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Correlation Study Between Subclinical Hypothyroidism and Coronary Atherosclerotic Heart Disease

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Abstract

Subclinical hypothyroidism (SCH) is recognized as a potential independent risk factor for coronary artery disease (CAD). This review systematically explores the association between SCH and CAD, examining mechanisms including atherogenesis, inflammatory responses, and interactions with traditional CAD risk factors. We found that varying TSH levels, sex, and the presence of comorbidities in patients with SCH are associated with the development and progression of CAD, though the underlying mechanisms remain unclear. While thyroid hormone replacement therapy can improve lipid profiles and endothelial function, the cardiovascular benefits regarding hard endpoints in patients with mild SCH (TSH<10 mIU/L) or in elderly populations require confirmation through large randomized controlled trials (RCTs). In conclusion, the association between SCH and CAD is multifactorial and synergistic, and clinical intervention should consider individualized TSH levels, age, and the presence of comorbidities.

Keywords: coronary heart disease, subclinical hypothyroidism, atherosclerosis, thyroid hormone replacement therapy

1. Introduction

Cardiovascular Disease (CVD) represents a major global public health challenge. While mortality rates from CVD have decreased, the overall disease burden it imposes remains substantial, driven by increasing population aging and disparities in healthcare resource allocation[1-2]. Coronary atherosclerotic heart disease (CAD), a major manifestation of cardiovascular disease (CVD), is a leading contributor to CVD's high global incidence and mortality rates. While conventional risk factors like hypertension, dyslipidemia, diabetes mellitus, smoking, and obesity are crucial in the pathogenesis and progression of CAD, a significant proportion of CAD patients lack these factors, implying the existence of alternative mechanisms driving coronary atherosclerosis.

Subclinical hypothyroidism (SCH), a prevalent endocrine condition, is noteworthy for its epidemiological features. SCH is characterized by elevated serum thyroid-stimulating hormone (TSH) levels, while free thyroxine (FT4) and free triiodothyronine (FT3) levels remain within normal reference intervals[3]. The prevalence of SCH increases with advancing age[4-5], and it is generally higher in women than in men[6]. Furthermore, individuals positive for thyroid peroxidase antibodies (TPOAb) are at an increased risk of progressing to overt hypothyroidism[7].

The significant effects of overt hypothyroidism on the cardiovascular system are well-established[8]. Thyroid hormones are essential for maintaining cardiovascular homeostasis, directly regulating myocardial contraction and relaxation, heart rate, and vascular resistance. They also influence energy metabolism and gene expression within cardiomyocytes[9]. However, the cardiovascular effects of subclinical hypothyroidism (SCH), characterized by mildly elevated serum TSH levels but normal thyroid hormone levels, and its association with coronary heart disease (CHD) remain debated in previous research. Considering the high prevalence of SCH and its potential cardiovascular risks, further investigation into its relationship with CHD is crucial for improving patient management and developing preventive strategies. Therefore, this article systematically reviews and analyzes existing literature to clarify the complex relationship between subclinical hypothyroidism and coronary heart disease, providing a basis for future research and clinical decision-making.

2. Correlation Between Thyroid-Stimulating Hormone and Atherosclerosis

atherosclerosis is the central pathological process in the development of coronary heart disease (CHD). Several studies have established a correlation between subclinical hypothyroidism (SCH) and CHD and/or atherosclerosis. The primary focus is on the multifaceted effects of elevated serum TSH levels on the cardiovascular system. These effects include atherosclerosis, the main pathological basis of CHD, as well as various pathophysiological processes, such as inflammation, oxidative stress, platelet function, and thrombus formation.

2.1 Inflammation and Macrophage Activation

Macrophage-associated inflammation is critical in the pathogenesis of atherosclerosis[10-11]. Inflammatory mediators secreted by macrophages within atherosclerotic plaques worsen local tissue damage and initiate additional inflammation, creating a self-perpetuating cycle. Research suggests that TSH may regulate macrophage function through the TSH receptor, activating mitogen-activated protein kinases (MAPK) and nuclear factor-κB (NF-κB) signaling pathways. This activation directly promotes inflammatory responses and is amplified by increased monocyte recruitment, thereby accelerating atherosclerotic progression[12-13]. Specific knockout of the TSH receptor gene leads to reduced inflammation and fewer macrophages, further establishing macrophages as a key target through which TSH exerts its pro-inflammatory and pro-atherosclerotic effects[12]. Emerging evidence identifies adipokines, molecules secreted by adipose tissue with various physiological roles, as crucial regulators of energy metabolism and inflammatory responses. Studies have shown that retinol-binding protein 4 (RBP4), a novel adipokine, is elevated in the serum of SCH patients with concurrent coronary artery disease, and its levels correlate positively with body mass index (BMI), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and TSH levels[14]. The precise mechanism remains unclear. This research offers new insights into the molecular link between SCH and atherosclerosis, potentially revealing therapeutic and preventative targets. Aly et al.[15] investigating Hashimoto's thyroiditis (a common cause of subclinical hypothyroidism), demonstrated significant associations between serum TSH levels and red blood cell distribution width (RDW), as well as platelet parameters like mean platelet volume (MPV), platelet distribution width (PDW), platelet count (PC), and large platelet count ratio (LPCR). These hematological markers correlated strongly with levels of the inflammatory marker high-sensitivity C-reactive protein (Hs-CRP), indicating a possible subclinical inflammatory state. Variations in these blood parameters might serve as new biomarkers for early detection of subclinical hypothyroidism and its associated inflammation, offering a window for early interventions to prevent atherosclerotic cardiovascular disease.

2.2 Endothelial Dysfunction and Microvascular Injury

Endothelial dysfunction is an early and critical step in the development of atherosclerosis[16]. Hypothyroidism has been proven to damage vascular endothelial function. Studies have indicated that abnormal coronary microvascular function is often associated with SCH patients[17], specifically manifesting as a decrease in stress myocardial blood flow reserve (CFR)[17-18], and is particularly prominent in female SCH patients. Abnormal CFR persists even after adjusting for other confounding factors[19], and after receiving levothyroxine (L-T4) replacement therapy, patients' CFR significantly improved[17]. These findings provide strong support for the view that SCH causes endothelial dysfunction, suggesting that this dysfunction may be reversed by therapeutic intervention.

The underlying cause of endothelial dysfunction likely involves reduced nitric oxide (NO) bioavailability. NO, a critical vasodilator produced by endothelial cells, plays a key role in vasodilation, anti-inflammatory processes, preventing blood clot formation, and inhibiting cell proliferation. Obradovic et al.[20] observed that individuals with subclinical hypothyroidism (SCH) exhibited significantly lower nitrite and nitrate levels, as well as decreased NO bioavailability. They suggested that NO levels could potentially serve as a biomarker for evaluating cardiovascular risk in SCH patients. However, the precise relationship between serum TSH levels and NO concentrations in vivo, along with the impact of levothyroxine (L-T4) treatment on NO levels, remains incompletely understood and warrants further investigation through robust studies.

2.3 Platelet Dysfunction and Hypercoagulability

Platelet dysfunction and activation of the coagulation system are critical in thrombus formation after atherosclerotic plaque rupture, directly contributing to acute coronary syndrome (ACS) and cardiovascular events. Research suggests that SCH might elevate thrombosis risk by influencing platelet function and coagulation parameters. A study involving patients with non-ST-segment elevation ACS demonstrated a correlation between serum TSH levels and increased thrombotic burden, even with optimal antiplatelet and secondary prevention treatment. This suggests that individuals with SCH exhibit a significantly higher thrombotic burden than those with normal thyroid function, independent of other known cardiovascular risk factors[21]. This finding potentially

elucidates the mechanism through which SCH elevates cardiovascular risk, highlighting the need for thorough evaluation of personalized antithrombotic and thyroid hormone replacement therapies to mitigate atherosclerotic thrombosis risk. Furthermore, Guo et al.[22] investigated the impact of serum TSH levels on coagulation markers and disease severity in coronary heart disease patients. Although specific results were not detailed, prior research indicates that SCH may worsen coronary heart disease progression by disrupting coagulation mechanisms. To summarize, SCH may promote a prothrombotic state by modulating platelet activity and coagulation, thereby increasing the potential for acute thrombotic events in patients with CAD.

2.4 Alternative Markers of Atherosclerosis: CIMT and CACS

In addition to examining the direct impact of serum TSH levels on atherosclerosis, numerous studies have indirectly shown a strong link between SCH and the progression of atherosclerosis by assessing alternative indicators of the condition, including Carotid Intima-Media Thickness (C-IMT) and Coronary Artery Calcium Score (CACS).

Carotid intima-media thickness (CIMT) is an important predictor of cardiovascular disease risk and is closely associated with atherosclerotic plaque formation and cardiovascular events[23-24]. Research indicates a significant positive correlation between subclinical hypothyroidism (SCH) and CIMT[25-26]. Isailă et al.[27] found that CIMT was significantly higher in SCH patients compared to individuals with normal thyroid function, especially in women and older adults. Notably, even in patients with mild SCH and TSH levels below 10 μIU/ml (the lower limit of normal), CIMT remained significantly elevated compared to healthy controls, suggesting a potentially increased cardiovascular risk in these patients[25]. Aída et al.[28] further demonstrated that both diabetes and SCH, when present individually, correlate with increased CIMT. However, no additive effect on CIMT was observed when both conditions were present simultaneously. Knapp et al.[18] highlighted the prominence of this association in women and noted its presence even in SCH patients without coronary artery disease symptoms, emphasizing the relevance of this association across different genders, ages, and disease states. Conversely, Cabral et al.[29] found no significant difference in CIMT between SCH patients and controls. While CIMT was slightly higher in TPO-Ab-positive SCH patients compared to TPO-Ab-negative patients, this difference was not statistically significant. In conclusion, the correlation between SCH and increased CIMT suggests a potentially detrimental impact on vascular structure. These findings have significant implications for informing clinical practice and developing treatment strategies for SCH patients.

Coronary artery calcification (CAC) is a hallmark of coronary atherosclerosis, strongly associated with poor patient outcomes and increased complexity and risk during percutaneous coronary intervention (PCI). The coronary artery calcium score (CACS) serves as a valuable metric for quantifying the degree of CAC and is frequently elevated in patients with subclinical hypothyroidism (SCH), particularly those at intermediate to high cardiovascular risk[30-31]. A study by Guo et al.[22] demonstrated a positive correlation between serum thyroid-stimulating hormone (TSH) levels and the extent of coronary artery stenosis, as determined by the Gensini score, in patients with coronary artery disease (CAD). Furthermore, patients with SCH and concomitant CAD exhibited a higher likelihood of multi-vessel disease and more severe coronary artery stenosis, suggesting that hypothyroidism may exacerbate the extent and severity of coronary artery disease. It is important to note, however, that this relationship varies across different populations. Park et al.[32]conducted a retrospective analysis of 2404 asymptomatic subjects with intermediate to high cardiovascular risk, revealing a significantly higher prevalence of CAD and a greater proportion of CACS > 100 in the SCH group compared to the euthyroid group, particularly among male patients. Similarly, a retrospective study involving 2499 patients with SCH[33] observed a more prominent association between SCH and CACS or coronary artery plaque in men, with no such correlation detected in women. This pattern was also confirmed in healthy individuals[34]. Zhou et al.[35] used coronary computed tomography angiography (CCTA) to evaluate coronary lesion characteristics in patients with SCH. Their findings indicated that severe SCH was independently associated with the presence of non-calcified plaques, and the total plaque burden was greater in male SCH patients compared to their female counterparts. Non-calcified plaques are considered "vulnerable plaques" that are more prone to rupture, and their increased presence suggests that SCH may contribute to more high-risk atherosclerotic lesions. Of particular interest is the observation that, despite the higher prevalence of SCH in women, existing research indicates a greater coronary plaque burden in men with the condition. Furthermore, a cross-sectional study by Carlos et al.[30] highlighted a noteworthy finding: SCH patients with non-alcoholic fatty liver disease (NAFLD) demonstrated a significant association with metabolic syndrome, insulin resistance, and subclinical coronary atherosclerosis (CACS > 0), whereas this association was not observed in SCH patients without NAFLD. This suggests that NAFLD may play a significant role in the association between SCH and cardiovascular risk, indicating that the effects of SCH on the cardiovascular system may not be mediated by a single pathway but rather by a synergistic interaction with other metabolic abnormalities.

3. The Association of TSH with Conventional Risk Factors for Coronary Heart Disease

3.1 TSH and Dyslipidemia

Thyroid hormone (TH) plays a critical role in regulating lipid metabolism[36–38]. Low-density lipoprotein cholesterol (LDL-C) is a key lipid factor in the development of atherosclerosis. TH precisely regulates LDL synthesis and clearance through various mechanisms[39–41]. Importantly, even when serum TH levels are within the normal reference range, alterations in serum TSH concentration can still trigger unfavorable changes in the lipid profile[40]. The study by Sujoy et al.[42] demonstrated a significant positive correlation between SCH and lipid abnormalities, specifically manifesting as elevated levels of total cholesterol (TC), triglycerides (TG), and LDL-C, along with decreased levels of high-density lipoprotein cholesterol (HDL-C). A study involving thyroidectomy patients treated with L-T4 showed that stimulation with recombinant human TSH led to a decrease in serum FT3 levels, accompanied by adverse lipid profile changes, including increased apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), and TG, and decreased HDL-C. This suggests that TSH may directly influence peripheral TH metabolism and lipid levels[39,43]. These unfavorable lipid alterations are closely associated with the decrease in T3 levels, suggesting that TSH may indirectly regulate lipid metabolism by influencing T3 levels. Furthermore, the quality of lipids may also change, resulting in more atherogenic and oxidized LDL and HDL particles. These lipid abnormalities coexist with insulin resistance and oxidative stress, creating a vicious cycle that contributes to the increased risk of coronary artery disease in patients with SCH[44]。

The potential mechanisms through which TSH impacts lipid levels are likely closely tied to LDL production and clearance. HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase), a key enzyme that limits the rate of cholesterol biosynthesis, is significantly regulated by AMPK (AMP-activated protein kinase)[45]. When TSH binds to its receptors on hepatocytes, it activates the cAMP/PKA signaling pathway, leading to PKA-mediated phosphorylation that inhibits AMPK. This process reduces AMPK activity in hepatocytes, promoting increased HMGCR expression, which ultimately boosts cholesterol synthesis and disrupts lipid metabolism[46]. PCSK9 (proprotein convertase subtilisin/kexin type 9), a serine protease, binds to LDL-R (low-density lipoprotein receptors) on hepatocytes. These receptors are critical for clearing LDL particles from the bloodstream. Elevated PCSK9 levels accelerate LDL-R degradation in lysosomes, reducing LDL-R levels and consequently increasing LDL-C levels in the blood[47]. A cross-sectional study involving 1003 middle-aged individuals examined PCSK9 levels in euthyroid individuals compared to those with SCH (subclinical hypothyroidism), excluding individuals on thyroid medication or with a history of metabolic disorders to ensure reliable results. The study found significantly elevated serum TSH levels in SCH patients, while FT3 and FT4 levels remained normal. Compared to individuals with normal TSH, those with SCH exhibited a significant trend toward increased serum PCSK9 levels, suggesting a possible association. To further investigate how TSH specifically regulates PCSK9 expression in hepatocytes, in vitro experiments were conducted. These experiments showed that TSH binding to its receptors activates adenylate cyclase (AC), which elevates intracellular cAMP levels. This activates the cAMP-PKA-CREB signaling pathway, ultimately increasing PCSK9 expression, synthesis, and secretion[48]. However, this study had limitations, including the difficulty in directly correlating TSH concentrations in the in vitro experiments with TSH levels in human serum and the absence of subgroup analysis based on varying TSH levels. Therefore, future studies should stratify subjects based on serum TSH levels to perform more precise and in-depth analyses.

3.2 TSH and Type 2 Diabetes

Type 2 diabetes mellitus and metabolic syndrome are both significant risk factors for coronary heart disease (CHD). Studies have found that subclinical hypothyroidism (SCH) is closely related to them. There is a certain correlation between SCH and type 2 diabetes, and it can worsen blood glucose control in diabetic patients. When the two coexist, the risk of cardiovascular disease will be significantly increased[38]. In particular, SCH patients with diabetic nephropathy (DMN) have a further increased risk of cardiovascular disease, and thyroid hormone replacement therapy may reduce this risk to some extent[49]. Existing studies have also confirmed that patients with type 2 diabetes combined with SCH have a significantly increased probability of developing cardiac and cerebral macrovascular complications[50], and there is a dose-dependent relationship with serum TSH and insulin levels, suggesting that SCH may promote the occurrence of CHD and adverse cardiovascular risks by affecting glucose metabolism and insulin sensitivity. Spilack et al.[51] pointed out in a study that there is a significant correlation between diabetes combined with SCH and coronary artery calcification in the young population, although this association was not observed in the overall study population. These results emphasized the need to conduct age-stratified studies when analyzing such data. However, some studies have denied this correlation. A study from the Netherlands found that plasma TSH levels within the normal range were not significantly associated with new-onset type 2 diabetes in patients with high cardiovascular risk, and the comprehensive results of systematic reviews and meta-analyses did not support an association between plasma TSH levels within the normal

range and new-onset type 2 diabetes[52]. In summary, TSH may increase the risk of developing CHD by regulating blood glucose concentrations, and the potential mechanism may be related to TSH-induced insulin resistance in the body. However, the reliability of the above argument remains to be confirmed by further research.

3.3 The Relationship Between Varying TSH Levels and Coronary Artery Disease

While the diagnosis of subclinical hypothyroidism (SCH) depends on elevated serum TSH levels, the extent of TSH elevation has a variable impact on the risk and prognosis of coronary artery disease, with age playing a differentiating role.

Subclinical hypothyroidism (SCH) can be further categorized into Grade 1 (TSH between the upper reference limit and 9.9 mU/L) and Grade 2 (serum TSH ≥ 10 mU/L)[53]. Large meta-analyses and prospective cohort studies have consistently demonstrated a positive correlation between TSH levels and the risk of coronary heart disease (CHD) events and mortality. This association is particularly strong when serum TSH is ≥ 10 mIU/L, with a significantly increased risk of CHD-related death, stroke, and heart failure[6,54–57]. Further analysis indicates that SCH patients with TSH levels between 4.5 and 6.9 mIU/L do not exhibit a significantly elevated risk of CHD events compared to euthyroid individuals. However, a slight upward trend in risk emerges when TSH levels rise to 7.0-9.9 mIU/L. Notably, when TSH levels range from 10 to 19.9 mIU/L, the risk of CHD events increases substantially. These findings suggest that a TSH level of 10 mIU/L may serve as a critical clinical intervention threshold. SCH patients with TSH levels below this threshold may have a relatively lower cardiovascular risk, warranting a more refined assessment. A trend of increasing CHD mortality risk with rising TSH levels has also been observed. The study of Christine et al.[58] on high-risk CAD populations corroborated this observation, finding that overt hypothyroidism and moderate SCH (TSH 6.1-10 μU/mL) were associated with a higher prevalence of CAD and all-cause mortality, while mild SCH (TSH 3.1-6.0 μU/mL) did not show such an association. Moreover, this increase in mortality was more pronounced in patients under 65 years and those not receiving thyroid hormone replacement therapy.

Beyond cardiovascular events and mortality, changes in TSH levels also impact the severity of coronary artery disease. An analysis of type 2 diabetes patients with SCH revealed a significant association between severe SCH (TSH ≥ 10.0 mIU/L) and the risk of coronary heart disease, with TSH levels positively correlated with the number of diseased coronary arteries[49]. Zhou et al.[35] further demonstrated that, across varying severities of SCH (mild, moderate, severe), while plaque burden (SIS and SSS) did not differ significantly, the proportion of non-calcified plaques was significantly elevated in severe SCH. This suggests that severe SCH may promote the formation of plaques prone to rupture, thereby increasing the risk of acute cardiovascular events. Han et al.[59] also confirmed that persistent SCH is closely linked to the severity of coronary artery lesions and major adverse cardiovascular and cerebrovascular events (MACCE), with TSH levels emerging as an independent risk factor for moderate and severe coronary artery disease. Collectively, these findings suggest that TSH levels are not only associated with the risk of CAD development but may also significantly influence plaque composition and disease progression.

The association between TSH levels and cardiovascular risk is not consistent across all populations; the potential cardiovascular effects of SCH may be age-dependent[60]. Shinje et al.[60] demonstrated that in older adults aged 65 and above with a higher baseline risk of cardiovascular disease (including a history of coronary artery disease, diabetes, or chronic kidney disease), SCH remained significantly associated with increased all-cause mortality. This difference may stem from the natural age-related decline in hypothalamic-pituitary-thyroid (HPT) axis function, leading to a physiological increase in TSH levels with age and a subsequent compensatory slight increase in TSH secretion[45] Furthermore, cardiovascular risk in elderly patients with SCH may be more influenced by the presence of multiple comorbidities than by elevated TSH levels alone. Stefano et al.[61] similarly found that the impact of SCH on cardiovascular risk can vary by age group, potentially increasing the risk of cardiovascular events in middle-aged and older individuals (over 55-60 years), while mild hypothyroidism in very elderly individuals (>85 years) may even confer some protection and be associated with extended lifespan. Consequently, the clinical relevance of SCH and corresponding treatment approaches in elderly patients require a more cautious and individualized assessment.

4. The Clinical Significance of Thyroid Hormone Replacement Therapy

Thyroid hormone replacement therapy (THRT), mainly through the administration of L-T4, has become the standard treatment for overt hypothyroidism. THRT is widely accepted for managing overt hypothyroidism, significantly improving cardiovascular function and addressing associated abnormalities[50,58-59]. However, the clinical benefits of THRT in patients with subclinical hypothyroidism (SCH) complicated by coronary artery disease (CAD), particularly those with slightly elevated serum thyroid-stimulating hormone (TSH) levels, remain

a point of debate. This controversy stems from the absence of large, long-term, randomized controlled trials using cardiovascular disease hard endpoints to provide definitive evidence.

4.1 Potential Benefits of Alternative Therapies

The effect of thyroid hormone replacement therapy (THRT) on cardiovascular events and mortality in hypothyroidism, particularly subclinical hypothyroidism (SCH), continues to be a subject of academic interest and debate. Some observational studies suggest that THRT may have the potential to reduce cardiovascular event risk, particularly in certain patient subgroups. One study of SCH patients with diabetic nephropathy demonstrated an association between THRT and reduced cardiovascular event risk[49], with a relatively low number of adverse cardiovascular events in the THRT group, suggesting that levothyroxine (L-T4) treatment may reduce cardiovascular event risk by improving lipid metabolism and cardiac function[51]. A meta-analysis indicated that SCH is significantly associated with increased cardiovascular disease and all-cause mortality, especially in high-risk populations, such as those with a history of coronary artery, cerebral artery, or peripheral artery disease, or with conditions like dilated cardiomyopathy, heart failure, atrial fibrillation, venous thromboembolism, diabetes, or chronic kidney disease, indirectly supporting the potential benefits of THRT in high-risk SCH patients[60]. A small study involving SCH patients with coronary artery disease found that 6 months of L-T4 treatment did not significantly alter overall blood lipid levels or left ventricular diastolic function, although some patients showed some degree of improvement[64]. Christine et al.[58] found that THRT may be associated with lower all-cause mortality in moderate SCH patients (thyroid-stimulating hormone [TSH] levels between 6.1 and 10 μU/mL) at high cardiovascular risk. In a large U.S. population-based study, Ramirez et al.[65] reported that hypothyroid patients with diabetes receiving L-T4 treatment had significantly reduced healthcare utilization for coronary artery disease and stroke/transient ischemic attack, along with increased use of cholesterol-lowering medications, β-blockers, and diuretics, suggesting a potential benefit of L-T4 treatment in reducing cardiovascular risk. However, it is important to note that this study was a retrospective analysis and lacked evidence from randomized controlled trials, limiting its ability to establish causality.

Of note, current randomized controlled trials provide insufficient evidence to definitively demonstrate that THRT effectively reduces hard cardiovascular event endpoints (e.g., myocardial infarction, stroke, and cardiovascular death) in patients with SCH, particularly in older or low-risk individuals. Existing clinical guidelines remain conflicted on the routine treatment of all SCH patients. Treatment is generally recommended for SCH patients with significantly elevated serum TSH levels (e.g., >10 mIU/L), or those who are younger, symptomatic, or possess cardiovascular risk factors[63]. Considering their elevated cardiovascular risk, SCH patients with concurrent coronary artery disease may derive a greater potential benefit from THRT; however, further high-quality randomized controlled trials are needed to better validate the long-term effects of THRT on cardiovascular outcomes[49,66].

4.2 Treatment Risks

When administering thyroid hormone replacement therapy, the risk of overtreatment must be carefully managed. Excess thyroid hormone can cause iatrogenic hyperthyroidism, potentially leading to tachycardia, cardiac arrhythmias (particularly atrial fibrillation), myocardial ischemia, and even heart failure in severe cases. This can place an increased burden on the cardiovascular system, a risk that is particularly pronounced in elderly patients or those with pre-existing heart disease[66]. Therefore, THRT regimens should be meticulously tailored to individual needs, with close monitoring of thyroid function indicators, especially serum TSH levels. It is essential to maintain TSH values within the normal reference range, avoiding over-suppression. In patients with concomitant coronary artery disease, initiating THRT with a low starting dose is recommended, with gradual, progressive dose increases, while closely observing for cardiovascular symptoms and electrocardiogram changes to ensure treatment safety.

In conclusion, THRT has shown notably positive effects in decreasing cardiovascular disease incidence and improving cardiovascular function in SCH patients. In SCH patients also diagnosed with coronary heart disease, implementing THRT may help lower their cardiovascular event risk, particularly among those at high cardiovascular risk. However, the impact of THRT on long-term, definitive cardiovascular outcomes in patients with only mildly elevated TSH levels requires further in-depth investigation and validation. Consequently, more clinical trials are still needed to comprehensively assess the value and safety of THRT in coronary heart disease patients. In clinical practice, THRT should always be administered cautiously to avoid overtreatment, with close monitoring of the patient's cardiovascular status.

5. Conclusion

This review extensively explored the association between subclinical hypothyroidism (SCH) and coronary atherosclerotic heart disease. The pathophysiological mechanisms by which SCH contributes to coronary heart disease are multifaceted, encompassing both direct impacts on vascular structure and function and indirect influences on traditional cardiovascular risk factors. Notably, age and the presence of other comorbidities can modulate the progression of coronary heart disease. The clinical utility of thyroid hormone replacement therapy (THRT) in coronary heart disease patients with concurrent SCH remains a point of contention. While levothyroxine (L-T4) therapy has demonstrated improvements in vascular function and a potential reduction in cardiovascular event risk in SCH patients, robust evidence from large-scale randomized controlled trials is still lacking to definitively prove a significant reduction in coronary heart disease events and mortality across all SCH patients with coronary heart disease. Particularly in patients with mildly elevated serum TSH levels (<10 mIU/L) or in older populations, a careful evaluation of the risk-benefit ratio of treatment is warranted, as mild hypothyroidism may even correlate with increased longevity in very elderly individuals. In conclusion, a significant association exists between subclinical hypothyroidism and coronary atherosclerotic heart disease. Although its underlying pathophysiological mechanisms are intricate, and treatment strategies remain somewhat debated, ongoing research is expected to provide clearer guidance for clinicians, thereby optimizing cardiovascular risk management in SCH patients and ultimately improving patient outcomes.

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