

Impact of hormone replacement therapy on cardiovascular risk in patients with hypothyroidism: a systematic review

Impacto de la terapia de reemplazo hormonal sobre el riesgo cardiovascular en pacientes con hipotiroidismo: una revisión sistemática

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ABSTRACT

Hypothyroidism, which is developed in 4-10 % of the population, and subclinical hypothyroidism found in more than 10 % of people which are highly associated with cardiovascular pathophysiology at some level. Hypothyroidism, which is the most frequent endocrine disorder with a lack of enough thyroid hormones, presents a wide range of cardiovascular complications, including coronary artery disease, heart failure, and dyslipidemia. Thyroid hormone replacement therapy, particularly levothyroxine (LT4), continues to be the central management of hypothyroidism, which aims to restore euthyroidism and other cardiac comorbidities as well as relieving symptoms. Nonetheless, the complex interworking of thyroid function and cardiovascular health requires a detailed clarification of the processes associated with disease development and drug therapy. Hypothyroidism triggers a chain of cardiovascular alterations such as aberrant lipid metabolism, endothelial dysfunction, and lessened cardiac contractility primarily by lowering the thyroid hormone level. Besides, these modifications eventually lead to raised rates of atherosclerosis, myocardial infarction, and heart failure. LT4 replacement therapy achieves normalization of hyperthyroidism with the replacement of thyroid hormone deficiency, which restores the cardiovascular system to normal by doing so. LT4 modulates lipid metabolism, improves endothelial function, and stimulates myocardial contractility via several different mechanisms. LT4 therapy acts on systemic inflammation and oxidation to accentuate the protective effects of the cardiovascular system. Apart from this, there is an increasing awareness about the use of new thyroid hormone formulations, like LH4, in the therapy of hypothyroidism. LH4, the thymimetic compound, demonstrated a similar binding affinity at the thyroid hormone receptor as T3 (triiodothyronine) but with better tissue selectivity and more metabolic stability. Clinical trials have proven the potency of LH4 in lowering symptoms of hypothyroidism, for example, fatigue, weight gain which are leading cause of cardiovascular disorders. LH4 administration has been safe for up to six months, and only mild adverse effects have been reported when it is used more than a year.

Keywords: hormone replacement therapy. cardiovascular risk. hypothyroidism. systematic review.

RESUMEN

El hipotiroidismo, que se desarrolla en el 4-10% de la población, y el hipotiroidismo subclínico que se encuentra en más del 10% de las personas y que están altamente asociados con la fisiopatología cardiovascular en algún nivel. El hipotiroidismo, que es el trastorno endocrino más frecuente con falta de suficientes hormonas tiroideas, presenta una amplia gama de complicaciones cardiovasculares, que incluyen enfermedad de las arterias coronarias, insuficiencia cardíaca y dislipidemia. La terapia de reemplazo de hormona tiroidea, particularmente levotiroxina (LT4), sigue siendo el tratamiento central del hipotiroidismo, cuyo objetivo es restaurar el eutiroidismo y otras comorbilidades cardíacas, así como aliviar los síntomas. No obstante, la compleja interconexión de la función tiroidea y la salud cardiovascular requiere una aclaración detallada de los procesos asociados con el desarrollo de enfermedades y la terapia farmacológica. El hipotiroidismo desencadena una cadena de alteraciones cardiovasculares, como metabolismo aberrante de los lípidos, disfunción endotelial y disminución de la contractilidad cardíaca, principalmente al reducir el nivel de hormona tiroidea. Además, estas modificaciones eventualmente conducen a tasas elevadas de aterosclerosis, infarto de miocardio e insuficiencia cardíaca. La terapia de reemplazo de LT4 logra la normalización del hipertiroidismo con el reemplazo de la deficiencia de la hormona tiroidea, lo que restablece el sistema cardiovascular a la normalidad al hacerlo. La LT4 modula el metabolismo de los lípidos, mejora la función endotelial y estimula la contractilidad del miocardio a través de varios mecanismos diferentes. La terapia LT4 actúa sobre la inflamación y la oxidación sistémicas para acentuar los efectos protectores del sistema cardiovascular. Aparte de esto, existe una conciencia cada vez mayor sobre el uso de nuevas formulaciones de hormona tiroidea, como la LH4, en el tratamiento del hipotiroidismo. LH4, el compuesto tiromimético, demostró una afinidad de unión similar en el receptor de la hormona tiroidea a la T3 (triyodotironina), pero con mejor selectividad tisular y más estabilidad metabólica. Los ensayos clínicos han demostrado la potencia de la LH4 para reducir los síntomas del hipotiroidismo, por ejemplo, la fatiga y el aumento de peso, que son las principales causas de trastornos cardiovasculares. La administración de LH4 ha sido segura durante hasta seis meses y sólo se han informado efectos adversos leves cuando se usa durante más de un año.

Palabras clave: Terapia de reemplazo hormonal. riesgo cardiovascular. hipotiroidismo. revisión sistemática.

INTRODUCTION

The butterfly-shaped thyroid gland located at the lower neck regulates hormones, primarily triiodothyronine (T3) and thyroxine (T4), that act as chemical messengers that influence nearly every cell, dictating basal metabolic rate, heart rate, blood pressure, body temperature, and even brain functions and development. When this gland malfunctions and underproduces hormones, a condition called hypothyroidism arises. Hypothyroidism is a condition characterized by an underactive thyroid gland and affects millions of people globally. Untreated hypothyroidism can lead to several complications, such as cardiovascular diseases (CVD)¹. Research has shown a positive correlation between overt hypothyroidism and a significant increase in cardiovascular disease mortality and morbidity, ranging from 20% to 80%, which is evident in coronary heart disease (CHD) and cerebrovascular diseases. Stable angina, acute coronary syndrome (ACS), and heart failure are all recognized complications of CHD², and these complications can be worsened with thyroid gland dysfunction. Rodoni et al., 2010 stated that subclinical hypothyroidism is linked to hypercholesterolemia and atherosclerosis, leading to recommendations for screening and treatment to prevent cardiovascular disease development³. Kaushik et al., 2023 specified that subclinical hypothyroidism has been associated with dyslipidemia and enhanced cardiovascular risk, indicating the potential cardiovascular implications of this condition⁴. Cardiovascular complications induced by hypothyroidism are reversible with hormonal replacement therapy⁵. Hormone replacement therapy (HRT) with levothyroxine is the frequently prescribed treatment for hypothyroidism, where it effectively restores thyroid hormone levels, solving hypothyroid symptoms while ultimately reducing CHD symptoms and heart failure. Levothyroxine is the preferred thyroid hormone formulation, with dosages typically adjusted based on weight. For patients without cardiac issues, the regimen typically commences at a moderate level (25 or 50 mcg daily). Those population with cardiac conditions and advanced age, a cautious approach is advised, often beginning with a lower dosage to minimize potential risks. Thyroid hormone replacement therapy has been found to attenuate the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism, suggesting potential benefits beyond cardiovascular health⁶. Levothyroxine is the most frequently prescribed hormonal replacement therapy for hypothyroidism. There is an association between subclinical hypothyroidism and cardiovascular disease, as well as the beneficial effect of levothyroxine replacement, is still under debate, indicating the need for further research in this area⁷. Levothyroxine effectively treats hypothyroidism, but gaps exist. Research has not entirely addressed root causes in all cases, and safety for treating mild hypothyroidism for CVD risk reduction still needs clarification. Currently, available therapies might not fully consider individual CVD risk profiles. A deeper understanding of the mechanisms behind CVD risk in hypothyroidism and better risk prediction tools are crucial. Overall, addressing these gaps can help in comprehensive therapy for hypothyroidism, ultimately lowering CVD risk⁸.

Mechanisms Linking Hypothyroidism with Cardiovascular Disease

The thyroid hormone (TH) plays a significant role in maintaining the cardiovascular system through its receptors in the vascular endothelium and myocardium muscle produces effects. Contraception with a low TSH level, even of little difference, has been strongly linked to vascular morbidity and overall mortality rates due to cardiovascular disease (CVD). The main link between hypothyroidism and cardiovascular disease is the acceleration of atherosclerosis, which is a multifunctional process involving many mechanisms that can be regarded as parallel conduits. This imbalance leads to the fundamental pathophysiological behavior known as endothelial dysfunction, where the balance between vasoconstriction and vasodilatation is disturbed. Nitric oxide (NO) plays a crucial role as an endothelial function and vasodilatory force regulator; therefore, NO can be called a critical factor in this process. Thyroid hormones, which do so via direct and non-direct mechanisms and through genomic and non-genomic pathways, play a significant role in NO production by endothelial cells. They activate phosphatidylinositol 3-kinase (PI3K) and serine/threonine-protein kinase pathways. Finally, the reduction in the NO formation in hypothyroidism entails endothelial dysfunction that further leads to negative processes like platelet adhesion, monocyte infiltration, lipid peroxidation, smooth muscle cell proliferation, and others promoting the atherosclerotic process. Disruption of the lipid metabolism system can be considered an alternate central mechanism for the development of atherosclerosis among people with hypothyroidism. To this end, THs (th3 and th4) directly control HMG-CoA reductase, a hepatic enzyme responsible for cholesterol homeostasis, alongside the LDL-R, i.e., the low-density lipoprotein receptor. Hampered THs levels offer a rather dyslipidemic environment with increased LDL cholesterol and triglyceride levels, followed by intensified LDL oxidation, which develops atherogenic evolution. Apart from dyslipidemia, the other manifestations of a depressed thyroid state include vascular remodeling and hemodynamic changes, which, not surprisingly, make the person more susceptible to cardiovascular diseases. Blood pressure instability, disruption in endothelial cells' tight junctions, and arterial stenosis progressively increase plaque build-up, while hemostatic dysfunction intensifies the hypercoagulable milieu associated with hypothyroidism. Thoroughly explicating the interactions of these different mechanisms highlights the vital point of focusing on specific interventions oriented toward preventing cardiovascular risks in patients predisposed to this condition.

Hypothyroidism is manifested on a cardiovascular level by impairing function and thus interfering with the physiological processes. One of the significant things here is the reduction in expression of the sarcoplasmic reticulum Ca^{2+} -ATPase, which provokes the muscle contraction capacity. This change, along with the increased phospholamban amount, creates disorganization in the fine regulatory detail, leading to ineffective contractions and relaxation of the heart. With this, cardiac output decreases, and there is a progression towards the situation where diastolic dysfunction occurs, which in turn aggravates heart failure. Hypothyroidism interferes with the activity of the renin-angiotensin-aldosterone system, which can be responsible for hypertension in diastolic and sodium-sensitive situations, thus negatively affecting cardiac strength. Dyslipidemia, which shows an increase in total cholesterol, LDL-cholesterol, and apolipoprotein B levels, could form atherosclerotic plaques and thus can increase the risk of coronary artery disease³⁵. At the electrophysiological level, hypothyroidism may prolong QT intervals and lead to varying degrees of atrioventricular block, resulting in ventricular tachycardias, which in turn escalates the ventricular arrhythmias risks. Since that's the case, hypothyroidism could be related to a lower chance of developing heart arrhythmias because of its bradycardic effect and the raised threshold for arrhythmogenicity. Added to that, amiodarone-implicated hypothyroidism also draws cardiovascular treatment, and the root cause here might be either excessive iodine or disruption of thyroid function by design. This event, which is initially manifested to be primary hypothyroidism, needs LT4 thyroid replacement therapy coupled with the restoration of thyroid hormone levels to minimize cardiovascular risks. Severe, subclinical form of hypothyroidism, as opposed to elevated thyroid-stimulating hormone levels in most of the patients with TSH levels over ten mIU/L. Regarding dose adjustments and lithium being tried concurrently with levothyroxine, findings are mixed. Some studies demonstrate benefits, while others report no change. Hence, hypothyroidism ties in with myocardial contractility, vascular tone regulation, lipid metabolism, and electrical conduction in cardiovascular procedures. A detailed comprehension of the unpredictable aspects is fundamental to tailoring therapeutic measures and minimizing CV risks in the affected. Effective therapies demand a patient-centered approach to vigilant monitoring and tailored intervention, including prothyroxine replacement when necessary for optimal cardiovascular outcomes in hypothyroid patients³⁵. The research aims to systematically evaluate the current literature on the association between hormone replacement therapy and cardiovascular risk in patients with hypothyroidism.

METHODS

Inclusion Criteria

This paper includes studies examining the impact of thyroid dysfunction, particularly hypothyroidism, on cardiovascular health. Research papers were selected focusing on people who underwent levothyroxine (LT4) replacement therapy and its impact on cardiovascular outcomes. We selected investigations involving various study designs, including retrospective cohort studies, randomized controlled trials (RCTs), systematic reviews, meta-analyses, and cross-sectional studies where content was about cardiovascular structure and function, major adverse cardiovascular events, and heart failure outcomes about thyroid dysfunction and LT4 therapy. Studies were also selected to explore the relationship between thyroid hormone levels, particularly TSH, and cardiovascular risk markers such as lipid profiles, arterial stiffness, and heart function parameters. This paper includes only peer-reviewed papers published from 2010-2024 to understand LH4 therapy over time comprehensively. Studies published in English and on human subjects were selected.

Exclusion Criteria

Studies unrelated to thyroid dysfunction or cardiovascular health were promptly excluded, and investigations that did not focus on levothyroxine replacement therapy or its impact on cardiovascular outcomes were not selected. We have not included single case reports, grey literature, published papers, or editorials. Papers about hypothyroidism that did not discuss hormonal replacement therapy and its relevance to cardiovascular health are omitted, and those articles focus solely on non-cardiovascular aspects of thyroid dysfunction or LT4 therapy. Papers published back in 2010 or in other languages were excluded.

Search Strategy

we decided to conduct our search on PubMed, Embase, and Web of Science. We designed criteria for primary and secondary keywords, where our primary keywords were "hypothyroidism," "thyroid hormone replacement therapy," "cardiovascular risk," "myocardial infarction," and levothyroxine. We used Boolean operators and combined them with our secondary search terms.

Our Mesh terms were:

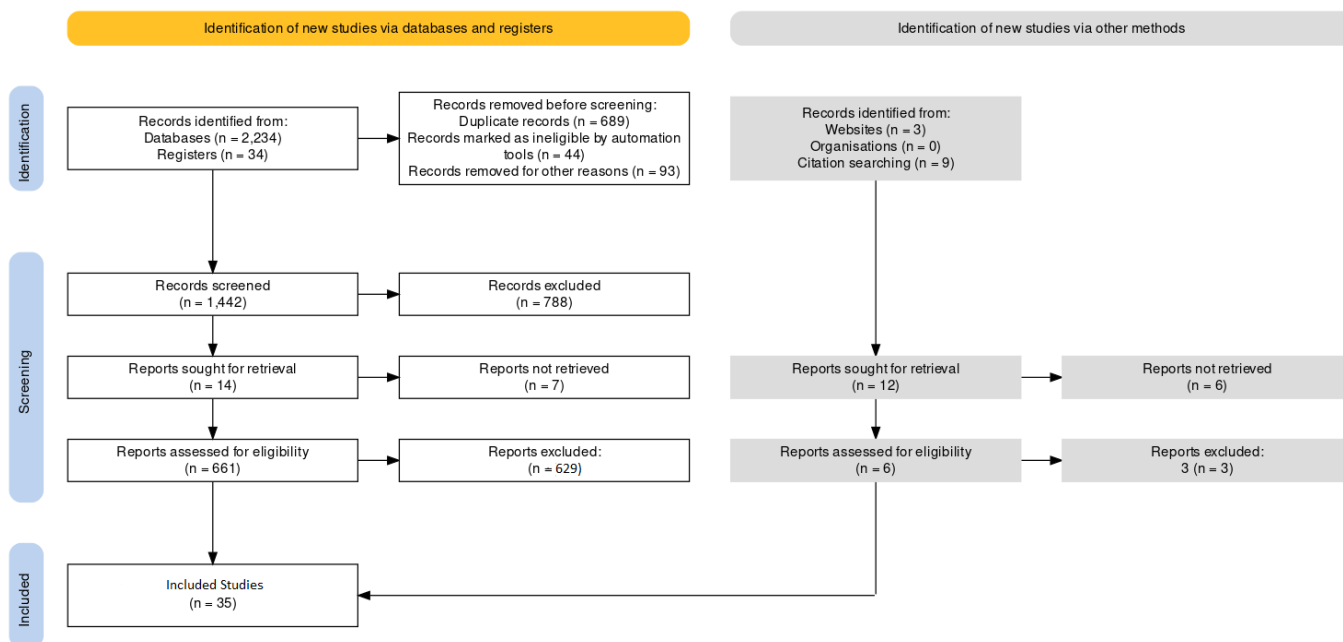
("thyroid dysfunction" OR "hypothyroidism") AND "levothyroxine" AND "cardiovascular health"

("thyroid dysfunction" OR "hypothyroidism") AND "levothyroxine" AND "cardiovascular health"

("hypothyroidism") AND "levothyroxine" OR Hormonal Replacement Therapy OR Hormonal therapy AND "cardiovascular health OR HEART health OR CHD").

We selected studies, including relevant information such as study characteristics, patient demographics, HRT details, and cardiovascular outcomes.

Figure 1. PRISMA Flowchart



Source: the authors.

Initially, 2,234 records were identified from databases, and 12 other papers were identified from citations and manual searches. After removing duplicates and ineligible records, 1,442 were screened from databases, resulting in 788 exclusions. Following this, 14 reports were sought, but seven could not be retrieved for several reasons; of the 661 reports assessed for eligibility, 629 were excluded, leaving 32 studies included in the review from databases. Additionally, three more records were identified from websites and citations, which are included, and this paper includes a total of 35 studies.

RESULTS AND DISCUSSION

Table 1. Summarizing Hormone Replacement Therapy and Cardiovascular Risk

Study ID	Study Design	Participant Demographics	HRT Regimen(s)	Association with CVD Risk	Impact on CVD Outcomes	Moderators/Confounders
Evron et al., 2022 (JAMA et al. 2022;5(5):e2211863)⁹	Retrospective cohort study	Adults (≥18 years) treated with thyroid hormone from Veterans Health Administration (n=705,307), Median age: 67 years, Predominantly male (88.7%)	Synthetic thyroid hormones	Both over-treatment and under-treatment are associated with increased cardiovascular mortality compared to euthyroidism	There is a stronger association between TSH levels and CVD risk in older adults, especially ≥85 years	Confounders: Alcohol status, BMI/obesity rates, Medications/supplements affecting thyroid function; Adjusted for hypertension, diabetes, prior CVD
Seo et al., 2018,¹⁰	Retrospective, non-randomized	257 patients, mean age: THRT group 62.7 ± 12.3, non-THRT group 66.8 ± 12.4; Male: THRT 40.0%, non-THRT 53.1%	Levothyroxine therapy (≥180 days)	Inverse association between THRT and CVD risk	Lower prevalence of acute coronary syndrome and cerebrovascular events in the THRT group	Moderators: Severity of kidney damage, Initial thyroid hormone levels, Levothyroxine formulation type; Confounders: Age, Gender, Other health conditions, Medications, Lifestyle factors
Shah R., 2023¹¹	Randomized controlled trial (RCT), median follow-up 6.2 years	Participants: Age ≥ 50 years, diagnosed with diabetes, additional CV risk factors (n=8,401), Gender: 34% female, Average age: 63.7 years, Diabetes at baseline: 88%, Prior CV event at baseline: 59%	Levothyroxine use at baseline	Subclinical hypothyroidism associated with increased incident CV events and mortality	Levothyroxine use associated with decreased mortality	Same as above
Shi C., 2022¹²	Systematic review and meta-analysis of	1314 adults (56.7% men), mainly from China	Thyroid hormone replacement therapy	Improved cardiac function indicators in heart failure with low-	Improved cardiac function in heart failure with LT3S	Not mentioned

	RCTs		(formula and dosage not mentioned)	triiodothyronine syndrome (LT3S)		
Liu G, 2023 ¹³	Meta-Analysis	Adult patients with subclinical hypothyroidism (SCH), n=568, Majority Female, Age > 18	Levothyroxine	Levothyroxine treatment positively influences LV diastolic function and myocardial strain.	No significant changes in LV morphology post-treatment	Moderators: Severity of kidney damage, initial thyroid hormone levels, levothyroxine formulation type; Confounders: Age, gender, other health conditions, medications, lifestyle factors.
Mazahri et al., 2022 ¹⁴	Cross-sectional study	412 adult hypothyroid patients from King Abdulaziz Medical City, Riyadh	Thyroid hormone therapy	Hypothyroidism associated with coronary artery disease (CAD)	CAD prevalence is higher in men; older age is associated with higher CAD prevalence	Gender, age, smoking, hypertension, family history of CAD, TSH levels influence CAD in hypothyroid patients
Isaila et al., 2024 ¹⁵	Meta-analysis	3430 subjects: 1545 subclinical hypothyroidism (SCH-), 1885 euthyroid subjects (EU)	Levothyroxine therapy	Levothyroxine decreases cardiovascular risk markers (CMT)	SCH subjects had significantly increased CMT compared to the EU	As above

Source: the authors.

Table 2. Other Observational Studies on Thyroid Status and Cardiovascular Health

Author/year	Cardiovascular Outcome	Population
M Tohidi et al., 2018 ¹⁶	There is no association between subclinical hypothyroidism (SCH) or overt hypothyroidism and major adverse cardiovascular events (MACE)	Population-based (with/without known thyroid dysfunction, with/without coronary heart disease (CHD) at baseline)
Selmer et al., 2014 ¹⁷	SCH and overt hypothyroidism are associated with higher all-cause mortality and increased risk of MACE (lower mortality for TSH 5–10 mIU/L)	Population-based (with/without known thyroid dysfunction, with/without CHD at baseline)
Molinaro et al., 2012 ¹⁸	SCH increases the risk of mortality in acute CHD	Population-based (with/without known thyroid dysfunction, with acute CHD)
Tseng FY., 2012 ²²	SCH increased the risk of all-cause and cardiovascular mortality	Population-based (with/without known thyroid dysfunction)
Chaker L, 2015 ¹⁹	SCH increases the risk of stroke in adults	Population-based (with/without known thyroid dysfunction)
Chin et al., 2014 ²³	SCH increased total and CHD mortality	Population-based (with/without known thyroid dysfunction)
Lim HJ, 2017 ²⁰	Increased 10-year cardiovascular disease (CVD) risk score in people with SCH vs. euthyroid	Population-based (with/without known thyroid dysfunction)
Kannan L.m 2018 ²¹	Higher TSH associated with more severe congestive heart failure (CHF) presentation	Patients with or at risk of heart failure (HF)
Chen et al., 2014 ²³	Higher TSH associated with adverse clinical outcomes in patients with HF	Patients with or at risk of HF
Perez et al., 2014 ²⁴	Hypothyroidism predicted adverse clinical outcomes, but the association was not independent and disappeared after adjustment for other covariates.	Patients with or at risk of HF
Kang et al., 2018 ²⁵	Low-free triiodothyronine (FT3) is associated with a higher risk of developing HF after myocardial infarction.	Patients with or at risk of HF
Mitchell et al., 2013 ²⁶	Hypothyroidism increased the 5-year risk of death in patients with left ventricular ejection fraction (LVEF) <35%	Patients with or at risk of HF
Nanchen et al., 2012 ²⁷	SCH increased the risk of HF in older subjects at elevated cardiovascular risk	Patients with or at risk of HF

Source: the authors.

Evidence declared that thyroid dysfunction, notably hypothyroidism, exerts a substantial influence on cardiovascular health, encompassing a spectrum of effects from altered cardiac function to increased risk of heart failure. Observational studies have provided crucial insights into these associations, although findings have exhibited variability attributed to diverse study populations, differing severities of hypothyroidism, patient age, and concurrent comorbidities. Studies examining cardiovascular function in individuals with hypothyroidism have yielded diverse results. Our findings suggested there is a noteworthy connection between hypothyroidism characterized by serum TSH levels ≥ 10 mIU/L and adverse cardiovascular outcomes. The nexus between hypothyroidism and adverse cardiovascular outcomes is particularly pronounced in individuals with heart failure. Subclinical hypothyroidism is a predictor of primary prognostic outcomes in heart failure, including cardiac death and hospitalization. Studies suggested elevated TSH levels, even within the euthyroid range, cause a risk of heart failure events. Longitudinal studies have corroborated these findings, demonstrating that TSH levels exceeding ten mIU/L are strongly associated with an increased risk of developing new heart failure, particularly among elderly populations. Thyroid dysfunction applies discernible effects on lipid profiles, with more severe increases in TSH levels correlating with adverse lipid profile alterations²⁸. Hypothyroidism's impact on "non-traditional" cardiovascular risk factors, such as markers of hemostasis or systemic inflammation, exhibits variability; there is evidence suggesting that hypothyroidism may exacerbate atherosclerosis²⁸. Notably, the relationship between cardiovascular diseases and thyroid function is

bidirectional. Conditions such as heart failure can influence thyroid function, with low circulating T3 levels commonly observed in patients with heart failure, contributing to adverse outcomes in this population²⁹.

Hypothyroid patients often exhibit abnormal heart rate variability, a condition amenable to correction with adequate LT4 replacement therapy³⁰. Hypothyroidism can cause Bradyarrhythmias. Bradyarrhythmias refers to a group of heart rhythm disorders which is characterized by a slower-than-normal heart rate, typically below 60 beats per minute; long-term levothyroxine (LT4) replacement therapy has been noted to reduce the occurrence of bradyarrhythmias that is induced frequently by hypothyroidism³¹. LT4 treatment may reduce QT interval dispersion, thereby diminishing the risk of malignant cardiac arrhythmias in patients with subclinical hypothyroidism³². Various studies have demonstrated impaired systolic and diastolic cardiac performance in patients with subclinical hypothyroidism, and these patients show improvements with LT4 treatment. In multiple studies, LT4 therapy has shown promise in ameliorating markers of atherosclerosis and arterial stiffness, enhancing atrial volume while controlling cholesterol levels³². Retrospective researches suggest cardiovascular benefits, including reduced risk of myocardial infarction and mortality while reducing major adverse events. At the same time, those patients with under-treatment of LT4 have been associated with an increased risk of ischemic heart disease, heart failure, and mortality³³. Evron et al., 2022 found that both over-treatment and under-treatment with thyroid hormones were associated with higher cardiovascular mortality compared to maintaining a healthy thyroid balance, which means proper diagnosis and treatment for optimal cardiovascular health is imperative. Gluvic et al., 2015 focus on six months of levothyroxine (LT4) treatment, with significant reductions observed in total cholesterol (TC), low-density lipoprotein (LDL), and carotid artery intima-media thickness (IMT), with a reduction of 11%³⁴.

Various studies have explored the relationship between thyroid hormone therapy and cardiovascular health. Evron et al. (2022) found that both over- and under-treatment with synthetic thyroid hormones were associated with increased cardiovascular mortality, especially in older adults. Seo et al. (2018) observed an inverse association between long-term levothyroxine therapy and cardiovascular disease risk, suggesting a potential protective effect. Similarly, Shah R. (2023) highlighted the increased cardiovascular risk associated with subclinical hypothyroidism but noted a decreased mortality risk with levothyroxine use. Shi et al. (2022) and Liu et al. (2023) indicated positive impacts of thyroid hormone replacement therapy on cardiac function indicators, specifically in heart failure and subclinical hypothyroidism, respectively. Mazahri et al. (2022) found a correlation between hypothyroidism and coronary artery disease, particularly in older men. Finally, Isaila et al. (2024) demonstrated that levothyroxine therapy reduced cardiovascular risk markers, particularly carotid intima-media thickness, in patients with subclinical hypothyroidism. These findings collectively underscore the importance of thyroid hormone therapy in managing cardiovascular health, with considerations for individualized treatment approaches and risk assessments. Various results show that LT4 replacement therapy can improve lipid profiles in individuals with SCH. A meta-analysis (analysis of multiple studies) revealed that LT4 treatment improved total and LDL cholesterol and reduced markers of vascular disease, such as carotid artery stiffness.

Subclinical hypothyroidism (SCH), as one of the many diseases molecularly caused by thyroid hormone insufficiency, has presented research on the treatment with levothyroxine (LT4). Research has shown that SCH, increased TSH (thyroid-stimulating hormone), and higher cholesterol levels are close factors. The renin-angiotensin-aldosterone and its contribution to diastolic hypertension is one of the hypothyroidism-induced changes and has an impact on the cardiovascular complications being worseness. Slowing conduction is the primary mechanism of action of SCH alongside protraction of QT intervals and possible induction of atrioventricular block. Such a combination increases the risk of arrhythmias. LT4 therapy in SCH patients delivers outcomes that average lipid profiles. This includes lowering cholesterol and LDL levels.

Furthermore, the LT4 therapeutic mode of treatment can decrease blood pressure and arterial stiffness, thus improving the health of our vascular system. The impact of the medication might be more significant in patients with coronary heart disease (CHD) due to a decrease of triglycerides and cholesterol and, after that, a reduced risk of heart disease. In the effect of SCH on heart function, the LT4 is complicated and varies in different studies. Short-term researches within six months demonstrate the improvement in the specific diastolic function parameter in subclinical hypothyroidism patients with levothyroxine therapy. Studies carried out for approximately one year with levothyroxine replacement therapy shown in some subclinical hypothyroidism patients showed improvement in heart function parameters and possibly the correction of observed impairment of heart function in some cases. Studies in kids with SCH came up with contradictory results, as the best effect of LT4 therapy was partial prevention or at least some slowing down of the disorder of heart function in some cases. LT4 therapy, which may negatively impact cardiovascular parameters, does not demonstrate consistent efficacy in terms of clinical outcomes. It is important to note that the retrospective analyses show a tendency towards a decreased incidence of heart attacks or strokes for those patients that have L-Thyroxine (LT4) replacement. At the same time, trial experiments (RCTs) provide mixed data. It was the case with an additional infinite number of RCTs, according to which there were no significant differences in death rates, heart attacks, or hospital admissions being treated by LT4 therapy. In contrast, others have hints of benefits, especially with younger patients.

Management Guidelines of Subclinical Hypothyroidism

The management of subclinical hypothyroidism (SCH) requires a more strategic approach involving different variables like age, nature of symptoms, and cardiovascular risk and levels of TSH. These guidelines provide specific additions to the knowledge gained by each international agency. The 2012 American Thyroid Association guidelines' median TSH level is higher than 10 mIU/L. While consideration of thyroid hormone treatment is vague for those with increased cardiovascular disease (CVD) risk under the range of 4.5–10 mIU/L. Treatment in subclinical hypothyroidism begins with lower comparative dose to overt hypothyroidism which is about 25-75 mcgde daily, patient's response is monitored after that depending on symptoms and TSH monitoring. The 2013 European Thyroid Association guidelines recommend a treatment initiation in symptomatic or thyroid-stimulating hormone (TSH) levels >10 mIU/L patients less than 65 years of age, even if TSH <10 mIU/L, according to the recent analysis of three large-scale studies. Comfort observation without treatment is a reasonable strategy for elderly patient with TSH below 10 mIU/L, especially those asleep in 80-85 years old. Latinoamerican Thyroid Society (2013) guidelines increase the completion of handling SCH takes levels starting and based on the risk of progression to overt hypothyroidism as a criterion. Treatment is advised for cases when TSH >10 mIU/L persists and considered for cases when TSH 4.5–10mIU/L are found with increased CVD risk among <65-year-olds. Elder patients with age equal or above 65 years without TSH less than 10 mIU/L seem to not require treatment. In the 2014 American Thyroid Association guidelines, treatment of SCH with levothyroxine is emphasized taking into account the presence of CVD; patients are advised to begin at a low dose, monitoring is suggested to be done closely to check for the development of cardiac symptoms. Along this line, 2019 dossett UK guideline recommended no use of levothyroxine, in generally-accepted cases of SCH, except in pregnancy or trying-to-pregnant cases, or those with TSH >20 mIU/L ³⁶.

CONCLUSION

All the above studies conclude that hypothyroidism is a significant risk factor for various complications, including cardiovascular morbidity, necessitating meticulous management strategies to optimize patient outcomes. Hormonal replacement therapy, particularly LT4 supplementation, stands out as a pivotal therapy for restoring euthyroidism and ameliorating cardiovascular complications. The emergence of novel thyromimetic compounds, such as LH4, offers promising avenues for improving the treatment efficacy of hypothyroidism while minimizing adverse effects. More research is warranted to delineate the long-term safety and efficacy of LH4 therapy in hypothyroid patients with cardiovascular comorbidities.

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