

Review

Lipid Profile Pitfalls in Subclinical Hypothyroidism Pathophysiology and Treatment

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Abstract: Background: Lipids encompass a diverse group of biomolecules that are crucial for maintaining the body's internal equilibrium and for a range of functions, including energy storage, maintenance of cellular membranes, and cellular signalling. Their synthesis and metabolism are intricately linked to hormonal regulation, particularly by thyroid hormones, which influence lipid metabolism by modulating gene expression, enzyme activity, and mitochondrial function. Thyroid hormones enhance the metabolic rate, lipid clearance, and cholesterol conversion to bile acids, which are regulated through feedback mechanisms involving the hypothalamic–pituitary–thyroid axis. Subclinical hypothyroidism (SCH) presents a complex challenge in understanding lipid metabolism. **Methods:** Research on SCH's impact on lipid profiles has yielded conflicting results. Some studies indicate that SCH is associated with increased levels of cholesterol and triglycerides, while others report no significant changes. These discrepancies underline the necessity for more comprehensive studies to clarify how SCH affects lipid metabolism and its potential cardiovascular implications. **Conclusions:** This review aims to consolidate the existing knowledge, exploring the biochemical pathways and clinical evidence that link thyroid dysfunction with lipid abnormalities and cardiovascular health risks. It emphasizes the critical need for further research to elucidate the full impact of SCH on lipid metabolism and its broader effects on cardiovascular health, guiding future interventions and treatment strategies.

Keywords: lipids; lipid profile; free thyroxine (FT4); thyroid stimulating hormone (TSH); subclinical hypothyroidism



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1. Introduction

Subclinical hypothyroidism (SCH) is a prevalent endocrine disorder defined by elevated levels of thyroid-stimulating hormone (TSH) with normal concentrations of free thyroxine (T4) [1]. Despite its often-asymptomatic nature, SCH has been increasingly recognized for its association with a variety of metabolic abnormalities, with lipid profile disturbances being particularly notable [2]. Lipids, a diverse group of biomolecules, are indispensable for various physiological functions, including energy storage, forming the structural foundation of cellular membranes, and facilitating cellular signalling. They are crucial for maintaining the body's internal equilibrium and for a range of functions, including energy storage, maintenance of cellular membranes, and cellular signalling [3]. The lipid abnormalities seen with SCH significantly contribute to cardiovascular risk, making it a critical area of study [4]. This literature review aims to comprehensively examine the general lipid biochemistry and the changes in lipid profiles associated with SCH, exploring the biochemical pathways and mechanisms driving these alterations. The review also explores the current evidence regarding lipid abnormalities in SCH, aiming to elucidate the clinical significance of this relationship. Additionally, it summarizes the evidence on the

therapeutic potential of thyroxine replacement therapy in normalizing lipid levels in SCH patients. Understanding the intricate balance of thyroid hormones and lipid metabolism is essential for addressing conditions like atherosclerosis and hyperlipidaemia and enhancing the treatment strategies that could mitigate the health risks associated with SCH.

2. General Biochemistry of Lipids

Lipids encompass a diverse group of biomolecules that are insoluble in water and soluble in organic solvents [5]. They are crucial for maintaining the body's internal equilibrium and for a range of functions, including energy storage, maintenance of cellular membranes, and cellular signalling [3]. The three main lipid categories are triglycerides, phospholipids, and steroids [6]. Triglycerides act as the primary energy storage molecules, which can be mobilized and utilized as needed. Phospholipids form the fundamental building blocks of cellular membranes, providing an essential barrier and structural foundation for cells [7]. Steroids have a distinctive four-ring molecular structure [8]. An important example of a steroid is cholesterol, which is synthesized in the liver and acts as a precursor for various other steroid hormones, including oestrogen, testosterone, and cortisol [8]. Cholesterol also plays a crucial role in cell membranes, where it embeds itself within the phospholipid bilayer, thereby influencing the fluidity and permeability of the membrane [8].

Lipid synthesis via the endogenous system, which is primarily active in adipose tissue and liver cells, is a complex biochemical process relying on the precursor acetyl-coenzyme A (acetyl-CoA), which is derived from the breakdown of excess carbohydrates. During lipogenesis, acetyl-CoA undergoes enzymatic transformations, with acetyl-CoA carboxylase catalysing its conversion to malonyl-CoA [9]. The enzyme fatty acid synthase complex then elongates the growing fatty acid chain by adding 2-carbon units, ultimately producing the 16-carbon saturated fatty acid palmitate. Next, triglycerides, the principal storage form of lipids, are synthesized [9]. Three fatty acids are esterified to a glycerol backbone, a reaction catalysed by enzymes like glycerol-3-phosphate acyltransferase. The resulting triglycerides coalesce into lipid droplets [10].

Cholesterol biosynthesis usually occurs in the endoplasmic reticulum of liver cells. It also starts from acetyl-CoA and involves over twenty enzymatic steps, with the enzyme β -Hydroxy β -methylglutaryl-CoA (HMG-CoA) reductase as the rate-limiting enzyme [11]. This pathway produces squalene, which is then cyclized to form the characteristic four-ring structure of cholesterol [11,12]. HMG-CoA reductase, the key enzyme in the cholesterol biosynthesis pathway is controlled by Sterol Regulatory Element-Binding Protein (SREBP), through a transcriptional regulation mechanism [12,13]. This intricate balance maintained by SREBPs helps keep cholesterol levels in check and mitigates the risks of conditions like atherosclerosis and hypercholesterolaemia.

Once lipids are synthesized, they cannot directly traverse the aqueous environment of cells and the bloodstream to reach their target tissues due to their hydrophobic nature. Instead, lipids are packaged into complex lipoprotein particles for transport throughout the body [7]. These lipoprotein particles have a core of hydrophobic lipids surrounded by a shell of phospholipids, cholesterol, and apolipoproteins. Apolipoproteins play crucial roles in the assembly, secretion, and cellular uptake of these lipoproteins. Various types of lipoproteins exist, each with a distinct composition and function [13,14].

The synthesis, transport, and metabolism of these lipid species are intricately connected to various hormonal systems, with thyroid hormones playing a central regulatory role in lipid homeostasis [15]. Specifically, thyroid hormones, including thyroxine (T4) and triiodothyronine (T3), govern a wide range of metabolic processes throughout the body, directly influencing the synthesis, transport, and utilization of lipids [16]. To be able to understand how thyroid hormone imbalances affect the lipid profile, it is important to first appreciate normal thyroid physiology.

3. The Role of Thyroid Hormones in Regulating Metabolism and Lipid Homeostasis

Thyroid hormones have a well-established role in regulating metabolism and lipid homeostasis through complex mechanisms that involve gene expression modification, enzyme activity, and mitochondrial function.

Specifically, thyroid hormones enhance the basal metabolic rate by upregulating the expression of genes involved in energy production and thermogenesis. To further increase the metabolic rate, thyroid hormones also activate the Na^+/K^+ ATPase enzyme, which is necessary for preserving ionic gradients in cells [17]. All the above processes increase the production of heat and ATP, thus increasing the total energy expenditure. In addition, in skeletal muscles, T₃ can cause a switch from slow-twitch type I muscle fibres to fast-twitch type II fibres. The expression of key proteins involved in glucose uptake, muscle contraction, and mitochondrial heat production are increased as a result of this change, enhancing the muscle's capacity for heat production and elevating the total energy expenditure [18,19].

Furthermore, thyroid hormones play a major role in lipid metabolism by influencing the production, absorption, and breakdown of cholesterol. In particular, they reduce the expression of SREBPs, which are important regulators of cholesterol synthesis, thereby lowering lipid synthesis in the liver [20]. In addition, the active form of the hormone, T₃, can speed up the liver's ability to convert cholesterol into bile acids, thus facilitating cholesterol clearance from the blood [18,21]. In order to accomplish this, the expression of the LDL receptor gene is also upregulated [18,21]. Higher numbers of LDL receptors on the surface of liver cells leads to the enhanced binding and uptake of LDL cholesterol (LDL-C) from the bloodstream. This process effectively clears LDL cholesterol, reducing its levels in the circulation [18]. Thyroid hormones also affect triglyceride (TG) metabolism by enhancing the lipid profile and promoting the clearance of triglyceride-rich lipoproteins from the blood. They achieve this by activating lipoprotein lipase, an enzyme critical for breaking down TG in lipoproteins [22].

In addition, thyroid hormone signals are integrated in the hypothalamus, where they modulate the melanocortin system, including POMC neurons that reduce food intake and increase energy expenditure by activating MC4R, and NPY/AgRP neurons that stimulate appetite and decrease energy expenditure by inhibiting POMC action on MC4R [18]. These neurons are sensitive to thyroid hormones, which can either activate or inhibit them, highlighting the critical role of these hormones in regulating appetite and feeding [18]. All the above proposed mechanisms are summarized in Figure 1.

Overall, thyroid hormones play a key role in regulating metabolic processes, lipid metabolism, and total energy balance. Consequently, imbalances in thyroid hormone production can significantly impact metabolism. For instance, hyperthyroidism, which involves excess thyroid hormones, typically results in a hypermetabolic state marked by low cholesterol levels, low triglyceride levels, and weight loss. On the other hand, hypothyroidism, characterized by a deficiency in thyroid hormones, is commonly linked to a decreased basal metabolic rate, weight gain, and elevated cholesterol and triglyceride levels [17].

Primary hypothyroidism, the failure of the thyroid gland itself, is the most common cause of hypothyroidism. The most prevalent aetiology for it is Hashimoto's thyroiditis, an autoimmune thyroid disease, whilst other causes entail iodine deficiency, thyroid surgery, radioiodine therapy, or radiation therapy [23,24]. The decreased production of thyroid hormones from the thyroid gland causes an increased secretion of TSH from the anterior pituitary gland, thus giving rise to the characteristic high TSH and low FT₄ levels seen in overt hypothyroidism. The term subclinical hypothyroidism (SCH) is used to characterize a grade of primary hypothyroidism in which there are high levels of TSH in the blood but normal levels of FT₄ [1]. This means that the thyroid gland is slightly underactive, but not nearly enough to cause the symptoms observed in overt hypothyroidism. It is estimated that approximately 3% to 15% of the population is affected by SCH, with a greater incidence among women and older adults [25]. The causes of SCH are the same as those of overt hypothyroidism. The primary concern with SCH is its high potential to progress to overt

hypothyroidism, with a risk ranging from 2% to 6% annually [26]. Patients with SCH are usually asymptomatic, and the thyroid dysfunction is picked up incidentally [25,26]. However, based on its severity and duration, it can manifest with hypothyroidism symptoms including metabolic, cardiovascular, musculoskeletal, reproductive, and cognitive problems which can negatively impact the patient's quality of life [25–27]. The clinical significance of SCH and the necessity for treatment remains up to debate. Research findings have been inconsistent, with many studies linking SCH to various adverse outcomes, including lipid profile pitfalls which is the focal point of this review.

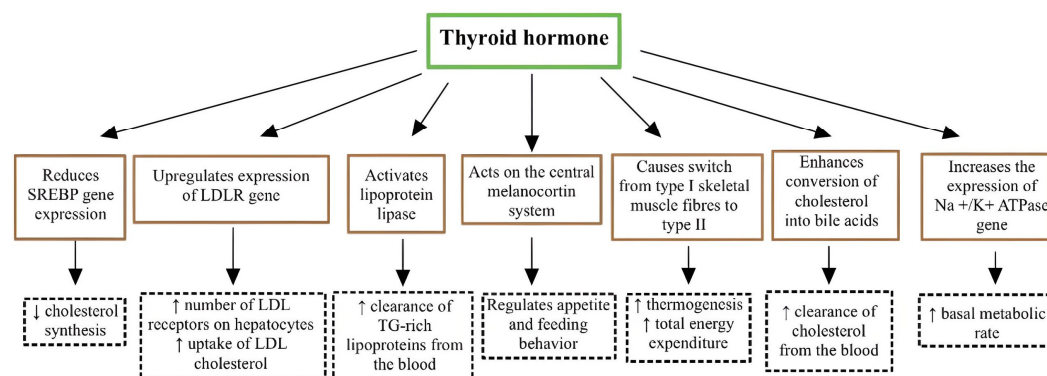


Figure 1. Mechanisms of thyroid hormone metabolism and actions. Diagram depicting established mechanisms and impacts of thyroid hormone on metabolism. This includes the regulation of genes involved in cholesterol synthesis and breakdown; the activation of enzymes such as lipoprotein lipase and Na^+/K^+ ATPase which facilitate clearance of triglycerides and increase the basal metabolic rate, respectively; effects on the central melanocortin system; changes in skeletal muscle fibres; and enhanced conversion of cholesterol into bile acids. In the figure above, upward-pointing arrows ($\uparrow$) represent an increase or upward trend, while downward-pointing arrows ($\downarrow$) indicate a decrease or downward trend.

4. Studies on Lipid Profile Changes on Subclinical Hypothyroidism

It is widely recognized that thyroid hormones can affect lipid metabolism. The exact pathophysiology of dyslipidaemia in hypothyroidism is unclear, but several mechanisms have been proposed. A few of these mechanisms include the reduction in LDL cholesterol receptors and subsequent accumulation of LDL cholesterol, the development of hypertriglyceridaemia secondary to reduced activity of lipoprotein lipase, and diminished clearance of cholesterol from the bloodstream due to the impaired ability of the liver to convert cholesterol into bile acids [18,21,22]. As dyslipidaemia can be a significant risk factor for atherosclerosis, a prerequisite for cardiovascular disease (CVD) [4], it is crucial to understand the extent of SCH's impact on the lipid profile to intervene and prevent irreversible damage. Various studies have examined the relationship between the lipid profile and SCH, but to date, the evidence remains scarce and contradictory.

A cross-sectional study on 5862 participants in Colorado showed that individuals with SCH had higher mean total cholesterol (TC) and LDL-C levels compared to subjects with normal thyroid function, whilst HDL cholesterol and TG levels did not change significantly [28]. Similarly, a cross-sectional study on 66 patients and a longitudinal study on 179 patients in Pakistan made the same observations, that TC and LDL-C levels were significantly higher in participants with SCH compared to euthyroid individuals [29,30]. This increase in TC and LDL-C levels in patients with SCH is evident in a substantial number of studies [31–34]. Other studies and a recent meta-analysis found the same observations, but they also showed a statistically significant increase in the TG levels of individuals with SCH when compared to euthyroid groups [35–38]. Moreover, studies suggest that the level of dyslipidaemia is positively correlated with the level of TSH, meaning that the higher the TSH level, the more extensive the lipid disorder [28,39,40]. It has also been shown that the

transition from SCH to euthyroidism following treatment with levothyroxine significantly decreased the TC, LDL-C, and HDL-C levels, further supporting the argument [32,41].

Conversely, other studies found no statistically significant differences in TC, LDL-C, TG, and HDL-C levels in patients with SCH compared to euthyroid controls [42–45]. Interestingly though, in the National Health and Nutritional Examination Survey (NHANES) III and in a recent long-term study, changes in lipid parameters were observed between SCH and euthyroid groups but these differences were statistically insignificant after adjusting for age and sex [41,46]. In line with the above, a recent study showed that TSH has a stronger effect on LDL-C and TC levels in older individuals compared to younger subjects [47]. Hence, this may suggest that the inconsistencies among the studies could have been the result of poor control of confounding factors [37].

Some of the most recent primary studies [2,30,36,42,48–57] on lipid changes in SCH are summarized in Table 1 below.

Table 1. Recent studies examining the effect of SCH on lipid profiles. Table summarizing some of the most recent primary studies examining the impact of SCH on lipid profile parameters. This includes changes in mean total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and very-low density lipoprotein (VLDL) levels. The upward-pointing arrows (↑) represent an increase or upward trend, while downward-pointing arrows (↓) indicate a decrease or downward trend.

Authors and Publication Year	Study Type	Sample Size	Lipid Changes with Increasing Serum TSH Levels
Tarboush et al., 2023 [42]	Cross-sectional study	324	No significant difference in lipid parameters in SCH compared to euthyroidism
Sindhu et al., 2022 [48]	Case-control study	100	↑ TC, LDL-C, TG, and VLDL ↓ HDL-C
Jawzal et al., 2022 [49]	Cross-sectional study	100	↑ LDL-C ↓ HDL-C
Luo et al., 2022 [41]	Cohort study	11,512	No statistically significant changes after adjusting for age and sex
Han Y et al., 2022 [50]	Cross-sectional	10,747	↑ LDL-C and TG
Ejaz et al., 2021 [30]	Longitudinal study	900	↑ TC and LDL-C
Chang et al., 2019 [51]	Longitudinal study	24,765	↑ TC, LDL-C, and TG ↓ HDL-C
Jadhav et al., 2018 [36]	Case-control study	25	↑ TC, LDL-C, and TG ↓ HDL-C
Verma et al., 2017 [52]	Case-control study	50	↑ TG and VLDL No significant difference in TC, LDL-C, and HDL-C
Haghi et al., 2017 [2]	Case-control study	106	↑ LDL-C ↓ HDL-C No difference in TG
Langén et al., 2017 [53]	Longitudinal study	2486	↑ TC, LDL-C, ApoB, and TG
Mehran et al., 2017 [54]	Randomized control trial	5422	↑ risk of metabolic syndrome in SCH subjects
Jayasingh et al., 2016 [55]	Cross-sectional study	110	↑ TC and TG No significant difference in LDL-C and HDL-C
Zhao et al., 2015 [47]	Case-control study	17,046	↑ TC only in the 40–70 age group ↑ LDL-C in both 40–49 and 50–59 age groups ↑ TG level only in the 50–59 age group No relationship between TSH and HDL-C TSH presented a stronger effect on the TC and LDL-C levels in moderately old subjects than in younger subjects
Guntaka et al., 2014 [56]	Observational study	30	↑ TC and LDL-C No statistically significant difference in TG, and HDL-C

5. Subclinical Hypothyroidism, Cardiovascular Disease, and Mortality

The effects of SCH on the cardiovascular system (CVS) have gained recent attention and became an important research topic. The dyslipidaemia commonly observed in SCH is one of the main indirect risk factors associated with cardiovascular disease. However, thyroid hormones are also known for their ability to influence the cardiovascular system directly, i.e., by acting on the heart and its vasculature [57]. For instance, they can decrease the heart's afterload by reducing the peripheral vascular resistance (PVR) and decreasing the diastolic blood pressure (DBP) [58] while also increasing the heart's sensitivity to catecholamines, leading to an increased heart rate [59]. In addition, they can influence the expression of key cardiac genes which control intracellular calcium cycling in cardiac myocytes and enhance the contractile function of the heart [60]. When thyroid hormone levels are impaired, functional disorders can arise. In SCH, these may include disturbances in the systemic vascular resistance and cardiac output, changes in arterial blood pressure, an increase in arterial stiffness, and impaired endothelial function [61]. Given the above, the relationship between SCH and CV risk has been examined in a number of studies and meta-analyses.

For instance, a cross-sectional study ($n = 119$) demonstrated that SCH participants had a significantly higher prevalence of coronary heart disease compared to euthyroid individuals [62]. A meta-analysis suggested that this is evident only in subjects younger than 65 years of age [63]. This is in line with a cross-sectional study ($n = 212$) that found SCH to be a predictor of CVD in males less than 50 years old [64]. Furthermore, SCH may be associated with an increased incidence of coronary artery calcification (CAC). A retrospective study ($n = 2404$) found that SCH subjects ($n = 49$), especially men ($n = 42$), had higher CAC scores and were significantly more likely to develop coronary artery disease when compared to euthyroid individuals ($n = 2272$) [65]. Moreover, a meta-analysis of eight observational studies ($n = 3602$) investigated the relationship between SCH and carotid intima-media thickness (C-IMT). C-IMT has been increasingly used to evaluate changes in atherosclerosis, with values above the threshold indicating a high risk of progression into atherosclerosis. The aforementioned analysis indicated that SCH is associated with an increased C-IMT [66]. Consistently, a more recent meta-analysis of 39 observational studies ($n = 3430$) found the same results [67].

The relationship between SCH and BP is not entirely clear [68–70]. A study examining the association between TSH levels and blood pressure ($n = 14,353$) in individuals with no history of thyroid disease found that subjects with high normal TSH levels had an increased risk of developing high BP levels in the future [70]. Similarly, a cross-sectional, population-based study ($n = 30,728$) found a positive association between TSH levels and both systolic and diastolic blood pressure [71]. In addition, a data analysis derived from the Thyroid disease, Iodine nutrition, and Diabetes Epidemiology (TIDE) study showed that the positive correlation between SCH and hypertension is particularly evident in female subjects less than 65 years of age [72]. Likewise, a metaanalysis of seven cross-sectional studies revealed that SCH is associated with both high systolic and diastolic BP when compared to healthy individuals [73]. Conversely, three cross-sectional studies conducted in China ($n = 6992$), Osaka ($n = 3607$), and Busselton ($n = 2033$) demonstrated that there is no discernible difference in mean SBP, DBP, or the prevalence of hypertension between patients with SCH and euthyroid individuals [74–76].

Furthermore, there is growing evidence that SCH increases the incident of heart failure. Specifically, the Cardiovascular Health Study, a longitudinal study ($n = 3044$) investigating the association between SCH and heart failure (HF), found that individuals with TSH levels ≥ 10.0 mU/L had a higher risk of developing HF in the future compared to euthyroid individuals [77]. Consistently, a prospective cohort study ($n = 5316$) showed that SCH was associated with heart failure only in patients with a TSH threshold of ≥ 10.0 mU/L [78], while a different study ($n = 2730$) found an increased risk of congestive heart failure among older adults with TSH levels ≥ 7.0 mIU/L [79]. In addition, a cross-sectional study ($n = 83$) examining the relationship between the cardio-ankle vascular index (CAVI) and

left ventricular diastolic function in patients with SCH found that the CAVI score and level of the N-terminal prohormone of brain natriuretic peptide (NTP-proBNP), a marker of heart failure, were higher in patients with SCH when compared to euthyroid subjects [80]. Moreover, a different study ($n = 338$) demonstrated that SCH patients with a background of chronic heart failure had an increased chance of heart failure progression [81].

According to numerous studies, SCH may also increase the risk of cardiac mortality. A recent cohort study ($n = 9020$) in the US examined the extent to which CVD-related mortality is associated with SCH. They found that SCH participants with high normal TSH levels had an increased risk of all-cause mortality when compared to individuals with middle normal TSH levels [82]. Similarly, a data analysis of 11 prospective cohort studies ($n = 55,287$) in Europe, the US, Japan, Australia, and Brazil revealed that CVD-related events and mortality were particularly higher in patients with TSH levels above 10 mU/L [83]. Likewise, a meta-analysis of 10 population based prospective cohort studies revealed that the risk for CVD and mortality was higher in SCH individuals [84]. In addition, both a longitudinal study ($n = 101$) in Busselton and a cohort study in Taiwan ($n = 115,746$) found that the risk of coronary heart disease events and CVD-related mortality was higher in SCH subjects compared to euthyroid individuals [6,85]. This was also evident in a large prospective observational study ($n = 3308$) which demonstrated that after adjustment for other risk factors, the hazard ratios for cardiac mortality were increased in the SCH group compared to the euthyroid group [86]. A different retrospective cohort study showed that in patients with congestive heart failure (CHF), those with coexisting SCH were at higher mortality risk compared to euthyroid individuals [87]. On the other hand, other studies did not find any association between SCH and CV-related or all-cause mortality [88–90].

6. Effects of Levothyroxine Treatment

Secondary hyperlipidaemia, which can arise from SCH, is an atherosclerotic risk factor that can be prevented with optimal levothyroxine (L-T4) treatment. There is no consensus for the beneficial effect of L-thyroxine treatment on the lipid profile in patients with SCH. However, as lipids proportionately increase with increasing TSH levels, there is a tendency to use L-T4 replacement therapy when TSH levels exceed 10 mIU/mL [91–93].

A meta-analysis of 12 randomized control studies, which included 940 patients with mild SCH, showed beneficial effect of L-T4 on TC and LDL-C levels. Thyroxine replacement therapy resulted in a mean reduction in TC (-0.29 mmol/L, $[-0.42$ to $-0.16]$) and LDL-C (-0.22 mmol/L, $[-0.36$ to $-0.09]$) levels compared to controls. HDL-C and triglyceride levels were not significantly affected [94]. A study by the same group, which was included in the meta-analysis, showed an improvement in TC and LDL-C levels even in patients with mild SCH (TSH levels < 10 mIU/mL). The beneficial effects were obvious in the first 6 months of treatment, with significant effects on TC (-0.19 mmol/L $[-0.35, -0.03]$ vs. -0.50 mmol/L $[-0.68, -0.31]$, $p = 0.047$) and LDL-C (-0.09 mmol/L $[-0.16, -0.02]$ vs. -0.46 mmol/L $[-0.68, -0.25]$, $p = 0.006$) levels [95].

A review by Denese et al., which involved 247 participants with mild hypothyroidism from 13 studies, showed an improvement in TC levels with L-T4 treatment compared to untreated patients. The total cholesterol level declined significantly by -0.44 mmol/L (-17 mg/dL) in treated patients compared to a smaller decline of -0.14 mmol/L (-5.6 mg/dL) in untreated patients ($p = 0.05$). The decline in the serum TC level was directly proportional to its baseline concentration. The LDL-C concentration decreased by -0.26 mmol/L (-10 mg/dL), with a 95% confidence interval of -0.12 to -0.41 . The serum HDL-C and triglyceride concentrations did not show a statistically significant change. Also, the same review reported a greater improvement in TC levels in hypothyroid patients with normalization of TSH after treatment with suboptimal doses of L-T4 [96].

Although most of the reviews provide strong evidence of the effect of L-T4 on lipid profiles in patients with SCH, the large heterogeneity of the studies included in the meta-analyses can cause controversy [61]. As SCH has been related to an increased carotid intima-media thickness (C-IMT), some studies examined the effect of L-T4 on the reduc-

tion in C-IMT as a result of TC improvement. Such studies found that long-term L-T4 therapy significantly reduced the C-IMT in SCH patients [68,69]. A meta-analysis by Zhao et al. showed a decrease in C-IMT after L-T4 treatment for more than 6 months in SCH patients [69]. These studies provide evidence of the impact of abnormal lipid profiles on cardiovascular risk in untreated patients with SCH [97,98].

7. Discussion

This review has emphasized the complex interplay between thyroid hormones and lipid metabolism, highlighting significant clinical implications. Despite its often asymptomatic presentation, SCH has been increasingly associated with various metabolic abnormalities, particularly lipid profile disturbances, which contribute to an elevated risk of cardiovascular disease. The relationship between SCH and lipid changes has been widely reviewed, but the findings are inconsistent. Part of the existing research indicates a clear association between SCH and elevated lipid levels, while others find no significant difference in lipids in patients with SCH compared to euthyroid individuals. These discrepancies may be attributed to variations in study design, population characteristics, and the presence of confounding factors such as age, sex, and comorbidities. Double-blind control studies on mild forms of SCH and their effects on the lipidemic profile are mandated as most of the existing studies are observational and include patients with SCH in cohorts with overt hypothyroidism.

Levothyroxine therapy can help normalize lipid levels, particularly in patients with TSH levels above 10 mIU/L, but its effect on reducing cardiovascular events is still debated. More studies are needed to confirm the beneficial effect of L-T4 therapy on the C-IMT in SCH patients and to suggest an optimal dose and treatment duration. While some studies indicate that levothyroxine may lower lipid levels even in mild cases of SCH, the evidence is inconclusive. Thus, there is still a debate among physicians regarding treating the mild forms of SCH. The current guidelines do not universally recommend treatment for mild SCH, particularly in the absence of symptoms or significant cardiovascular risk factors. There is a trend toward treating patients with TSH levels above 8 or 10 mIU/mL. Although it is not recommended by the scientific societies' guidelines, some of the aforementioned studies suggest that treatment for patients with SCH should start as early as possible as cardiovascular risk can be triggered even with TSH values lower than 8 mIU/mL [99].

8. Conclusions

In conclusion, although there is some evidence for lipid profile changes in patients with SCH, the adverse outcomes of hyperlipidaemia in patients with SCH and especially with milder forms need further research. Treatment with L-T4 should be individualized, considering both the patient's lipid profile and cardiovascular risk. A close follow up is mandatory in order to prevent SCH from progressing to overt hypothyroidism and avert its complications. Further research is necessary to clarify the long-term lipid and cardiovascular outcomes of treating various forms of SCH, and to develop more precise guidelines for managing this common endocrine disorder.

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