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CLINICAL AND METABOLIC PARAMETERS AND LOW-GRADE INFLAMMATION IN PATIENTS WITH AUTOIMMUNE HYPOTHYROIDISM

321.02 – ENDOCRINOLOGY

Abstract of the Doctoral Dissertation in Medical Sciences

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This thesis was prepared at the Department of Endocrinology, "Nicolae Testemițanu" State University of Medicine and Pharmacy.

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CUPRINS

CONCEPTUAL FRAMEWORK OF THE RESEARCH

The relevance and importance of the issue addressed. Thyroid hormones are essential for growth, neural development, reproduction, and the regulation of various types of metabolism, including energy metabolism [1]. Hypothyroidism is a common condition with potentially adverse health consequences [2,3]. Due to the wide variation in clinical presentation and the lack of specific symptoms, the diagnosis of hypothyroidism is predominantly biochemical and is based on statistical reference ranges for relevant hormonal parameters. The prevalence of overt hypothyroidism in the general population ranges from 0–3% to 3–7% in the United States and from 0–2% to 3–5% in Europe [4], depending on the definition used. A meta-analysis of studies conducted in 9 European countries estimated the prevalence of undiagnosed hypothyroidism—including both overt and subclinical cases—at approximately 5% [5]. In the Republic of Moldova, the prevalence of autoimmune thyroiditis is 11.3%, that of hypothyroidism is 9.5%, and that of hypothyroidism associated with autoimmune thyroiditis is 6.1% [6]. In regions with adequate iodine intake, the most common cause of hypothyroidism is chronic autoimmune thyroiditis [7]. The issue of subclinical hypothyroidism remains relevant. Studies show an increased atherogenic and cardiovascular risk, and the need for treatment continues to be debated [8,9]. Thyroid hormone replacement therapy with levothyroxine is the standard treatment for patients with hypothyroidism [10,11]. However, a significant proportion of patients treated with levothyroxine continue to experience persistent symptoms despite achieving the biochemical targets of therapy, which has raised the question of whether levothyroxine treatment is sufficient for all patients or whether alternative therapies should be adopted [12].

The low grade inflammation involves activation of the immune system, which does not manifest as obvious clinical signs but may contribute to the progressive deterioration of thyroid function [13,14]. Low grade inflammation associated with autoimmune hypothyroidism is believed to play an important role in the progression of the disease, affecting both thyroid function and the risk of other comorbidities, such as cardiovascular disease, metabolic disorders, and even neuropsychiatric impairment [15]. Subclinical inflammation is considered an independent risk factor for atherosclerosis [16]. Autoimmune hypothyroidism—both overt and subclinical—can accelerate the atherosclerotic process through inflammatory mechanisms and dyslipidemia [17–19]. Systemic inflammatory markers, such as hs-CRP, interleukins, and TNF-α, may correlate with the severity of thyroid dysfunction and cardiovascular risk [20].

There is conflicting evidence regarding the effect of levothyroxine treatment on reducing subclinical inflammation. Some studies show a decrease in inflammatory markers after TSH normalization, while others find no significant difference [20,21].

Therefore, subclinical inflammation may have a significant impact on the health of patients with autoimmune hypothyroidism, highlighting the need for systematic assessment of inflammatory markers and cardiovascular risk, even in the asymptomatic stages of the disease (subclinical hypothyroidism).

Another current focus in the management of individuals with autoimmune hypothyroidism is quality of life, as Hashimoto's thyroiditis not only affects thyroid function but also has a significant impact on overall well-being [22,23]. Even after hormone levels have normalized through replacement therapy, some patients continue to experience symptoms such as chronic fatigue, sleep disturbances, depression, anxiety, and cognitive problems [24]. Studying quality of life in autoimmune hypothyroidism is important for providing holistic

treatment—not just hormonal therapy—as well as for improving mental health, increasing satisfaction, and enhancing treatment adherence [25,26].

Therefore, low-grade systemic inflammation—recognized as an important factor involved in the pathogenesis and progression of several chronic noncommunicable diseases, but insufficiently studied in autoimmune thyroiditis—requires further investigation in autoimmune hypothyroidism.

Purpose of the study. To evaluate biomarkers of low-grade systemic inflammation and their relationship to clinical and metabolic parameters and quality of life in individuals with autoimmune hypothyroidism, before and after treatment with levothyroxine, in order to integrate the concept of low-grade inflammation into the management of autoimmune hypothyroidism.

Research objectives:

1. Characterization of the clinical and hormonal profile in individuals with autoimmune hypothyroidism.
2. Analysis of the metabolic profile in individuals with autoimmune hypothyroidism.
3. Assessment of inflammatory biomarkers in individuals with autoimmune hypothyroidism and analysis of their relationship with the hormonal and metabolic profiles.
4. Evaluation of the effects of levothyroxine treatment on clinical and metabolic parameters and inflammatory biomarkers.
5. Assessment of quality of life in individuals with autoimmune hypothyroidism before and after levothyroxine treatment.

General methodology of the scientific research. To achieve the research aims and objectives, a longitudinal case-control study was conducted. The study included individuals with a confirmed diagnosis of overt and subclinical autoimmune hypothyroidism, as well as healthy individuals in the control group. The subjects were selected from the republican outpatient department of the ISMP "Timofei Moșneaga" Republican Clinical Hospital, district and municipal outpatient departments.

The research was conducted based on the positive opinion of the Research Ethics Committee (Minutes No. 3/5 dated March 15, 2019) and based on Decision No. 2/4 of the Scientific Council of the Consortium.No. 15 of April 10, 2025, regarding the approval of the research project, the research topic, the scientific advisor, the co-advisor, and the advisory committee for the doctoral dissertation in medical sciences.

Research Hypothesis. Autoimmune hypothyroidism is characterized by the presence of subclinical inflammation, which is associated with an increased risk of metabolic disorders. Identifying the role of subclinical inflammation in autoimmune hypothyroidism may contribute to optimizing therapeutic strategies and improving the prognosis of the disease.

Theoretical significance. This study contributes to a deeper understanding of the role of subclinical inflammation in autoimmune hypothyroidism and highlights its interaction with thyroid dysfunction, lipid metabolism, and cardiovascular risk factors. The presence and persistence of subclinical inflammation after initiation of levothyroxine therapy suggest pathogenic mechanisms in the progression of hypothyroidism that are independent of the normalization of thyroid function. These results underscore the need for monitoring and reevaluation of treatment in autoimmune hypothyroidism.

The practical value of this study lies in demonstrating the need to assess the presence of subclinical inflammation as a relevant pathogenic factor and to determine the degree of inflammation. It is also appropriate to assess the persistence of inflammation after initiating levothyroxine treatment, using inflammatory markers. Administration of the ThyPRO-39 questionnaire revealed a significant impairment of QOL, despite levothyroxine replacement therapy, which underscores the need for a comprehensive diagnostic and therapeutic approach that aims not only to normalize hormonal parameters but also to assess and improve QOL. These results thus contribute to the development of individualized clinical recommendations for the management of this condition.

Scientific novelty and originality. The presence of subclinical chronic inflammation was identified in individuals with autoimmune hypothyroidism (both overt and subclinical), which indicates an increased cardiovascular risk (not determined solely by dyslipidemia), especially in young women without obesity, who are considered *a priori* to be at low cardiovascular risk. It was determined that individuals with very elevated creatine phosphokinase (>1000 U/L) have an hs-CRP level < 1 mg/L, indicating a low level of inflammation. The study highlighted the complex interaction between subclinical inflammation, lipid metabolism, renal function, and hypothyroidism, as well as the impact of inflammation on an atherogenic lipid profile. These results contribute to our understanding of the common pathogenic mechanisms underlying thyroid dysfunction, chronic inflammation, and cardiovascular risk, offering new perspectives for the evaluation and management of patients with hypothyroidism and dyslipidemia. A direct relationship was established between elevated TSH levels (>100 μUI/mL) and elevated CK levels (>1000 U/L). Also original are the findings regarding the negative impact of the disease on quality of life (QoL), particularly in the areas of cognition and depression, as well as the persistence of certain symptoms (anxiety, emotional sensitivity), despite replacement therapy, which suggests that standard levothyroxine therapy is not always sufficient and that an individualized approach is necessary in the management of hypothyroidism.

Implementation of scientific findings.

These practical recommendations are used in the Endocrinology Department of the "Timofei Moșneaga" Republican Clinical Hospital (SCR), the Endocrinology Department of the "Holy Trinity" Municipal Clinical Hospital, in the educational training of students, residents, and medical staff at the Department of Endocrinology of the "Nicolae Testemițanu" State Medical University (IP USMF).

Approval of the research results.

The results of the thesis were presented, discussed, and approved at a meeting of the Department of Endocrinology and the Endocrinology Laboratory of the "Nicolae Testemițanu" State University of Medicine and Pharmacy (Minutes No. 14 of May 12, 2026) and at a meeting of Specialized Seminar 321. General Medicine/Specialty: 321.01. Internal Medicine (Gastroenterology, Hepatology); 321.02. Endocrinology; 321.08 Dermatology and Venereology (Minutes No. dated June 15, 2026).

Publications on the research topic. The results obtained have been published in 8 articles in scientific journals (including 1 in the Web of Science database and 1 in the Scopus database), 12 abstracts at international and national conferences, and 1 National Clinical Protocol. The results were presented at 13 international and national conferences, in the form of active

presentations and moderated posters forums (Moldova, Romania, Turkey, Finland, Sweden, and the U.S.). Based on the research results, 4 innovation certificates and 4 implementation documents were registered.

Thesis Length and Structure. The thesis consists of 107 pages of main text and includes: an introduction, 7 chapters, 23 figures, 13 tables, general conclusions, practical recommendations; a bibliography with 355 references, appendices, innovation certificates and implementation documents, a list of publications and participation in scientific forums, a statement of responsibility.

Keywords: autoimmune hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis, low grade inflammation, hs-CRP, cardiovascular risk, nonHDL-cholesterol, creatine kinase, levothyroxine, quality of life, ThyPRO-39.

CONTENTS OF THE THESIS

Chapter 1 (Primary Autoimmune Hypothyroidism—Current Status) provides a synthesis of the specialized scientific literature regarding the latest findings on metabolic disorders and cardiovascular risk in both overt and subclinical hypothyroidism. It presents current information on chronic (subclinical) inflammation in autoimmune thyroiditis and the treatment of hypothyroidism resulting from autoimmune thyroiditis. Some pathogenic mechanisms involved in the development of *low-grade* inflammation in hypothyroidism are described. Current information regarding the quality of life of individuals with hypothyroidism and the impact of hormone replacement therapy is presented. The characteristics of the course of hypothyroidism, its complications, and treatment based on the degree of thyroid dysfunction are discussed.

Chapter 2 (Research Material and Methods). In accordance with the proposed aims and objectives, a longitudinal case-control study was conducted. The research methodology was developed, including the determination of inclusion and exclusion criteria for patients in the study. The research was conducted between 2018 and 2024 in accordance with the Principles of the Declaration of Helsinki – WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (revision 2013, Fortaleza). The study was approved at a meeting of the Research Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy (Minutes No. 3/5 dated March 15, 2019).

The scientific study was conducted in several stages. Patients were selected from the Consultative-Diagnostic Department of the "Timofei Moșneaga" Republican Clinical Hospital (SCR) and from district and city consultative centers, and were examined on an outpatient basis; some of the patients were hospitalized in the endocrinology department of the SCR for diagnostic testing and treatment. The patient group included 65 individuals with autoimmune hypothyroidism, and the control group included 65 otherwise healthy individuals. Data on each patient were entered into a questionnaire, which included chief complaints, medical history, physical examination, laboratory tests, and the quality-of-life assessment questionnaire for individuals with thyroid disorders (ThyPRO-39). The second stage involved monitoring patients 8 and 16 weeks after the initial visit, with assessment of hormonal and biochemical profiles as well as inflammatory markers; the ThyPRO-39 questionnaire was re-administered at the 16-week mark.

The study design is presented in Figure 1.

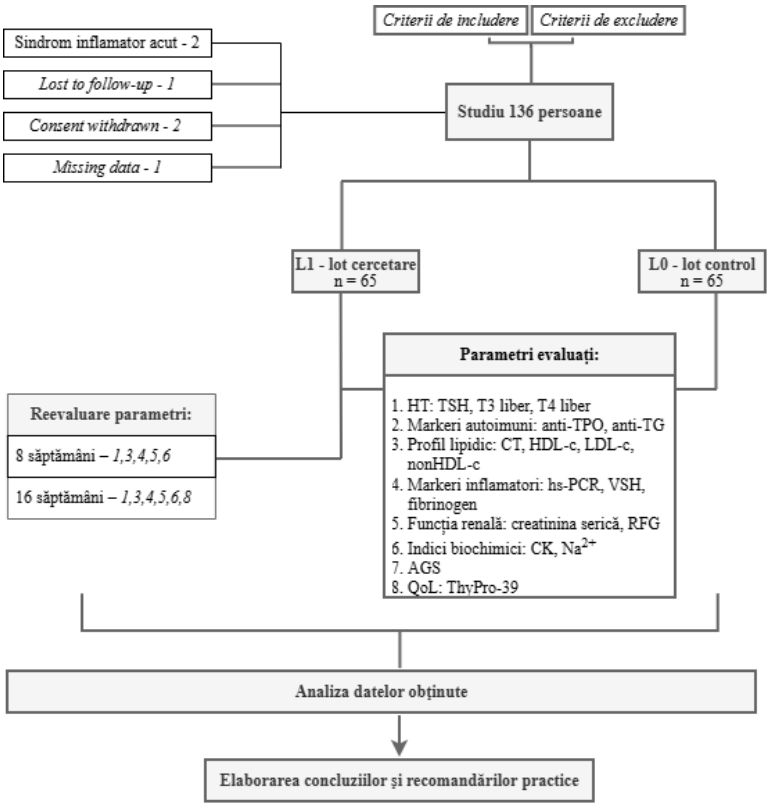

Figure 1. **Study design**

Dose adjustments were made as needed, based on TSH levels, as follows: 1) TSH < 0.4 μUI/mL – the dose was reduced by 25 mcg/day; 2) TSH ≥ 0.4 and ≤ 4 μUI/mL – the dose remained unchanged; 3) TSH > 4 but < 15 μUI/mL – 12.5–25 mcg/day was added; 4) TSH > 15 μUI/mL – 50 mcg of levothyroxine.

The diagnosis of primary hypothyroidism was established based on the patient's complaints, medical history, clinical examination, and biochemical and immunological tests, in accordance with the International Classification of Diseases and the ATA/AACE *Clinical Practice Guideline for Hypothyroidism in Adults*, 2014/2012.

Inclusion criteria:

- Age between 18 and 65 years
- Untreated autoimmune hypothyroidism, with no signs or symptoms of recent or ongoing associated pathology
- Informed consent from the patient to participate in the study

Exclusion criteria:

- Use of medications that may interfere with thyroid function (interferon, amiodarone, lipid-lowering agents, appetite suppressants, vitamin supplements, antioxidants, beta-blockers, metoclopramide, domperidone)
- Systemic diseases (connective tissue diseases), diabetes mellitus, obesity grade II or higher, malignant tumors, history of respiratory and cardiovascular diseases, other acute and chronic intercurrent diseases
- Active smoking, alcoholism
- Pregnant women

Patients enrolled in the study underwent a comprehensive examination. Initially, they were interviewed to collect anamnestic data regarding the main symptoms, duration, and onset of the disease, as well as family and personal medical history; a clinical and laboratory examination was then performed. All data obtained were entered into coding tables according to a predefined questionnaire. The following parameters were evaluated: complete blood count, thyroid hormone profile—TSH, free T4, free T3, anti-TPO antibodies, anti-TG antibodies, inflammatory markers—hs-CRP, fibrinogen, ESR, and blood biochemistry: lipid profile—total cholesterol (TC), LDL-c, HDL-c, non-HDL-c; renal function—serum creatinine and glomerular filtration rate (GFR), serum Na^+, creatine phosphokinase (CK).

Quality of life was assessed using the ThyPRO-39 questionnaire. A questionnaire completed at the initial visit (from the HM subgroup) was lost. ThyPRO-39 consists of 39 items summarized into 13 scales covering physical, functional, and mental symptoms (cognitive impairment, anxiety, depression, emotional sensitivity), physical appearance, well-being, as well as the level of participation in daily activities and social life. The individual provides responses for the reference period of the past 4 weeks. Each scale contains questions and is rated by the patient on a 5-point scale: 0 — not at all; 1 — very little; 2 — a little; 3 — quite a bit; 4 — very much. The resulting score ranges from 0 to 100; higher scores indicate a lower quality of life, while lower scores indicate a better quality of life. Items 3B, 6G, and 7H must be calculated in reverse, i.e., “not at all” is scored as 4, “very little” as 3, “a little” as 2, “quite a lot” as 1, and “very much” as 0. The score is calculated using the formula “Transformed score = (gross total score / highest possible gross total score) * 100.”

Statistical analysis methods. The following software was used for statistical analysis: MS Excel, PSPP 2.0.1 (GNU PSPP Statistical Analysis Software, Release 2.0.1, Boston, MA: Free Software Foundation), and IBM SPSS Statistics (Version 29). The significance threshold applied was $p < 0.05$.

The following measures were used when reporting the data:

For categorical variables: frequency and proportion; for numerical variables: mean, standard deviation (SD), 95% confidence interval (95% CI), median, interquartile range (IQR), 25th and 75th percentiles, minimum, and maximum values. The set of categorical variables was analyzed using the χ^2 test, with Bonferroni correction for multiple comparisons. The Bonferroni correction was used for subplot comparisons and paired comparisons in the dynamic analysis. For large families (subplot comparisons in Chapter 6), the less conservative Holm-Bonferroni sequential procedure was used. Differences between the mean values across subgroups for numerical variables were analyzed using a parametric procedure (ANOVA) with calculation of the F-statistic. To highlight statistical differences between groups, the Student’s t-test was applied when necessary. If the variance of the values across subgroups was unequal, as determined by Levene’s test, the nonparametric Kruskal-Wallis test was applied. To investigate the dynamics of these values, the parametric Student’s t-test and the non-parametric Wilcoxon Signed-Rank Test were used.. To analyze the associations between and the numerical variables, Pearson’s correlation coefficient (r) was applied. For multivariate analysis, the multiple linear regression method was used. For the QOL questionnaire, the Cronbach’s alpha test was applied to verify the integrity of the questionnaire sections. To visualize the numerical data, vertical bar charts, box plots, and scatter plots were used.

Chapter 3 (Assessment of Clinical, Hormonal, and Metabolic Abnormalities in the Study Group) consists of 5 subsections, the first of which is devoted to describing the overall

study population. The study included 130 participants, of whom 65—diagnosed with autoimmune hypothyroidism—constituted the research group (L1), while the control group (L0) included 65 healthy individuals. The groups were comparable in terms of age and sex. Group L1 included 55 women (86%) and 10 men (14%), while Group L0 consisted of 53 women (83%) and 12 men (17%). The mean age in Group L1 was 41.3 ± 13.4 years, and in Group L0, 41.7 ± 6.6 years. Women predominate in our study, which is consistent with data from the literature showing a higher prevalence of thyroid disorders, including hypothyroidism, among women; this female predominance is attributed to sex differences in immune function, similar to many autoimmune diseases [27]. At the same time, it is important to note that our study included only individuals aged 65 or younger to reduce the risk of associated chronic conditions that could contribute to the presence of a chronic inflammatory process [28].

An analysis of the hormonal profile of the study groups revealed a TSH level of 50.59±63.82 μUI/mL, free T4 – 0.66±0.34 ng/dL, free T3 – 2.47 ± 1.11 pg/mL, anti-TPO – 635.05±447.89 IU/mL, and anti-TG – 246.84±608.17 IU/mL in L1. These findings are characteristic of autoimmune hypothyroidism and are consistent with data in the literature [29]. In L0, the TSH level was 1.80 ± 0.66 μIU/mL, and anti-TPO was 19.28 ± 32.15 IU/mL. The differences between groups in TSH ($F=37.4$, $p < 0.001$) and anti-TPO ($F=120.4$, $p < 0.001$) were statistically significant.

The results of our multi-year study of hypothyroidism and data from the relevant literature have allowed us to summarize the most common symptoms, clinical signs, and laboratory findings of hypothyroidism, which served as the basis for our clinical study. These clinical and paraclinical manifestations are as follows: metabolic-hypothermic syndrome (weight gain, sensitivity to cold, myopathy, dyslipidemia, etc.); hypothyroid dermopathy and ectodermal syndrome (periorbital and facial edema, carotenodermia, dry, thin, and brittle hair, hair loss, etc.); sensory organ disorders (hearing loss, olfactory disturbances); central and peripheral nervous system involvement (psycho-emotional disturbances, cognitive impairments, peripheral polyneuropathy, diminished tendon reflexes, etc.); disorders of the cardiovascular system (bradycardia, pathological ECG findings, hypotension, diastolic hypertension, etc.); disorders of the digestive organs (constipation, associated metabolic steatosis of the liver, biliary tract dyskinesia, atrophy of the gastric mucosa, decreased appetite, etc.); anemic syndrome (normochromic anemia, hypochromic anemia, vitamin B12-deficient anemia, impaired blood clotting, etc.); hyperprolactinemic hypogonadism (oligomenorrhea, amenorrhea, galactorrhea, etc.); hypoxemic-obstructive syndrome (snoring, hypoventilation, sleep apnea, etc.).

These data allowed us to determine the frequency of symptoms in patients with primary hypothyroidism without comorbidities (Fig. 2).

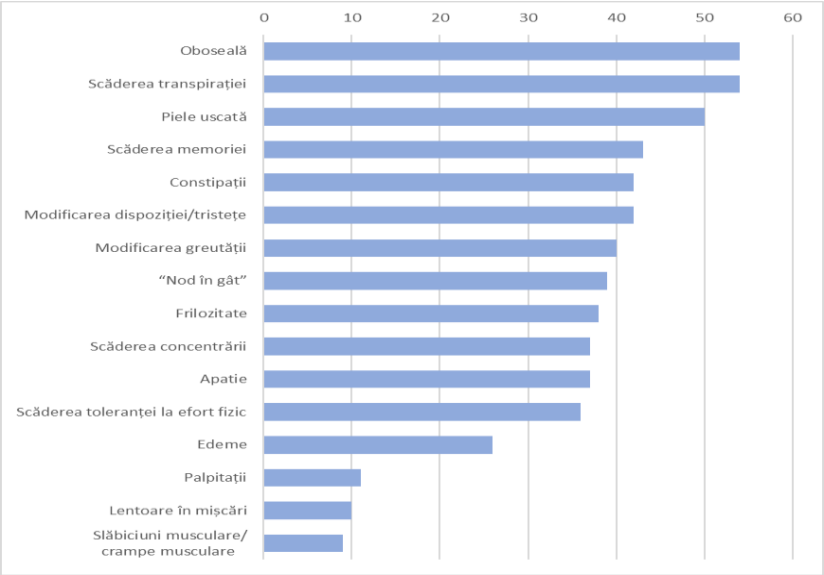

Figure 2. **Frequency of the main signs and symptoms in patients with autoimmune hypothyroidism.**

Clinical practice shows that relying solely on clinical symptoms has no significant diagnostic value; this is why they are considered nonspecific and often manifest even in euthyroid individuals [30]. An analysis of the symptoms of hypothyroidism presented in Figure 2, which shows disturbances in multiple organs and systems, suggests that the most commonly affected (and thus constituting the clinical pattern of hypothyroidism) in our study are:

- Slowing of metabolic processes (fatigue, cognitive dysfunction, weight gain, decreased sweating, sensitivity to cold, dry skin);
- The gastrointestinal system (constipation);
- Neuropsychological system (mood changes/sadness, apathy, anxiety, fatigue);
- Muscular system (muscle weakness, muscle cramps, slowed motor function, decreased tolerance to physical exertion);
- Accumulation of mucopolysaccharides (edema);
- Cardiovascular system (palpitations).

HTs are vital for regulating various metabolic processes; an imbalance in HTs can have significant clinical consequences, affecting multiple body systems. HTs have a major effect on the body's growth and development, as well as on energy, protein, lipid, carbohydrate, and water-salt metabolism. They regulate numerous genes involved in lipogenesis [31].

In our study, in the group of patients with hypothyroidism and in the control group, the mean total cholesterol (TC) level was 6.07±2.10 mmol/l and 5.54±1.01 mmol/l, respectively (F=3.20, p=0.076); LDL-c was 3.96±1.67 mmol/l and 3.39±0.76 mmol/l, respectively (F=6.12, p=0.015), and HDL-c was 1.53±0.46 mmol/l and 1.66±0.31 mmol/l, respectively (F=3.60, p=0.061). At the same time, the median HDL-c was 1.49 mmol/l and 1.69 mmol/l, respectively, in L1 and L0 (KW=6.57, gl=1, p=0.010).

The correlation analysis of CT revealed positive and negative correlations with some of the indices studied, as shown in Table 1.

Table 1. Correlation of CT with various parameters

	CT	p
TSH	0.35**	0.004

fT4	-0.51**	<0.001
fT3	-0.58**	<0.001
Creatinine	0.32 **	0.005
CK	0.25*	0.042
HDL	0.42 **	<0.001
LDL	0.94 **	<0.001
Non-HDL	0.97**	<0.001
Fibrinogen	-0.27*	0.029
ESR	0.39**	0.001

Note: Data are presented as correlation coefficients (r), which do not include "1" and range from -1 to +1.
** Correlations are significant at the 0.01 level. * Correlations are significant at the 0.05 level.

The correlation analysis showed that LDL-c has a weak positive correlation with age (r=0.25, p<0.01), BMI (r=0.36, p<0.001), CK (r=0.27, p<0.05), moderate with TSH (r=0.41, p<0.001), creatinine (r=0.41, p<0.001), ESR (r=0.46, p<0.001), non-HDL-c (r=0.96, p<0.001), TC (r=0.94, p<0.001), and a negative correlation with fT4 (r= -0.53, p<0.001), fT3 (r= -0.56, p<0.001).

The analysis of associations showed that HDL-c has a positive correlation with CT (r = 0.43, p < 0.001), non-HDL-c (r = 0.20, p < 0.05), and a significant negative correlation with BMI (r = −0.30, p = 0.001), hs-CRP (r = −0.22, p < 0.05), creatinine (r = −0.23, p < 0.01), and fT3 (r = −0.28, p < 0.05).

Analysis of the results obtained in individuals with hypothyroidism revealed specific characteristics of the assessed indicators; therefore, to study them in greater depth, it was decided to evaluate HM and HS separately.

Thus, statistically significant differences were found in the mean values of TC and LDL-c, but not HDL-c, between the HM and the control groups, as well as between the HM and the HS groups; in the HS group, there were no statistically significant differences in lipid profile indices compared to L0. At the same time, there was no statistically significant difference in the median CT values between the HM group and the control group. At the same time, the median values for HDL-c in the HS group and the control group were 1.52 mmol/l and 1.69 mmol/l, respectively, and in the HM and control groups: 1.41 mmol/l and 1.69 mmol/l, respectively (KW=6.65, df=2, p=0.036) (Fig. 3).

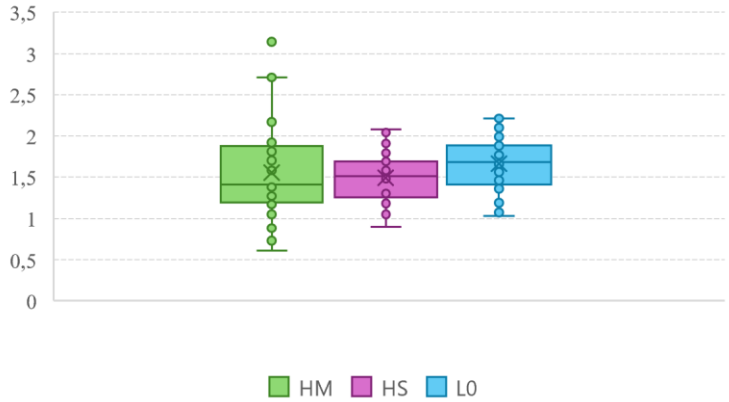

Figure 3**. Distribution of HDL-c levels in patients with HM, HS, and L0**

It is well known that the lipid metabolism dysfunction characteristic of hypothyroidism is proatherogenic and poses a significant cardiovascular risk. Hypothyroidism is associated with an increased risk not only of cardiovascular morbidity but also of cardiovascular mortality.

TC, LDL-c, HDL-c, and TG are the most commonly used predictors of CV risk. However, population-based studies have shown that both non-HDL-c and the TC/HDL-c ratio are better predictors of subclinical atherosclerosis; they are easy to measure and do not require *fasting* [32] . Recently, non-HDL has been increasingly used as an index for determining CV risk, serving as a reference parameter in vascular risk assessment formulas—SCORE2 and SCOREOP [33,34].

The mean non-HDL-c level in L1 was 4.54±1.92 mmol/l, and in L0—3.88±0.94 mmol/l (F=6.00, p=0.016); even at the 75th percentile, the non-HDL-c level was higher than 3.37 mmol/l.

Analysis of the non-HDL-c parameter in the HM subgroup showed a mean value of 5.31 ± 2.19 mmol/l, and in the HS subgroup, 3.63 ± 0.96 mmol/l ($p < 0.001$); a statistically significant difference was also observed between the HM subgroup and the control group ($p<0.001$), but not between the HS subgroup and the control group. Correlation analysis showed that non-HDL-c has a significant positive correlation with age (r=0.29, p=0.001), BMI (r=0.37, p<0.001), TSH (r=0.39, p<0.001), creatinine (r=0.41, p<0.001), ESR (r=0.42, p=0.001), HDL-c (r=0.20, p<0.05), CK (r=0.28, p<0.05), anti-TPO (r=0.21, p<0.05) and a significant negative correlation with fT4 (r= -0.55, p<0.001), fT3 (r= -0.56, p<0.001), fibrinogen (r= -0.27, p<0.05), and e (Fig. 4).

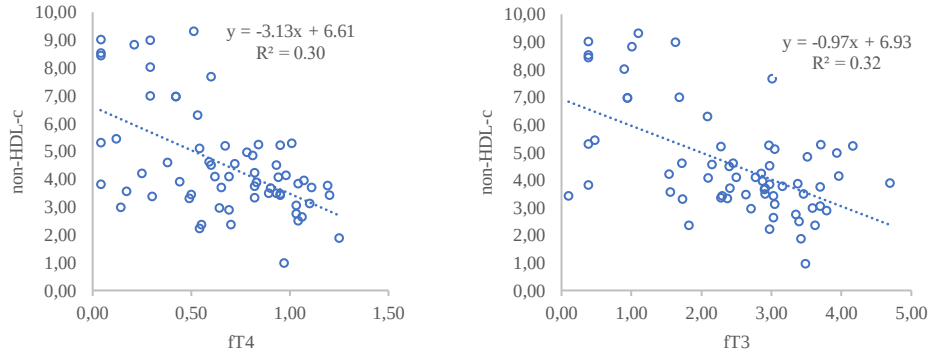

Figure 4. **Illustration of the inverse relationship between fT4 and fT3 and non-HDL-c**

From a clinical perspective, this relationship suggests that monitoring and managing fT4 and fT3 levels are important for patients' lipid profiles and cardiovascular risk. Given that approximately 30% of the variation in non-HDL-C is explained by the free forms of thyroid hormones (according to R^2), it is likely that other factors (genetic, dietary, or related to other comorbidities) contribute to non-HDL-C levels.

Elevated serum creatinine in hypothyroidism may represent either a simple functional alteration in renal blood flow or organic renal dysfunction. In our study, the serum creatinine level in the group of individuals with hypothyroidism was 69.66 ± 18.41 μmol/L, and in the control group, it was 62.23 ± 11.81 μmol/L ($F = 7.407$, $p = 0.007$). A statistically significant difference was also observed in the median serum creatinine levels in the group of individuals with hypothyroidism compared to those in the control group; the median was 68.30 μmol/L and 58.65 μmol/L, respectively (KW=5.23, df=1, p=0.022).

Statistically significant differences were also observed when estimating eGFR using the *Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation* (2021). Thus, the mean eGFR values calculated for individuals with hypothyroidism and the control group were 100.57 and 109.27 ml/min/1.73 m^2(F=9.126, p=0.003), respectively. Statistically significant differences were also observed in the median GFR values in the group of individuals with hypothyroidism compared to those in the control group; the median values were 101.00 and 113.50 ml/min/1.73 m^2(KW=5.62, df=1, p=0.018), respectively (Fig. 5).

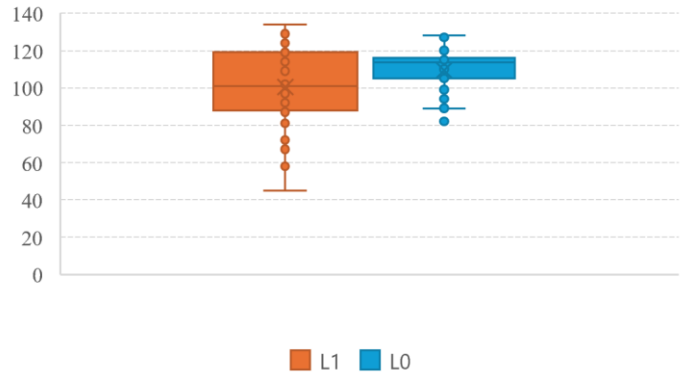

Figure 5. **Distribution of serum creatinine values in individuals from L1 and L0**

Thus, the clinical presentation of hypothyroidism is nonspecific in most cases, with metabolic changes and involvement of multiple organ systems.

Chapter 4. (Assessment of Subclinical Inflammation Markers in the Study Cohort) is devoted to the study of subclinical inflammation markers. In our study, the hs-CRP level was 2.20 ± 1.64 mg/L in individuals with hypothyroidism, and 1.05 ± 0.52 mg/L in the control group (F = 28.33, p < 0.001). The median hs-CRP level was significantly higher in individuals in L1 compared to those in L0, at 1.73 mg/L and 0.93 mg/L, respectively (KW=16.78, df=1, p=0.001).

In clinical practice, the question of whether HS treatment is necessary often arises. Given that subclinical inflammation and HS are risk factors for the development of cardiovascular disease, we set out to compare the level of subclinical inflammation among individuals with HM, HS, and the control group. Assessment of hs-CRP levels in different hypothyroidism subgroups revealed the following results: the mean hs-CRP value was 2.37 ± 1.8 mg/L in HM, a value significantly higher than that in L0 (p < 0.001), and in HS, the mean hs-PCR level was 2.0 ± 1.42 mg/L, which was also significantly higher than in L0 (p = 0.002) (Table 2).

Table 2. hs-PCR levels in the investigated sublots

	HM n=35	**HS n=30**
Mean	2.37	2.00
Standard deviation	1.80	1.42
Median	2.46	1.56
IIQ	2.81	1.76
25th percentile	0.74	0.98
75th percentile	3.55	2.78
Minimum	0.30	0.34
Maximum	6.90	5.50

The median hs-PCR value in individuals with HM was 2.46 mg/L and in individuals with HS, 1.56 mg/L (KW=16.83, df=2, p<0.001) (Fig. 6).

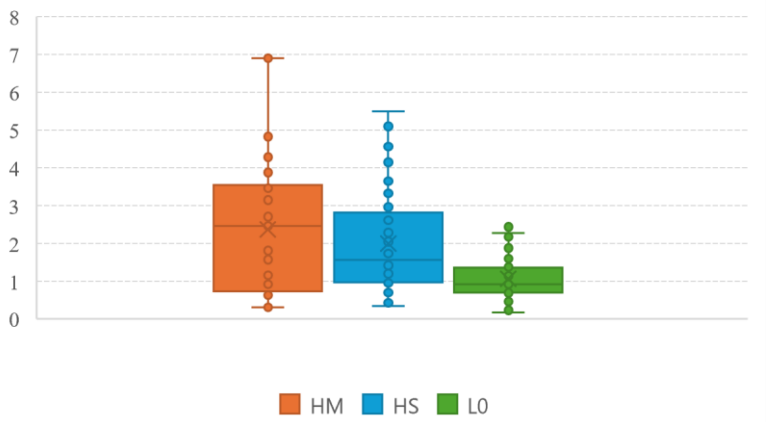

Figure 6. **Distribution of hs-CRP levels in individuals with HM, HS, and L0**

hs-CRP provides prognostic information regarding CV risk, comparable to that of cholesterol and blood pressure levels. hs-CRP levels < 1, 1–3, and > 3 mg/L indicate low, moderate, and high CV risk, respectively [35]. In L1, only in one-third of cases was the hs-CRP level < 1 mg/L; in 43.1%, the hs-CRP level was 1–3 mg/L, corresponding to moderate cardiovascular risk; and in 26.2%, it was > 3 mg/L (high CV risk). In L0, no individual had an hs-CRP level > 3 mg/L; 43.8% had an hs-CRP level in the 1–3 mg/L range; and 56.3% had hs-CRP levels < 1 mg/L. A comparison across subgroups showed that the distribution of individuals with HM was approximately 30% for each of the three hs-CRP values: < 1, 1–3, and > 3 mg/L, while in HS, the distribution was 30%, 50%, and 20%, respectively, for the same hs-CRP values, indicating that more individuals with HM have hs-CRP values corresponding to a high CV risk. hs-CRP levels > 3 mg/L, which correspond to a high CV risk, were found only in individuals with hypothyroidism—in 26.2% of cases, in HM—31.4%, and in HS—20% (Table 3).

Table 3. Distribution of hs-CRP levels according to the degree of inflammation

	HM				**HS**				**Control**		
	hs-CRP				**hs-PCR**				**hs-PCR**		
	<=1	**1–3**	**>3**	**Total**	**<=1**	**1–3**	**>3**	**Total**	**<=1**	**1–3**	**Total**
N	11	13	11	35	9	15	6	30	37	28	65
Average	0.57	2.06	4.53	2.37	0.74	1.80	4.38	2.00	0.69	1.53	1.05
DS	0.25	0.65	1.29	1.80	0.25	0.62	0.84	1.42	0.21	0.40	0.52
M	0.47	2.46	4.00	2.46	0.72	1.58	4.36	1.56	0.73	1.48	0.93
IIQ	0.43	0.96	1.43	2.81	0.39	1.05	1.45	1.8	0.35	0.53	0.66
P 25	0.31	1.57	3.55	0.74	0.57	1.23	3.65	0.98	0.53	1.21	0.70
P 75	0.74	2.53	4.98	3.55	0.96	2.28	5.10	2.78	0.88	1.74	1.36
Min	0.30	1.10	3.15	0.30	0.34	1.01	3.33	0.34	0.17	1.03	0.17
Max	0.97	2.75	6.90	6.90	0.99	2.96	5.50	5.50	0.98	2.44	2.44

Note: N – total number, Mean – mean value, SD – standard deviation, M – median, P 25 – 25th percentile, P 75 – 75th percentile, IIQ – interquartile range, Min – minimum value, Max – maximum value.

The correlation analysis showed that hs-PCR has a positive correlation with TSH (r=0.258, p=0.003), body weight (r=0.289, p=0.001), BMI (r=0.371, p<0.001), anti-TPO (r=0.232, p=0.009), CT/HDL-c ratio (r=0.263, p=0.034), and LDL-c (r=0.181, p=0.041), and a negative correlation with HDL-c (r=-0.215, p=0.014).

Analysis of CK levels revealed a mean value of 499.00 ± 1058.31 mg/L in individuals with hypothyroidism; with this value in the HM subgroup being 832.17 ± 1362.35 U/L and in the HS subgroup being 110.31 ± 74.30 U/L, representing a statistically significant difference (F = 8.382, p = 0.005). The median CK value was significantly higher in individuals in the HM subgroup compared to those in the HS subgroup, at 196.20 U/L and 87.90 U/L, respectively (DF=1, p<0.001).

The correlation analysis showed that CK has a positive correlation with TSH (r=0.432, p<0.001), serum creatinine (r=0.543, p<0.001), CT (r=0.253, p<0.05), LDL-c (r=0.268, p<0.05), non-HDL-c (r=0.275, p<0.05), the CT/HDL-c ratio (r=0.249, p<0.05), and body mass (r=0.292, p<0.05) and a negative correlation with fT4 (r=-0.473, p<0.001), fT3 (r=-0.473, p<0.001), and RFG (r=-0.378, p=0.002).

We also found that, in the HM subgroup, the mean CK level varies depending on hs-PCR levels. For hs-PCR < 1 mg/L, the mean CK was 1746.85 ± 2083.32 U/L, which is significantly higher compared to the mean CK of 354.22 ± 421.90 U/L for hs-PCR in the 1–3 mg/L range (p < 0.05). The mean CK level for hs-PCR > 3 mg/L was 482.34 ± 636.18 U/L. In the HS subgroup, no statistically significant differences in mean CK levels were observed across different hs-PCR levels. The mean CK value was 97.31 ± 33.89 U/L, 131.80 ± 96.30 U/L, and 76.08 ± 33.39 U/L for hs-PCR values < 1 mg/L, 1–3 mg/L, and > 3 mg/L, respectively.

Among individuals with HM, we identified 10 individuals with very high CK levels: > 1000 U/L, with a mean value of 2483.04±1881.27 U/L. The mean hs-PCR value in this group was 1.17 ± 1.36 mg/L, which is significantly lower compared to the mean hs-PCR value (2.62 ± 1.59 mg/L) among individuals with HM and CK < 1000 U/L (223.54 ± 190.77 U/L) (F=3.396, p<0.05) (Fig. 7).

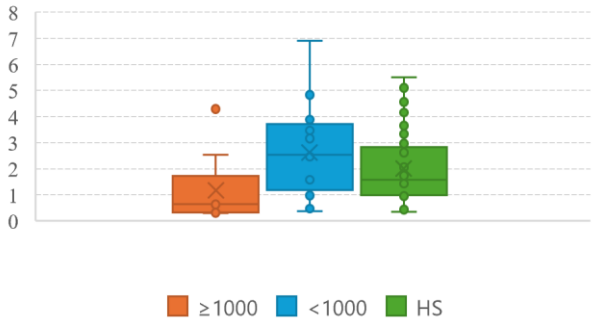

Figure 7. **Distribution of hs-PCR values as a function of CK levels in individuals with HM.**

Analysis of the distribution of CK values based on hs-PCR levels shows that for hs-PCR values ≤ 1 mg/L, the mean CK value was 1746.85 ± 2083.32 U/L (median 1128.70 U/L); for hs-PCR 1–3 mg/L – 354.22 ± 421.90 U/L, a value significantly different from the previous subgroup (p = 0.030), and for hs-PCR > 3 mg/L – 482.34 ± 636.18 U/L.

The median hs-PCR value in individuals with CK > 1000 U/L was significantly lower compared to the median value in individuals with CK < 1000 U/L, at 0.63 U/L and 2.53 U/L, respectively (KW=9.382, DF=1, p=0.009).

In individuals with HM and CK > 1000 U/L, the TSH level was 123.81±37.67 µUI/mL, compared with 74.65±73.23 µUI/mL in those with HM and CK < 1000 U/L ($p<0.05$). The fT4 level was 0.25±0.23 ng/dL and 0.46±0.21 ng/dL for CK > 1000 U/L and < 1000 U/L, respectively ($p<0.05$). The same relationship was found for fT3 levels, which were 1.07±0.81 pg/mL and 2.22±1.12 pg/mL, respectively, for CK > 1000 U/L and < 1000 U/L ($p<0.05$).

The mean serum creatinine level in individuals with HM and CK > 1000 U/L was 89.83 ± 24.80 µmol/L, which is significantly higher than the mean serum creatinine level of 72.59 ± 14.19 µmol/L among individuals with HM and CK < 1000 U/L. The mean serum creatinine level in individuals with HS was 60.37 ± 13.01 µmol/L ($F = 13.426$, $p < 0.001$) (Fig. 8).

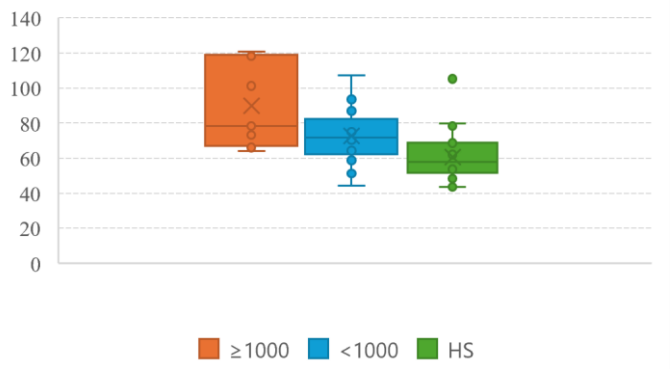

Figure 8. **Distribution of serum creatinine levels depending on CK levels in individuals with hypothyroidism**

An analysis of lipid metabolism parameters at in individuals with CK > 1000 U/L and < 1000 U/L revealed a mean TC level of 8.25±2.72 mmol/L and 6.31±2.22 mmol/L, respectively ($p<0.05$), LDL-c levels of 5.75±2.25 mmol/l and 4.07±1.69 mmol/l, respectively ($p<0.05$), and non-HDL-c levels of 6.60±2.24 mmol/l and 4.78±2.02 mmol/l, respectively ($p<0.05$).

Thus, the presence of subclinical inflammation—which is a cardiovascular risk factor—was identified in individuals with hypothyroidism, and correlations were found between inflammatory markers, lipid parameters, and renal function.

Chapter 5. (The Impact of Levothyroxine Replacement Therapy on the Studied Parameters). The treatment of choice for hypothyroidism is levothyroxine monotherapy. The presence of clinical symptoms and hormonal confirmation of hypothyroidism are indications for initiating replacement therapy [36]. The goals of levothyroxine treatment in hypothyroidism are symptom relief and normalization of TSH and fT4 levels. The average replacement dose is 1.6 mcg/day in hypothyroidism [36]. Most international society guidelines recommend basing the decision regarding the need for treatment on age, TSH level, symptoms, cardiovascular risk, and other comorbidities [37].

Analysis of TSH levels in L1 showed a significant decrease during treatment, from 50.59±63.82 µIU/mL to 6.22±12.10 µIU/mL and 4.46±8.43 µIU/mL, respectively, after 8 ($t=6.31$, $p<0.001$) and 16 weeks , respectively ($t=6.31$, $p<0.001$). The fT4 level increased

significantly over the same time period, from 0.66±0.34 to 1.16±0.23 (t=-9.93, p<0.001) and 1.20±0.24 (t=-10.26, p<0.001).

In the HM subgroup, the TSH level decreased after 8 weeks of T4 treatment, reaching a mean value of 8.60±16.08 μIU/mL, considerably lower than the baseline value of 87.71±67.75 μIU/mL (t=8.08, p<0.001), and 16 weeks after the start of treatment and , as a result of adjusting the T4 dose as needed, the mean TSH level was 5.68±11.01 μUI/mL (95% CI 1.91; 9.46) (t=8.01, p<0.001).

The fT4 level increased after 8 weeks of treatment, reaching a mean value of 1.18±0.28 ng/dL, which was considerably higher than the baseline value of 0.40±0.23 ng/dL (t=-13.79, p<0.001), and 16 weeks after treatment initiation, following adjustments to the T4 dose as needed, the mean fT4 level was 1.22±0.24 ng/dL (t=-14.35, p<0.001).

In the HS subgroup, the TSH level decreased significantly after 8 weeks of T4 treatment, reaching a mean value of 3.44 ± 2.27 μIU/mL, which was significantly lower than the baseline value of 7.30 ± 2.50 μIU/mL (t = 8.07, p < 0.001), and 16 weeks after treatment initiation—and as a result of T4 dose adjustments as needed—the mean TSH level was 3.03±3.28 μIU/mL (95% CI 1.80; 4.25) (t=7.10, p<0.001). The median TSH level also decreased significantly after 8 and 16 weeks of T4 treatment, from 6.72 to 3.08 (WSR=4.78, p<0.001) and 3.03 (WSR=4.54, p<0.001), respectively.

The fT4 level increased after 8 weeks of treatment, reaching a mean value of 1.13 ± 0.17 ng/dL, considerably higher than the baseline value of 0.96 ± 0.14 ng/dL (t = −6.23, p < 0.001), and 16 weeks after treatment initiation—and as a result of adjusting the T4 dose as needed—the mean fT4 level was 1.17 ± 0.24 ng/dL (t = −5.04, p < 0.001). The median fT4 level also increased significantly after 8 and 16 weeks of T4 treatment, from 0.95 to 1.11 (WSR=4.28, p<0.001) and 1.21 (WSR=3.86, p<0.001), respectively.

A comparison of the CT level in L1 before and after treatment showed a favorable trend after 16 weeks of treatment, from 6.07±2.10 mmol/l to 5.16±1.26 mmol/l (t=4.19, p<0.001), LDL-c from 3.96±1.67 mmol/l to 3.28±1.00 mmol/l (t=3.46, p=0.001), nonHDL-c from 4,54±1,92 to 3,68±1,17 mmol/l (t=4,44, p<0,001). No favorable change was observed in HDL-c levels during replacement therapy (from 1,53±0,46 mmol/l to 1,48±0,36 mmol/l (t=1.14, p=0,258).

The effects of levothyroxine treatment on lipid profile indices in subgroups are shown in Table 4.

Table 4. Effects of levothyroxine treatment on lipid profile indices.

Parameters	HM				HS			
	No treatment	8 weeks of treatment	16 weeks of treatment	p	No treatment	8 weeks of treatment	16 weeks of treatment	p
CT	6,87±2,45	5,05±1,36	5,32±1,50	<0,001*,†	5,13±1,02	5,29±1,13	4,98±0,90	0,011‡
LDL-c	4.56±1,96	3,00±0,94	3,36±1,12	<0,001*, <0,005†	3,26±0,83	3,38±1,02	3,19±0,84	0,103* 0,543†
HDL-c	1,56±0,57	1,32±0,34	1,46±0,44	<0,001*, <0,005‡	1,50±0,30	1,48±0,27	1,51±0,22	0,51* 0,671†
Non HDL-c	5,31±2,19	3,74±1,26	3,86±1,33	<0,001*,†	3,64±0,96	3,81±1,08	3,47±0,92	0,07* 0,144† 0,003‡

Note. * - p-value for the 0–8-week treatment period, † - p-value for the 0–16-week treatment period, ‡ - p-value for the 8–16-week treatment period.

An analysis of changes in serum creatinine levels in individuals with hypothyroidism revealed a decrease in concentration after 8 and 16 weeks of T4 treatment, from 69.66±18.41 µmol/L to 61.78±12.45 µmol/L (t=4.85, p<0.001) and 60.19±10.15 µmol/L (t=5.61, p<0.001), respectively. In the HM subgroup, the serum creatinine level prior to treatment was 77.62±18.77 µmol/L, and after 8 and 16 weeks of treatment with T4, it decreased to 63.21±12.41 µmol/L (t=6.34, p<0.001) and 61.71±9.96 µmol/L , respectively (t=6.91, p<0.001). In the HS subgroup, no statistically significant differences in serum creatinine levels were found after 8 and 16 weeks of T4 treatment .

The mean eGFR value in L1 was 100.57±20.40 ml/min/1.73 m^2 prior to treatment and 109.34±14.98 ml/min/1.73 m^2 after 8 weeks (t=-5.17, p<0.001) and 111.06±12.55 ml/min/1.73 m^2 (t=-6.10, p<0.001) after 16 weeks of treatment with T4.

The GFR level also underwent statistically significant changes in the HM subgroup, from 91.89±19.80 ml/min/1.73 m^2 to 107.77±14.88 ml/min/1.73 m^2 ($t = -6.83$, $p < 0.001$) and 109.51 ± 11.87 ml/min/1.73 m^2 ($t = -7.63$, $p < 0.001$), respectively, after 8 and 16 weeks of treatment. In the HS subgroup, no statistically significant differences in GFR levels were observed during T4 treatment.

The hs-PCR level also changes during levothyroxine treatment [38, 20]. The mean hs-PCR level after 8 and 16 weeks of T4 treatment in L1 decreased to 1.80±1.24 mg/L (t=1.98, p=0.053) and 1.63±1.10 mg/L, respectively (t=2.80, p=0.007), compared with 2.20±1.64 mg/L prior to treatment. At the same time, the median hs-PCR value at 16 weeks was 1.26 [0.84–2.00], compared with the median value prior to treatment of 1.73 [0.96–3.15]. When this difference was examined using nonparametric tests, a statistically significant difference emerged (p=0.017).

In the HM subgroup, the hs-CRP level was 2.37±1.80 mg/L prior to treatment and 1.92 ± 1.27 mg/L and 1.57± 0.91 mg/L, respectively (t=1.44, p=0.017) after 8 and 16 weeks of treatment. The median hs-PCR value decreased from 2.46 prior to treatment to 1.43 between 8 and 16 weeks of treatment (WSR=204.0, p=0.069), and after 16 weeks of treatment, it reached 1.29 (WSR=186,0, p=0.035) (Fig. 9).

In the HS subgroup, no statistically significant differences in hs-PCR levels were observed against the background of T4 treatment.

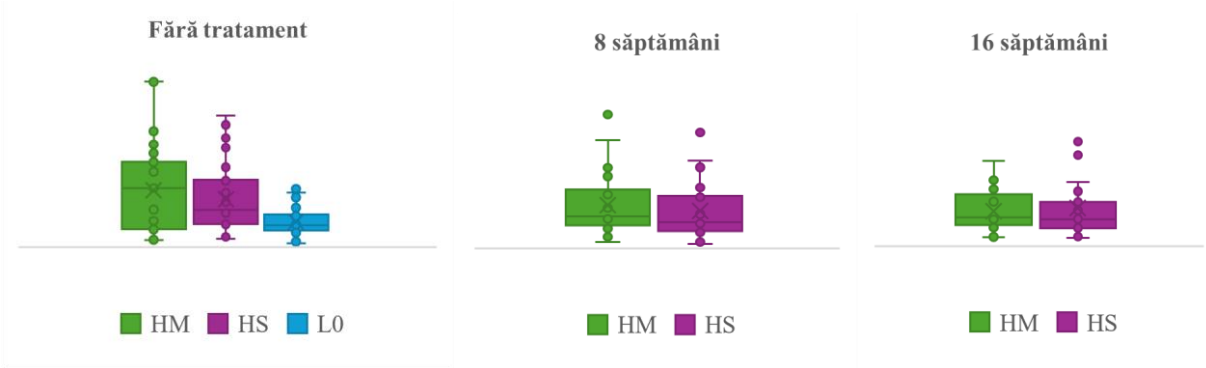

Figure 9. **Changes in hs-PCR levels in the HM and HS subgroups after 8 and 16 weeks of T4 treatment.**

The dynamics of hs-CRP levels during treatment, based on hs-CRP as an indicator of CV risk, revealed significant changes, as illustrated in Figure 10. Analyzing the evolution of hs-

CRP levels during treatment in the ranges <1, 1–3, and >3 mg/L in L1, compared to L0, we found that, while 26.2% of individuals with hypothyroidism had hs-CRP levels >3 mg/L before initiating T4 therapy, this figure dropped to 15.4% after 8 weeks and to just 9.2% after 16 weeks. In L0, no individual had an hs-CRP level > 3 mg/L. An hs-CRP level between 1 and 3 mg/L was observed in 43.1% of L1, and at 8 and 16 weeks of treatment, in 52.3% and 55.4% of individuals, respectively. An hs-PCR level <1 mg/L, which corresponds to a low CV risk, was observed in only 30.8% of patients in L1 (among those with CK > 1000 U/L), compared with 56.3% of patients in L0 (p<0.001).

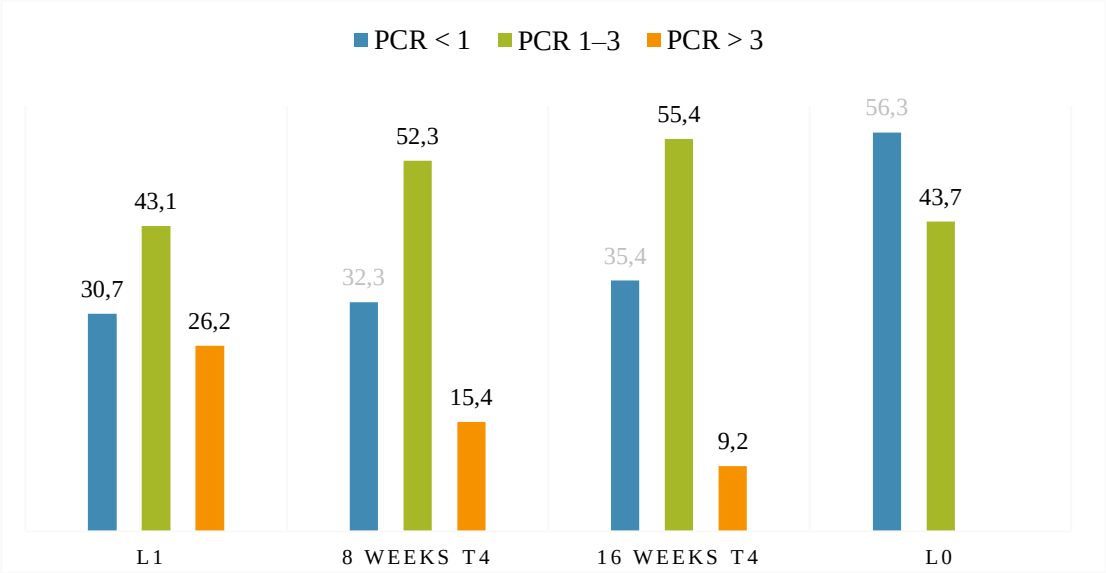

Figure 10. **Changes in hs-PCR levels in the ranges <1, 1–3, and >3 mg/L during T4 therapy.**

The analysis of CK levels in L1, following 16 weeks of treatment, showed a decrease in the mean value from 488.21±1063.06 U/L to 94.24±51.76 U/L (t=2.98, p=0.004) , and in the HM subgroup—from 832.17±1362.35 U/L to 92.38±39.89 U/L (t=3.23, p=0.003).

Among individuals with HM and CK levels > 1000 U/L (2483.04 ± 1881.27 U/L), the mean hs-PCR (1.17 ± 1.36 mg/L) did not change significantly over the course of 16 weeks of T4 treatment (1.12 ± 0.73 mg/L); however, the median hs-PCR value increased after 8 weeks of treatment, from 0.63 to 1.33 mg/L. At the same time, among individuals with HM and CK < 1000 U/L (223.54 ± 190.77 U/L), the mean hs-CRP level decreased from 2.62 ± 1.59 mg/L to 1.75 ± 0.93 mg/L during treatment.

We can conclude that the results of levothyroxine treatment suggest a beneficial impact on lipid metabolism, renal function, and subclinical inflammation, indicating an improvement in the cardiovascular risk factors associated with hypothyroidism.

Chapter 6. (Quality of Life in People with Autoimmune Hypothyroidism). The ThyPRO-39 questionnaire is used to assess physical, functional, and mental symptoms, physical appearance, well-being, and the level of participation in daily activities and social life among people with hypothyroidism.

The assessment of quality-of-life scales—Cognitive problems, Depressivity, Daily Life, Cosmetic Complaints, and Composite Score—showed differences between the L1 group and the L0 group. The mean score for the Cognitive problems scale was 34.58±26.47 in the L1 group, compared with 23.88±19.78 in the L0 group (F=6.71, p=0.011), on the Depressivity scale –

43.34±18.88 in L1, compared to 37.52±12.87 in L0 (F=4.16, p=0.043), Impaired Daily Life – 31.59±28.57 in L1, compared to 20.86±22.28 in L0 (F=5.62, p=0.019), Cosmetic Complaints – 33.00±26.24 in L1, compared to 13.16±16.69 in L0 (F=26.07, p<0.001), Composite Score – 39.75±16.29 in L1, compared to 33.20±13.60 in L0 (F=6.10, p=0.015). The quality-of-life scales—Anxiety, Emotional susceptibility, functional symptoms (Tiredness), and Social Life—were not significantly different in the L1 group compared to the L0 group. After adjustment, the only significant differences remain those for Goiter Symptoms, Hypothyroid Symptoms, and Cosmetic Complaints. The scores for Cognitive problems, Daily life, Depressivity, and the Composite Score did not reach statistical significance after correction, although they were significant at the raw threshold: Cognitive problems (p = 0.027; Holm's p = 0.216), Impaired Daily life (p = 0.048; Holm p = 0.334), and Composite Score (p = 0.021; Holm p = 0.186). For Tiredness, Anxiety, Depressivity, Emotional Susceptibility, and Impaired Social life, no differences were found even at the raw threshold.

After 16 weeks of levothyroxine replacement therapy, an improvement was observed in all QoL scales studied, compared to pre-treatment data (Table 5).

Table 5. Changes in QoL Scores in L1 Over Time During Treatment

Scale	Paired differences				t	p
			95% CI			
	Mean	DS	Lower	Upper		
Hypo_p-Hypo_d	21,39	17,78	16,95	25,83	9,63	<0,001
Goitre_p-Goiter_d	12,17	12,62	9,02	15,32	7,72	<0,001
Tiredness _p - Tiredness _d	12,84	14,70	9,17	16,52	6,99	<0,001
Cognitive _p - Cognitive_d	17,78	19,97	12,79	22,77	7,13	<0,001
Anxiety_p - Anxiety_d	18,70	16,33	14,62	22,78	9,16	<0,001
Depressivity_p - Depressivity_d	12,06	17,44	7,71	16,42	5,53	<0,001
Suscept_p - Suscept_d	9,45	14,99	5,71	13,20	5,05	0,001
Social_p – Social_d	10,69	20,50	5,57	15,81	4,17	<0,001
Daily_p – Daily _d	21,55	20,12	16,52	26,57	8,57	<0,001
Cosmetic_p - Cosmetic_d	14,41	18,30	9,84	18,98	6,30	<0,001
Composit_p – Composit _d	15,55	11,85	12,59	18,51	10,50	<0,001

Note: Cognitive – Cognitive problems scale, Suscept – Emotional Susceptibility scale, Daily – Impaired Daily life scale, Cosmetic – Cosmetic Complaints scale, Composit – Composite scale
_p – before treatment, _d – after treatment.

The differences remain significant even after adjustment.

An analysis of the QoL scales in the HM and HS subgroups showed that the overall test remains significant after adjustment for three scales: Goitre Symptoms (p Holm = 0.003; ε^2 = 0.116), Hypothyroid Symptoms (Holm p = 0.004; ε^2 = 0.109), and Cosmetic Complaints (Holm

$p < 0.001$; $\varepsilon^2 = 0.193$). Post-hoc analysis shows that each of these differences stems from a single clinical form. Goitre Symptoms scale differed in HS compared to L0 ($p = 0.001$; $r = 0.418$), while Hypothyroid Symptoms scale ($p < 0.001$; $r = 0.369$) and items regarding Cosmetic Complaints ($p < 0.001$; $r = 0.501$) distinguished HM from L0. Analysis of the Depressivity, Impaired Daily life, and Composite scales in the HM group at the raw threshold revealed statistical differences: Depressivity $p = 0.025$, Impaired Daily life $p = 0.044$, Composite Score $p = 0.042$; however, these did not reach statistical significance after adjustment. Cognitive problems, Tiredness, Anxiety, Emotional Susceptibility, and Impaired Social life scales did not show significant differences even at the raw threshold. In the HS group compared to the L0 group, no scale—except for Goiter Symptoms scale —showed significant differences.

All assessed scales showed significant improvement in the HM subgroup after 16 weeks of levothyroxine treatment. In the HS subgroup, all of the assessed scales showed significant improvement, with the exception of Depressivity and Impaired Social life scales. The extent of improvement was greater in the overt form, which corresponds to the more pronounced initial severity of symptoms in this subgroup.

Thus, the quality of life (QoL) of patients with hypothyroidism is low, and replacement therapy has a favorable effect on certain aspects of quality of life (Fig. 11).

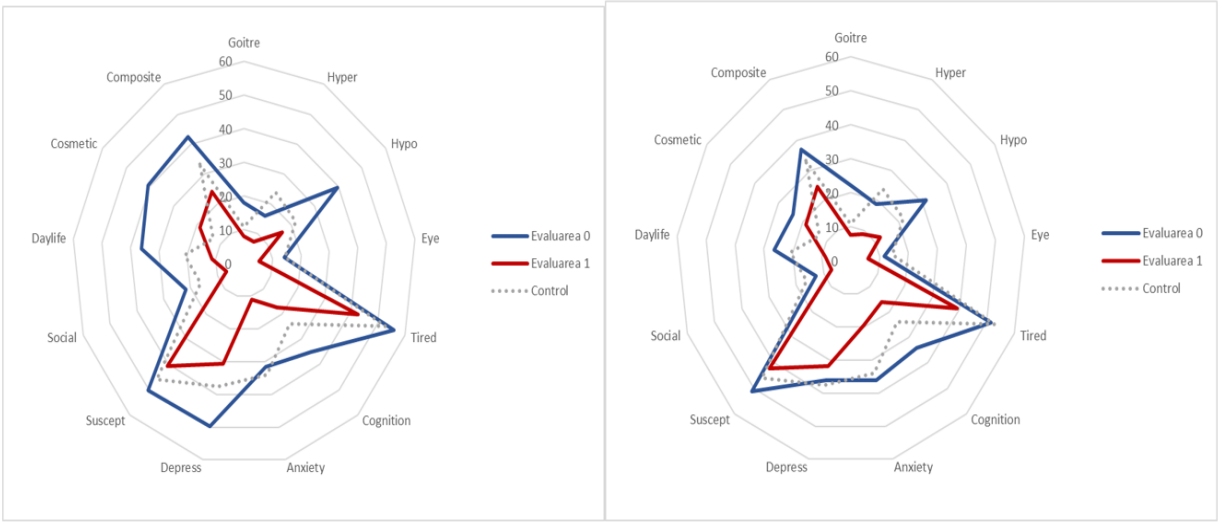

Figure 11. **QoL in HM (left) and HS (right) on T4 therapy**

To assess the impact of clinical and biochemical parameters on patients' quality of life, multiple linear regression analysis was performed, with the dependent variable being the ThyPRO-39 composite score at the initial visit. The explanatory variables tested were BMI, age, hs-CRP, TSH, creatinine, CT, Na^+, fibrinogen, free T4, free T3, anti-TPO, and RFG. The optimal model included four predictors: total cholesterol, fibrinogen, free T4, and free T3 (tab. 6)

Table 6. Regression coefficients for the ThyPRO-39 questionnaire

Predictor	B (ES)	β	t	p	95% CI for B
Constant	56,532 (13,472)	—	4,196	< 0,001	29,575; 83,489
Total cholesterol	1,545 (1,056)	0,199	1,462	0,149	-0,569; 3,659
Fibrinogen	-6,384 (2,877)	-0,260	-2,219	0,030	-12,140; -0,628
Free T4	14,317 (7,413)	0,298	1,931	0,058	-0,516; 29,151

Predictor	B (ES)	β	t	p	95% CI for B
Free T3	-6,138 (2,410)	-0,416	-2,547	0,013	-10,961; -1,316

The model is significant, $F(4;59) = 5.927$; $p < 0.001$, and explains 23.8% of the variance in the composite score (adj. $R^2 = 0,238$, $R^2 = 0,287$).

Free T3 and fibrinogen were found to be significant factors. Negative coefficients indicate an inverse relationship: as their levels decrease, the ThyPRO-39 score increases. Free T4 showed a trend toward a positive association with the ThyPRO-39 score, and total cholesterol was not significant.

The results of the quality-of-life assessment for individuals with HM and HS after 16 weeks of treatment with levothyroxine showed that the scores of the treated patients were significantly lower than those of the control group on certain scales: Tiredness, Anxiety, Depressivity, Impaired Social life, Impaired Daily life, and Composite scales. After adjustment, the differences remain significant for Tiredness, Anxiety, Depressivity, and the Composite scales. This may result not only from the favorable impact of replacement therapy but also from the convergence of several factors: the *"response* shift" phenomenon, the benefits of regular medical monitoring and associated healthy behaviors, as well as the heterogeneity of well-being within the "healthy" group, which may include individuals with emotional problems or chronic stress.

Therefore, multiple factors play an important role in determining the level of satisfaction with replacement therapy and the quality of life of people with hypothyroidism. Not only hypothyroidism itself, but also age, gender, patients' expectations, communication with medical staff have a major impact on satisfaction and quality of life.

GENERAL CONCLUSIONS

1. The clinical profile of primary hypothyroidism manifests as a complex of nonspecific symptoms (fatigue, hypohidrosis, dry skin), symptoms reflecting psychological impairment (memory loss, mood changes), and gastrointestinal system impairment (constipation).
2. Lipid metabolism abnormalities in hypothyroidism indicate a proatherogenic profile and increased cardiovascular risk in L1 and overt hypothyroidism. Renal function is impaired in L1 and in overt hypothyroidism, with significantly higher serum creatinine levels and lower eGFR values compared to healthy individuals.
3. Elevated hs-CRP levels in individuals with both overt and subclinical hypothyroidism, confirm the presence of subclinical inflammation. hs-CRP levels representing an increased cardiovascular risk (>3 mg/L) were observed only in patients with hypothyroidism, more frequently in overt hypothyroidism than in subclinical hypothyroidism.
4. Significantly elevated creatine kinase levels in overt hypothyroidism, along with correlations between creatine kinase and renal function – serum creatinine and eGFR - suggest a complex impact of hypothyroidism on the muscular system and renal function. In individuals with CK levels > 1000 U/L, hs-CRP levels were < 1 mg/L, suggesting distinct physiopathological mechanisms that require investigation.
5. Treatment with levothyroxine had a beneficial effect on renal function, lipid metabolism, and a trend toward a reduction in low-grade inflammation, indicating an improvement in cardiovascular risk factors associated with hypothyroidism. The effects of treatment were more pronounced in overt hypothyroidism compared to subclinical hypothyroidism.

6. The study of quality of life revealed a significant decline in quality of life among individuals with hypothyroidism, particularly as measured by scales assessing Hypothyroid Symptoms, Cosmetic Complaints, and Goitre Symptoms. With levothyroxine replacement therapy, all scales showed significant improvement in L1 and HM, while in HS, the improvement in Depressivity scale and Impaired Social life scale did not reach statistical significance after adjustment.

7. The identification of a nonspecific and heterogeneous clinical presentation, a proatherogenic metabolic profile, the presence of low-grade systemic inflammation, organ involvement (renal function, muscles), and impaired quality of life in autoimmune hypothyroidism among young people justifies an individualized approach to disease management.

RECOMMENDATIONS

1. Screen for cardiovascular risk factors in young individuals with hypothyroidism to initiate early treatment and prevent cardiovascular complications.

2. Identifying and monitoring subclinical inflammation via hs-CRP—a biomarker of low-grade systemic inflammation that provides important prognostic information about cardiovascular risk, similar to cholesterol and blood pressure, along with other biological parameters—could be useful for stratifying cardiovascular risk in individuals with hypothyroidism, who may benefit most from early interventions.

3. CK measurement should be included in the evaluation and monitoring of patients with hypothyroidism, with or without muscle symptoms, to detect severe muscle damage early. The correlations between CK levels and the severity of thyroid deficiency and renal function call for an integrated management approach that includes concurrent monitoring of renal function.

4. Assessing the quality of life of individuals with hypothyroidism using the ThyPRO-39 questionnaire, to identify persistent nonspecific symptoms that may go unnoticed during standard clinical evaluation, is a valuable tool that helps personalize treatment and optimize care for people with autoimmune hypothyroidism, providing a detailed perspective on the disease's impact on daily life.

5. Long-term monitoring of patients with autoimmune hypothyroidism, adopting an individualized approach that goes beyond normalizing TSH levels and providing high-quality, patient-centered information to increase satisfaction with treatment and improve quality of life.

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LIST OF PUBLICATIONS AND ACTIVE PARTICIPATION IN SCIENTIFIC FORUMS

by Mrs. Stela Vudu, Ph.D. graduate, Department of Endocrinology,
"Nicolae Testemițanu" State University of Medicine and Pharmacy in the Republic of Moldova,
as part of her doctoral dissertation in medical sciences on the topic
"Clinical and Metabolic Parameters and Low-grade Inflammation in Patients with Autoimmune Hypothyroidism"
Specialty 321.02 – Endocrinology

- **Articles in international scientific journals: articles in ISI, SCOPUS and other international databases**
  - ✓ **Vudu S.**, Behnke A. C-reactive Protein Levels in Patients With Autoimmune Hypothyroidism Before and After Levothyroxine Treatment. In: *Cureus*. 2023; 15(12):e50848.doi:10.7759/cureus.50848.(**IF:1.2**). https://pubmed.ncbi.nlm.nih.gov/38249164/
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Participation with presentations at scientific forums:

International

- ✓ **Vudu S**. Prevalence of metabolic diseases in the adult population of the Republic of Moldova – an epidemiological study (preliminary data). Poiana Brașov, România. 21-24 mai 2023.
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Participation with poster presentations at scientific forums:

International

- ✓ **Vudu S.** Lipid profile in subclinical and overt hypothyroidism. *ESE Young Endocrinologists and Scientists (EYES)*. Helsinki, Sweden, 6-8 septembrie 2024.
- ✓ **Vudu S.** Epidemiology of primary hypothyroidism in the Republic of Moldova. *The 26th European Congress of Endocrinology*. Stockholm, Sweden, 11-14 mai 2024.
- ✓ **Vudu S.** C reactive protein level in patients with autoimmune hypothyroidism before and after levothyroxine treatment. *25th European Congress of Endocrinology,* Istanbul, Turkey, 13-16 mai 2023.

National

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- ✓ Vudu L., Şeremet A., **Vudu S**., et al. Hipotiroidia: protocol clinic naţional PCN-34: (ediția II) Chișinău: 2023. 45 p. https://ms.gov.md/wp-content/uploads/2023/12/PCN-34-Hipotiroidia-editia-II-aprobat-prin-Ordinul-MS-nr.1163-21.12.2023.pdf

ANNOTATION

Stela Vudu „Clinical and metabolic parameters and low-grade inflammation in patients with autoimmune hypothyroidism".

PhD Thesis in Medical Sciences, 321.02 Endocrinology, Chișinău, 2026.

Thesis structure: The thesis includes an introduction, 7 chapters, general conclusions, recommendations, bibliography (354 references), 107 text pages, 24 figures, 13 tables, 4 inovator certificates, 4 implementation acts, appendices. The results generated 8 *in extenso* publications, 12 thesis at international and national conferences, 1 National Clinical Guideline and 13 presentations at international and national congresses.

Key words: autoimmune hypothyroidism, subclinical hypothyroidism, autoimmune thyroiditis, low grade inflammation, hs-CRP, cardiovascular risk, nonHDL-cholesterol, creatine kinase, levothyroxine, quality of life, ThyPRO-39.

Aim of the study: To evaluate biomarkers of low-grade systemic inflammation and their relationship to clinical and metabolic parameters, and evaluation of quality of life in individuals with autoimmune hypothyroidism, before and after treatment with levothyroxine, in order to integrate the concept of low-grade inflammation into the management of autoimmune hypothyroidism.

Objectives: Characterisation of the clinical and hormonal profile in individuals with autoimmune hypothyroidism. Analysis of the metabolic profile in individuals with autoimmune hypothyroidism. Assessment of inflammatory biomarkers in individuals with autoimmune hypothyroidism. Evaluation of the effect of levothyroxine treatment on clinical and metabolic parameters, and inflammatory biomarkers. Assessment of quality of life in individuals with autoimmune hypothyroidism before and after levothyroxine treatment.

Scientific novelty: The presence of low-grade inflammation in individuals with autoimmune hypothyroidism has been identified, which represents an increased cardiovascular risk factor, especially in young non-obese women, considered *a priori* to have low cardiovascular risk. It was determined that individuals with very high creatine phosphokinase (>1000 U/L) have a hs-PCR level < 1 mg/L, indicating a low inflammatory process. The study highlighted the complex interaction between low-grade inflammation, lipid metabolism, renal function and hypothyroidism. The results contribute to the understanding of the common pathogenic mechanisms between thyroid dysfunction, low-grade inflammation and cardiovascular risk, offering new perspectives for the evaluation and management of patients with hypothyroidism. Original are the data on the significant negative impact of the disease on quality of life, especially on the Hypothyroid Symptoms, Goitre Symptoms, and Cosmetic Complaints scales, as well as the persistence of some symptoms, despite substitution treatment, which suggests that standard levothyroxine therapy is not always sufficient and an individualized approach is necessary in the management of hypothyroidism.

Theoretical significance: The research contributes to the deepening of knowledge regarding the role of low-grade inflammation in autoimmune hypothyroidism and highlights its interaction with thyroid dysfunction, lipid metabolism and cardiovascular risk factors. The presence and persistence of low-grade inflammation after the initiation of levothyroxine treatment suggests pathogenetic mechanisms in the evolution of hypothyroidism, independent of the normalization of thyroid gland function.

Practical value: the need to assess the presence of low-grade inflammation as a relevant pathogenic factor and the degree of inflammation. Identification of the persistence of inflammation is also appropriate after the initiation of levothyroxine treatment. The application of the ThyPRO-39 questionnaire revealed a considerable impairment of quality of life, despite the substitution treatment with levothyroxine, which emphasizes the need for an extensive diagnostic and therapeutic approach, which provides not only the normalization of hormonal parameters, but also the assessment and improvement of QOL. The results thus contribute to the development of individualized clinical recommendations in the management of this condition.