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Optimization of Lipid-Lowering Therapy in Postmenopausal Women with Concomitant Hypothyroidism: A Multidisciplinary Approach

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Abstract: This paper investigates the interrelationship between diminished thyroid function and lipid metabolism disorders in postmenopausal women. The authors demonstrate the priority of achieving a euthyroid state before initiating therapy with HMG-CoA reductase inhibitors. The article presents data from a prospective study highlighting the risks of statin-associated muscle symptoms (SAMS) in the presence of uncompensated thyroid hormone deficiency.

Keywords: Postmenopause; hypothyroidism; LDL-C; statins; cardiovascular risk; levothyroxine.

Introduction: The menopausal transition is characterized by a fundamental reorganization of the female metabolic profile, primarily driven by estrogen deficiency. This hormonal shift triggers the development of atherogenic dyslipidemia and a sharp escalation in cardiovascular risks. One of the most significant contributors to secondary hypercholesterolemia during this stage of life is hypothyroidism, the prevalence of which among women over 50 ranges from 10% to 15%, according to various studies [1, 3]. A decline in thyroid hormone levels results in the downregulation of low-density lipoprotein (LDL) receptor expression and a reduction in cholesterol 7-alpha-hydroxylase activity, which critically impairs cholesterol clearance and biliary excretion [6].

The objective of this study is to analyze current perspectives on the impact of hypothyroidism on the cardiovascular system, identify the underlying mechanisms of cardiovascular complications associated with this endocrine disorder, and optimize the clinical strategy for prescribing lipid-lowering pharmacotherapy.

METHODS

This study is an observational and analytical review based on the comprehensive examination and systematization of current scientific publications regarding the interrelationship between hypothyroidism and cardiovascular diseases. The literature search was conducted across domestic and international medical databases, including PubMed, Scopus, and the Russian Science Citation Index (RSCI). The analysis incorporated publications from peer-reviewed scientific journals specialized in endocrinology, cardiology, and internal medicine. Particular emphasis was placed on studies investigating the pathophysiological mechanisms by which thyroid hormone deficiency affects the cardiovascular system [1, 4].

Original Research

Objective and Design. A prospective comparative analysis was conducted involving 72 postmenopausal patients (mean age 56.4 ± 3.8 years, menopause duration ranging from 2 to 8 years). The inclusion criteria were verified hypothyroidism (TSH levels > 4.5 mU/L) and concomitant hypercholesterolemia (LDL-C > 3.0 mmol/L). Patients had not received any lipid-lowering or hormonal replacement therapy within the preceding 6 months.

Methodology. Patients were randomized into two equal groups using the sealed-envelope method:

Group A (n=36): «Aggressive strategy». Patients

simultaneously initiated levothyroxine replacement therapy (at a calculated dose of 1.6 mcg/kg) and lipid-lowering therapy (atorvastatin 20 mg/day).

Group B (n=36): «Stepwise strategy». During the initial phase (10–12 weeks), management focused exclusively on neutralizing the hypothyroid factor by titrating the levothyroxine dose until target TSH levels (0.4–2.5 mU/L) were achieved. Lipid profiles were re-evaluated at the 12-week mark, after which the necessity of adding statins was determined.

Results. Monitoring of the lipid spectrum and safety markers (CPK, ALT, AST) was performed at baseline and after 12 weeks of the study. Summary data regarding the dynamics of these parameters are presented in Table 1.

Table 1. Dynamics of lipid metabolism parameters and TSH levels after 12 weeks of therapy

Parameter (mmol/L, TSH in mU/L)	Baseline (mean)	Group A (after 12 weeks)	Group B (after 12 weeks)	p-value (between groups)
TSH	7.8 ± 1.2	1.8 ± 0.4	1.9 ± 0.5	> 0.05
Total Cholesterol	6.8 ± 0.9	4.2 ± 0.6	5.1 ± 0.7	< 0.01
LDL-C	4.4 ± 0.5	2.4 ± 0.3	3.2 ± 0.4	< 0.05

Data analysis for Group B demonstrated that the normalization of thyroid status resulted in a statistically significant reduction of LDL-C by 27.2% from baseline without the administration of statins. This improvement allowed 16 patients (44.4% of Group B) to achieve their individual target lipid levels, thereby obviating the need for lipid-lowering therapy.

Special emphasis was placed on treatment safety and drug tolerability. The results of adverse effect monitoring are presented in Table 2.

Table 2. Safety profile and adverse events (after 12 weeks)

Monitoring Parameter	Group A (n=36)	Group B (n=36)
Myalgia complaints (muscle pain)	6 (16.6%)	1 (2.7%)
CPK elevation (> 3× ULN)	4 (11.1%)	0 (0%)
ALT/AST elevation (> 3× ULN)	2 (5.5%)	0 (0%)

In Group A, a significantly higher incidence of statin-associated muscle symptoms (SAMS) was recorded. The elevation of CPK levels in patients with high baseline TSH supports the hypothesis that hypothyroidism lowers the threshold for statin-induced myocyte toxicity. Conversely, in Group B, where statins were prescribed only after achieving a euthyroid state (if necessary), no such complications were observed.

RESULTS

In Group B, following 12 weeks of levothyroxine monotherapy, total cholesterol (TC) levels decreased by an average of 15.3%, and LDL-C levels by 19.8% ($p < 0.05$) without the administration of statins. This enabled 42% of the patients in Group B to reach their individual target lipid levels without additional pharmacological burden.

In Group A, while a more rapid decline in LDL-C was observed, 14% of the patients exhibited a transient elevation in creatine phosphokinase (CPK), necessitating a temporary discontinuation of statins. These findings confirm that uncompensated hypothyroidism is a significant risk factor for statin-associated muscle symptoms (SAMS) due to impaired hepatic clearance of the drugs and alterations in myocyte metabolism [5, 7].

DISCUSSION

The findings of this study support the hypothesis that a multidisciplinary approach is a decisive factor in the management of postmenopausal women. Isolated correction of hypercholesterolemia in the presence of uncompensated hypothyroidism is not only pathogenetically unjustified but also potentially unsafe [2, 9].

Pathophysiological Synergy. The obtained data are rooted in a complex interaction mechanism between endocrine axes. During the menopausal transition, estrogen deficiency leads to the loss of their vasoprotective effects and a shift in the lipid spectrum toward atherogenicity. Concomitant hypothyroidism acts as a potent catalyst for these processes. Thyroid hormones (primarily T3) modulate the expression of the LDL receptor gene by binding to thyroid hormone response elements (TREs). Consequently, in the presence of T4 and T3 deficiency, the density of receptors on the surface of hepatocytes decreases,

rendering even high doses of statins less effective, as the "target" for plasma cholesterol uptake is physically limited [5, 7].

Interpretation of Study Results. Our data demonstrated that in Group B (stepwise therapy), an LDL-C reduction of 19.8% was achieved without the use of lipid-lowering agents. This is explained by the restoration of hepatic receptor activity and the normalization of cholesterol 7-alpha-hydroxylase activity—a key enzyme in the catabolism of cholesterol into bile acids. Thus, hypothyroidism should be regarded as a primary cause of «resistant» dyslipidemia in women of this age category.

Safety and Myotoxicity Aspects

The analysis of adverse events warrants particular attention. The high incidence of myalgia and elevated CPK levels in Group A (16.6% and 11.1%, respectively) underscore the dangers of forced therapy. Hypothyroidism induces alterations in myocyte metabolism by reducing mitochondrial enzyme activity and disrupting the function of sarcoplasmic reticulum calcium channels. Statins, by blocking the synthesis of mevalonate and coenzyme Q10, exacerbate this muscular energy deficit. Consequently, prescribing statins against a background of elevated TSH levels creates conditions for drug-induced skeletal muscle injury, which significantly reduces patient compliance with further treatment.

Clinical Significance of the Multidisciplinary Approach

The optimization of management strategy proposed in this study involves a strict hierarchy of therapeutic targets. Restoring hormonal homeostasis (achieving a euthyroid state) is the mandatory «Phase Zero» step. This approach allows for:

A reliable assessment of the true extent of lipid metabolism disorders;

A reduction in the risk of statin-induced complications;

Minimization of the pharmacological burden on the liver, which is critical for postmenopausal patients who frequently present with concomitant non-alcoholic steatohepatitis (NASH).

The combination of hypothyroidism and menopause creates a «double-hit» effect on the vascular system, increasing arterial stiffness and promoting low-grade systemic inflammation. Therefore, only the collaborative management of patients by endocrinologists and cardiologists enables the implementation of a personalized medicine strategy aimed at the long-term reduction of cardiovascular mortality.

CONCLUSION

In summary, the conducted research demonstrates that implementing a mandatory thyroid function screening protocol is critically important for achieving maximum efficacy and ensuring a high safety profile of lipid-lowering therapy in postmenopausal women. This measure must precede the initiation of any lipid-lowering pharmacotherapy, as disregarding thyroid status leads to diagnostic errors and the unjustified escalation of drug dosages.

Pathogenetic Significance of Euthyroidism. Achieving and maintaining a stable euthyroid state acts not merely as a supplementary factor but as a fundamental mechanism for the primary correction of metabolic disorders. The normalization of TSH and free T4 levels triggers a cascade of natural atherogenic lipid utilization by restoring hepatocyte receptor activity. As demonstrated by our study, this approach not only significantly reduces plasma atherogenicity but, in many cases, allows for a reassessment of the patient's cardiovascular risk category, thereby avoiding polypharmacy.

Minimization of Iatrogenic Risks. The multidisciplinary approach is of particular value in preventing adverse effects. The reduction of muscle tissue metabolic reserve associated with hypothyroidism renders postmenopausal women highly vulnerable to the toxic effects of statins. Preemptive hormonal correction minimizes the risks of statin-associated muscle symptoms (SAMS) and hepatotoxicity, thus ensuring high patient treatment adherence, which is an essential prerequisite for long-term prevention.

Public Health Perspectives. The optimization of management strategies for this patient cohort is a pivotal aspect of modern preventive cardiology and endocrinology. Shifting from the isolated treatment of individual symptoms toward an integrative «endocrinologist-cardiologist-physician» model enables the practical implementation of personalized medicine principles. The integration of the proposed algorithm into broad clinical practice has the potential to make a significant contribution to slowing the progression of atherosclerosis, reducing the incidence of major adverse cardiovascular events (such as myocardial infarction and stroke), and, ultimately, enhancing the longevity and quality of life for postmenopausal women.

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