12(8):733-6

28. Shibata T, Akamine T, Nikki T, Yamashita H, Nobukuni K. (2003): Synthesis of betaine-homocysteine S-methyltransferase is continuously enhanced in fatty livers of thyroidectomized chickens. Poult Sci; 82(2):207-13

29. Nedrebo BG, Ericsson UB, Nygard O, Refsum H, Ueland PM, Aakvaag A, Aanderud S, Lien EA.(1998): Plasma total homocysteine levels in hyperthyroid and hypothyroid patients.Metabolism;47(1):89-93.

30. Toft JC, Toft H. (2001): Hyperhomocysteinemia and hypothyroidism. Ugeskr Laeger.20; 163(34):4593-4.

31. Muller B, Tsakiris DA, Roth CB, Guglielmetti M, Staub JJ, Marbet GA (2001): Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. Eur J Clin Invest 31:131–137

32. Sellitti DF, Dennison D, Akamizu T, Doi SQ, Kohn LD, Koshiyama H (2000): Thyrotropin regulation of cyclic adenosine monophosphate production in human coronary artery smooth muscle cells. Thyroid 10:219–225

33. O`Brien T, Katz K, Hodge D, Nguyen TT, Kottke BA, Hay ID.(1997): The effect of the treatment of hypothyroidism and hyperthyroidism on plasma lipids and apolipoproteins AI,AII and E. Clin Endocrinol; 46: 17-20.

34. Tsimihodimos V, Bairaktari E, Tzallas C, Miltiadus G, Liberopoulos E, and Elisaf M. (1999): The incidence of thyroid function abnormalities in patients attending an outpatient lipid clinic.THYROID.Vol.9, Number 4: 365 – 368.

35. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. (2000): Changes in lipoprotein (a) levels in overt and subclinical hypothyroidism before and during treatment.Thyroid; 10(9):803-808.

36. Tanis BC, Westerndorp GJ, And Smelt AHM (1996): Effect of thyroid substitution on hypercholesterolemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. Clin Endocrinol (Oxf) 44:643–649.

37. Danese MD, Ladenson PW, Meinert CL, Powe NR (2000): Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endocrinol Metab 85:2993–3001.

38. Morris MS, Bostom AG, Jacques PF, Selhub J, Rosenberg IH. (2001): Hyperhomocysteinemia and hypercholesterolemia associated with hypothyroidism in the third US National Health and Nutrition Examination Survey.Atherosclerosis; 155(1):195-200