

# Influence of Thyroid Function on Lipid Profile in Autoimmune Thyroiditis: Clinical and Experimental Insights

Najmutdinova D. K.<sup>1</sup>, Nasirova A. K.<sup>1</sup>, Rasulov A. D.<sup>2,\*</sup>

<sup>1</sup>Endocrinology, Department of Internal Diseases №2, Tashkent Medical Academy, Tashkent, Uzbekistan

<sup>2</sup>Anesthesiology and Resuscitation, Tashkent Medical Academy, Tashkent, Uzbekistan

**Abstract** Autoimmune thyroiditis (AIT) is a chronic disorder characterized by gradual onset, nonspecific early symptoms, and slow progression involving destructive processes in the thyroid gland. AIT ranks among the most prevalent thyroid diseases, contributing to 20-50% of thyroid pathology cases. Despite extensive data on thyroid tissue antibody prevalence and hypothyroidism frequency, AIT affects 3-20% of the global population, constituting 70-80% of primary hypothyroidism instances. Hypothyroidism is recognized as an atherogenesis initiator due to significantly elevated cholesterol levels, impeding lipid oxidation, transportation, and elimination, thereby accelerating atherosclerosis. The lipid profile alterations, including increased low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), along with decreased high-density lipoprotein cholesterol (HDL-C), exacerbate atherogenicity. L-thyroxine therapy in subclinical hypothyroidism mitigates atherogenic lipid changes. Thyroxine levels profoundly impact serum cholesterol and bone mineral density, potentially inhibiting atherosclerosis progression. Dyslipidemia in hypothyroidism involves reduced lipid breakdown, transportation, and bile excretion, alongside diminished LDL receptor quantity and activity. Hypercholesterolemia in hypothyroidism often remains refractory to conventional lipid-lowering therapies but improves with thyroid hormone supplementation. The lipid profile in primary hypothyroidism leans towards atherogenicity, accentuated in severe thyroid hormone deficiency, while anti-atherogenic lipid fractions remain relatively unaffected. Our study aimed to explore the influence of thyroid function on the lipid profile. Evaluating 73 AIT patients' blood samples and 58 healthy donors, we observed elevated thyroid-stimulating hormone levels in manifest and subclinical hypothyroidism phases. Lipid profile analysis revealed significant increases in total cholesterol and triglycerides, along with decreased HDL-C, particularly in overt hypothyroidism. LDL-C levels rose markedly across AIT phases, exacerbating atherogenicity, with overt hypothyroidism displaying the most pronounced effects. Our findings underscore the atherogenic nature of the lipid profile in hypothyroidism, especially in its overt phase, highlighting the importance of thyroid function assessment in managing dyslipidemia and cardiovascular risk in AIT patients.

**Keywords** Autoimmune thyroiditis, Hypothyroidism, Lipid profile, Cholesterol, Triglycerides, LDL-C, HDL-C

## 1. Introduction

AIT (Autoimmune thyroiditis) is a chronic disease with a gradual onset, nonspecific early signs, and slow progression with increasing destructive processes in the thyroid gland. AIT is one of the most common thyroid diseases, accounting for 20 to 50% of thyroid pathology [1]. There is extensive information available on the prevalence of thyroid tissue antibody carriage and the frequency of hypothyroidism in the population. However, according to available data, 3 to 20% of the world's population currently suffers from AIT, which accounts for 70-80% of all cases of primary hypothyroidism

[3,5]. In various countries, AIT is encountered with a frequency of 0.1 to 1.2% in children and 6 to 11% among the adult population [3,5,6].

According to numerous clinical and experimental studies, hypothyroidism is widely recognized as one of the initiators of atherogenesis, as it has been established that a deficiency of thyroid hormones significantly increases cholesterol levels [2,18,21,23,26]. Additionally, its oxidation slows down, transportation and elimination of triglycerides, low-density lipoproteins (LDL), and very-low-density lipoproteins (VLDL) worsen. Decreased elimination of atherogenic lipids leads to an increase in the atherogenicity coefficient and accelerated development of atherosclerosis, the clinical manifestations of which become predominant and create specific challenges in diagnosing thyroid gland hypofunction [4,9,10].

\* Corresponding author:

akirasulov@gmail.com (Rasulov A. D.)

Received: Apr. 9, 2024; Accepted: May 6, 2024; Published: May 9, 2024

Published online at <http://journal.sapub.org/ajmms>

For instance, some authors have presented results of a comparative assessment of the level of lipoprotein A in plasma in patients with hypothyroidism, hyperthyroidism, and euthyroid individuals. According to the researchers, the level of lipoprotein A in patients with hyperthyroidism and euthyroid individuals did not significantly differ. However, a significant decrease in the plasma level of lipoprotein A compared to patients with hyperthyroidism was found in patients with hypothyroidism. Individual analysis of the study results revealed that the level of lipoprotein A exceeding 30 mg/dL was registered in 37.5% of cases in patients with hypothyroidism, in 13.6% of patients with hyperthyroidism, and in 15.3% of euthyroid individuals. Compared to lipid metabolism indicators in euthyroid individuals, patients with hypothyroidism showed decreased levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apoB). In patients with hyperthyroidism, compared to euthyroidism, a decreased level of LDL-C and increased levels of HDL-C and apolipoprotein AI (apoAI) were determined.

The influence of L-thyroxine on the levels of various lipoproteins in long-standing subclinical hypothyroidism was also studied. Before treatment, researchers found significantly higher levels of triglycerides, LDL-C, apoB, and lipoprotein A in all patients, correlating with TSH levels. After 6 months of L-thyroxine therapy, only triglyceride and LDL-C levels among all lipid metabolism parameters studied were decreased. Based on the obtained results, it was concluded that atherogenic changes in the lipid profile in subclinical hypothyroidism undergo reversal during L-thyroxine replacement therapy.

In the opinion of several researchers, the main factor determining the level of serum cholesterol and bone mineral density is the level of T4. Adequate replacement therapy with thyroid hormones leads to normalization of the average values of basic lipid metabolism indicators, which may contribute to the inhibition of atherosclerosis progression [24,27,28,31].

During the studies, an elevated level of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) in the blood serum of patients with decreased thyroid function was also identified. Researchers note that the level of high-density lipoproteins (HDL) in these patients remains unchanged or decreases. According to the authors, the mechanism underlying hypercholesterolemia in hypothyroidism involves a decrease in the rate of synthesis and particularly the breakdown of lipids, deterioration of their transportation and excretion with bile, and a decrease in the quantity and activity of LDL receptors.

According to some data, in patients with hypothyroidism, the cholesterol level remains elevated despite adequate replacement therapy, necessitating the prescription of a hypocholesterolemic diet alongside hypocholesterolemic therapy. Additionally, M.D. Dániés et al. argue that hypercholesterolemia detected in hypothyroidism is not responsive to treatment with diet, statins, and other lipid-lowering

agents but is effectively corrected only by thyroid hormone preparations.

The results of a comparative assessment of the blood lipid spectrum in patients suffering from primary hypothyroidism of varying severity compared to patients with autoimmune thyroiditis and euthyroid individuals are presented in a study by Yu.N. Grishkin et al. According to the researchers, the lipid profile in patients with primary hypothyroidism becomes atherogenic in conditions of pronounced thyroid hormone deficiency, while the concentration of anti-atherogenic lipid fractions remains unchanged.

Numerous foreign studies have shown that a 7% decrease in LDL-C levels allows for a 15% reduction in the risk of developing coronary heart disease (CHD). The results of a meta-analysis of several multicenter studies on the effectiveness of secondary prevention of CHD using lipid-lowering agents indicate that the progression of the atherosclerotic process stops when LDL-C levels are reduced by 44%. An increase in TSH levels by 1 mIU/L is accompanied by an increase in total cholesterol levels by 0.09 mmol/L in women and by 0.62 mmol/L in men. However, researchers did not find a significant correlation between TSH levels and LDL-C, indicating the development of hyperlipidemia in the examined patients due to causes other than hypothyroidism [29].

Novitskaya A.B. (2004) studied the level of lipid peroxidation activity and the state of the body's antioxidant defense system in patients with various phases of autoimmune thyroiditis. According to the author, the level of lipid peroxidation and antioxidant system activity in autoimmune thyroiditis during the euthyroid phase is not significantly disturbed. In patients with autoimmune thyroiditis during the subclinical hypothyroidism phase, activation of free radical oxidation, depletion of the body's antioxidant defense, and accumulation of lipid peroxidation intermediates are registered. Thus, the severity of lipid peroxidation changes in autoimmune thyroiditis is closely related to the degree of thyroid dysfunction.

Alongside dyslipidemia and disturbances in central and intracardiac hemodynamics in hypothyroidism, abnormalities in the thrombotic-vascular and coagulation links of the hemostasis system and blood fibrinolytic activity have been detected. Most researchers have found an increase in the level and activity of plasminogen activator inhibitor, platelet aggregation activity, and a high concentration of activated factor VII in patients with hypothyroidism. It is believed that fibrinolytic activity in hypothyroidism is usually somewhat increased. Nevertheless, some researchers have obtained opposite results, indicating a lack of consensus on changes in blood fibrinolytic activity in hypothyroidism.

## 2. Materials and Methods

The study used samples of venous blood from 73 patients with autoimmune thyroiditis and 58 healthy donors, constituting the control group. The level of total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), very-low-density lipoproteins (VLDL), the atherogenic

coefficient, and triglycerides (TG) in the blood serum were determined by an enzymatic method using a Mindray autoanalyzer (China) with reagents from "Human" company (Germany). Reagents from the same company were used as control material.

### 3. Results and Discussions

The evaluation of thyroid gland hormonal activity and the level of antibodies to thyroperoxidase in the study groups are presented in Table 1.

As seen from the data in Table 1, patients with autoimmune thyroiditis in the phase of manifest and subclinical hypothyroidism showed a significant increase in the level of thyroid-stimulating hormone compared to the control group and the group of individuals in the euthyroid phase ( $p < 0.05$ ).

At the same time, the concentration of thyroid-stimulating hormone in manifest hypothyroidism was significantly higher than in individuals with subclinical hypothyroidism.

The euthyroid phase was characterized by a tendency to increase thyroid-stimulating hormone compared to the control group.

In the group of individuals with manifest hypothyroidism, a significant decrease in the level of free thyroxine was observed compared to the levels of patients with other phases of autoimmune thyroiditis (AIT) and the control group ( $p < 0.05$ ), while in patients with euthyroidism and subclinical hypothyroidism, it did not differ from the corresponding indicator in the control group.

Upon analysis of indicators characterizing the activity of the autoimmune process, a significant increase in the level of antibodies to thyroperoxidase (anti-TPO) was registered in all patients with AIT compared to the indicators of the control group ( $p < 0.05$ ). At the same time, the highest concentrations of anti-TPO antibodies were found in individuals with subclinical hypothyroidism ( $p < 0.05$ ) compared to the indicators of patients in the euthyroid and manifest hypothyroidism phases.

Thus, the level of thyroid gland functional activity in autoimmune thyroiditis, evaluated in our study by the concentrations of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) in the blood serum, is determined by the phase of the disease. The concentration of TSH in AIT progressively increases: from a tendency to increase its level in the euthyroid phase - through an increase in the hormone concentration in the subclinical course of the disease - to a pronounced increase in the plasma concentration of thyroid-stimulating hormone in manifest hypothyroidism, which is consistent with modern hypothyroidism syndrome diagnostics.

It should be noted that changes in the level of free thyroxine in the plasma in AIT, depending on the phase of the disease, are not as straightforward. The results of our studies indicate that in AIT during the euthyroid phase and subclinical hypothyroidism, a normal level of FT4 is registered, whereas in the manifest course of the disease, a significant decrease in the level of this hormone is established.

**Table 1.** Indicators of Thyroid Hormonal Activity and Levels of Thyroid Peroxidase Antibodies in the Studied Groups

Indicator	Control Group (n = 58)	Clinical Phase of Autoimmune Thyroiditis		
		Euthyroidism (n = 45)	Subclinical Hypothyroidism (n = 18)	Manifest Hypothyroidism (n = 10)
Thyrotropin hormone concentration (TSH), mIU/mL	1,48±0,79	1,6±0,14	6,2±0,36*	23,1±2,91*
Free thyroxine level (FT4), pmol/L	13,8±3,2	14,0±2,5	14,5 ± 2,5	5,6±2,2*
Antithyroid peroxidase antibodies (TPOAb) level, IU/mL	16,9±7,1	516,9±55,6*	726,9 ± 116,9*	454,1 ± 76,1*

**Table 2.** Clinical Phase of Autoimmune Thyroiditis

Parameter	Control Group (n = 58)	Clinical Phase of Autoimmune Thyroiditis		
		Euthyroid (n = 30)	Subclinical Hypothyroidism (n = 30)	Manifest hypothyroidism (n = 30)
Total Cholesterol (mmol/L)	4,79±0,40	5,19±0,96	5,89±1,37**	6,35±1,16** <sup>†</sup>
Triglycerides (mmol/L)	1,10±0,46	1,19±0,41	1,52±0,79	1,59±0,57*
High-Density Lipoproteins (mmol/L)	1,64±0,41	1,35±0,33	1,22±0,35*	1,45±0,56
Low-Density Lipoproteins (mmol/L)	2,61±0,38	3,33±0,92	4,03±1,33**	4,17±1,38*
Very Low-Density Lipoproteins (mmol/L)	0,50±0,19	0,54±0,21	0,69±0,36	0,72±0,26*
Atherogenic Coefficient (rel. units)	2,10±0,89	3,04±0,13*	4,31±2,00*** <sup>††</sup>	4,04±2,16*

\*\*Table Notes\*\*: \* -  $p < 0.05$ ; \*\* -  $p < 0.005$  denotes significance compared to the control group; + - significance between values in the Euthyroid (E) and Subclinical Hypothyroidism (SH) phases ( $p < 0.05$ ), † - significance between values in the Euthyroid (E) and Overt Hypothyroidism (OH) phases ( $p < 0.05$ ).

The obtained results of assessing the level of antibodies to thyroperoxidase in autoimmune thyroiditis indicate an increase in the activity of the autoimmune process in the euthyroid phase and subsequent subclinical hypothyroidism. However, in patients with manifest hypothyroidism, a decrease in the level of the investigated antibodies compared to the euthyroid and subclinical courses of AIT was detected, but the level of anti-TPO antibodies is significantly higher compared to the control group. Thus, the assessment of the level of antibodies to thyroperoxidase as a criterion for the activity of the autoimmune process is ambiguous due to the possibility of determining these immunological markers in healthy individuals. Anti-TPO antibodies have the ability to cause cytotoxic changes in the structural elements of the thyroid follicles, and their level can be considered as one of the criteria leading to the atrophic form and a decrease in thyroid gland function. For the verification of the diagnosis of AIT, a comprehensive approach should be used, including the assessment of the hormonal status of the thyroid gland with consideration of ultrasound data of the thyroid gland and the results of clinical and anamnestic examination of the patient.

The results of the study on the lipid profile of plasma in patients with autoimmune thyroiditis (AIT) and individuals in the control group are presented in Table 2. Compared to the control group, patients with AIT in the euthyroid phase showed a statistically non-significant increase in total cholesterol (TC) levels by 7.7% ( $p < 0.05$ ), while in the subclinical variant of AIT, there was a statistically significant increase in TC plasma content by 18.2% ( $p < 0.05$ ). However, patients with overt hypothyroidism showed a statistically significant increase in TC levels by 32.6% ( $p < 0.05$ ) compared to the control group. Similar dynamics were observed in triglyceride (TG) concentrations across the analyzed groups. Specifically, compared to the control group, patients with AIT in the euthyroid phase and subclinical hypothyroidism showed a non-significant increase in TG levels by 8.2% and 27.7% ( $p > 0.05$ ), respectively, while those with overt hypothyroidism demonstrated a significant increase in TG content by 44.5% ( $p < 0.05$ ).

When analyzing the levels of high-density lipoprotein cholesterol (HDL-C), it was found that in the subclinical variant of AIT, the concentration of this anti-atherogenic lipid fraction in blood serum was significantly lower than in the control group, whereas the decrease in HDL-C levels in patients with overt hypothyroidism was statistically insignificant.

The level of low-density lipoprotein cholesterol (LDL-C) in the analyzed groups of patients with AIT was elevated in all clinical variants of the disease compared to the control group. Thus, in patients with euthyroidism, a statistically non-significant increase in LDL-C concentration by 27.5% ( $p > 0.05$ ) was observed, while in patients with overt hypothyroidism, the increase in LDL-C levels was statistically significant ( $p < 0.05$ ) compared to the control group of healthy individuals.

The lipid metabolism status in patients with AIT, compared to subclinical hypothyroidism, showed a significant

increase in low-density lipoprotein cholesterol levels by 54.4% and 59.8% ( $p < 0.05$ ), respectively, compared to the control group of healthy individuals.

The serum cholesterol levels of very low-density lipoproteins (VLDL-C) in patients with autoimmune thyroiditis (AIT) in the euthyroid phase and in the subclinical course of the disease were elevated but did not reach statistical significance compared to healthy individuals in the control group. However, in overt hypothyroidism, a statistically significant increase in VLDL-C levels by 44% ( $p < 0.05$ ) was observed compared to the control group.

## 4. Conclusions

Thus, the lipid profile in patients with subclinical and overt hypothyroidism exhibits an atherogenic nature, most pronounced in the overt phase of the disease. Meanwhile, the level of anti-atherogenic lipid fraction in the analyzed groups of AIT patients did not significantly differ from that of healthy individuals. Our findings are consistent with data from the majority of domestic and foreign researchers [2,18,23,26].

## REFERENCES

- [1] Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study / A.M. Kanaya [et al.] // Arch. Intern. Med. 2002. Vol. 162. P. 773 - 779.
- [2] Blood coagulation and fibrinolytic activity in hypothyroidism / C. Erem [et al.] // Int. J. Clin. Pract. -2003.- Vol. 57, № 2. - P. 78-81.
- [3] Changes in plasma low-density lipoprotein (LDL) - and high-density lipoprotein cholesterol in hypo- and hypothyroid patients are related to changes in free thyroxine, not to polymorphisms in LDL receptor or cholesterol ester transfer protein genes / M. Diekmann [et al.] // J. Clin. Endocrinol. Metab.- Vol. 85, № 5.- P. 1857-1862.
- [4] Circulating levels of oxidized low-density lipoprotein in overt and mild hypothyroidism / L.H. Duntas [et al.] // Thyroid. 2002.- Vol. 12. -P. 1003 - 1007.
- [5] Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature / M. D. Danese // J. Clin. Endocrinol. Metab. -2000.- Vol. 85 (9).- P. 2993-3001.
- [6] Components of the fibrinolytic system are differently altered in moderate and severe hypothyroidism / R. Chadarevian [et al.] // J. Clin. Endocrinol. Metab.-200.- Vol. 86, N 2.- P. 732-737.
- [7] Decreased activity of lecithin: acyltransferase and hepatic lipase in chronic hypothyroid rats: implications for reverse cholesterol transport / M. Franco [et al.] // Mol. Cell. Biochem. -2013. -Vol. 246.- P. 51-56.
- [8] Duntas LH. Thyroid disease and lipids / L.H. Duntas // Thyroid. 2002. Vol.12 P. 287-293.

- [9] Duntas L.H. Lipoprotein(a) and apolipoprotein(a) isoform size in thyroid disease: the quest for the golden fleece / L.H. Duntas // *Thyroid*. - 2023. -Vol. 13 -P. 345 -346.
- [10] Effect of thyroid hormone on plasma apolipoproteins and apo-A and apo B- containing lipoprotein particles / X.Q. Liu [et al.] // *Eur. J. Clin. Invest.* Vol. 28. P. 266 - 270.
- [11] Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease / B. Muller [et al.] // *Eur. J. Clin. Invest.* -2011. - Vol.31, N 2. - P. 131-137.
- [12] Hepatic lipogenesis and cholesterol synthesis in hypothyroid patients / A. Cachefo [et al.] // *J. Clin. Endocrinol. Metab.* -2001. -Vol. 86.- P. 5353 - 5357.
- [13] Hofbauer L.C. Coagulation disorders in thyroid disease / L.C. Hofbauer, A. Heufelder // *Eur. J. Endocrinol.*- Vol.136.- P.782-787.
- [14] Lipid profile in subclinical hypothyroidism is L-thyroxine substitution beneficial? / Z. Efsthadiadou [et al.] // *Eur. J. Endocrinol.* 2001. Vol. 145. P. 705- 710.
- [15] Lipoprotein (a) levels and apolipoprotein (a) isoform size in patients with subclinical hypothyroidism: effect of treatment with levothyroxine / H.J. Millonis [et al.] // *Thyroid*. 2003.- Vol. 13.- P. 365 - 369.
- [16] Lipoprotein profile in subclinical hypothyroid: response to levothyroxine replacement, a randomised placebo-controlled study / N. Caraccio // *J. Clin. Endocrinol. Metab.*- 2002.- Vol. 87.- P. 1533 - 1538.
- [17] Low cholesteryl ester transfer protein (CETP) concentration, normal CETP activity in serum from patients with shortterm hypothyroidism. Lack of relationship to lipoprotein abnormalities / Dredecjus M. [et al.] // *Clin. Endocrinol.* -2003. - Vol. 58.- P. 581 -588.
- [18] Prediction of cardiovascular ill mortality in elderly people from one low serum thyrotropin result: a 10-year cohort N111 (1) / J.V. Parle [et al.] // *Lancet*. -2001. -Vol. 358. - P. 861 - 865.
- [19] Shin D.J. Thyroid hormone regulation and cholesterol metabolism are connected through Sterol Regulatory Element-Binding Protein (SREBP-2) / D.J. Shin, T.E. Osborne // *J. Biol. Chem.* -2003. -Vol. 278. - P. 34114-34118.
- [20] The prevalence of sub30. clinical hypothyroidism at different total plasma cholesterol levels in middle aged men and women: a need for case finding / A.J. Bindels [et al.] // *Clin. Endocrinol.* Vol. 50. P. 217-220.
- [21] Thompson C. Dietary recommendations for iodine around the world / C. Thompson // *IDD Newsletter*.-2002.- Vol. 18, № 3.- P. 38^12.
- [22] Thyroid and lipid metabolism / A. Puccl [et al.] // *Int. J. Obes. Relat. Molnb. Disord.* -2000- Suppl. 2.- P. 109 - 112.
- [23] Nikolaeva A.V. Lipid metabolism and functional status of the kidney in hypothyroid patients depending on the phase of disease / A.V.Nikolaeva, L.T. Pimenov // *Ter. Arkh.* -2002. -Vol. 74.- P. 20-23.
- [24] Yestestvennoe techenie subklinicheskogo gipotireoza / Yu.P. Sych [i dr.] // *Klinicheskaya i eksperimental'naya tireidologiya*.-2005.-T. 1.- № 1.- S.43-47.
- [25] Thyroid hormone and adrenergic signaling in the heart / B. Kim [et al.] // *Arq. Bras. Endocrinol. Metabol.*- 2004.- Vol.48, № 1.- P. 171-175.