Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 4
Open Access

Modifications In The Heart Caused By Clinical And Subclinical Thyroid Disorders

Indresh Yadav[1*], Mehak Hamid[2], Aqsa Bintae Abid Memon[3], Muhammad Zain Ali[4], Dr. Avrina Kartika Ririe MD[5], Husnain Akhtar[6]

[*1]MBBS, Department of Internal Medicine, Nuvance Health/ VBMC, USA
Email: yadavindresh104@gmail.com
[2]Postgraduate Resident General Surgery, Department of General Surgery, PNS Hafeez Hospital Islamabad, Pakistan, Email: Hamidmehak@gmail.com
[3]Doctor, Department of Biochemistry, Ziauddin University, Pakistan
Email: aqsabinteabid@gmail.com
[4]Student, Department of Clinical Medicine, Hunan Normal University, China
Email: Zin.1479.za20ml.com
[5]Brain & Heart Center Department, Mohammad Hoesin General Hospital, Palembang, Indonesia
Email: avrinaririe@gmail.com
[6]Medical University Pleven, United Kingdom, Email: husnain.akhtar.212@gmail.com

***Corresponding Author: Indresh Yadav,** MBBS, Department of Internal Medicine, Nuvance Health/ VBMC, USA, Email: yadavindresh104@gmail.com

Cite this paper as: Indresh Yadav, Mehak Hamid, Aqsa Bintae Abid Memon, Muhammad Zain Ali, Dr. Avrina Kartika Ririe MD, Husnain Akhtar (2024) Modifications In The Heart Caused By Clinical And Subclinical Thyroid Disorders. *Frontiers in Health Informatics, 13* (4), 864-873

ABSTRACT:

Background: Hypothyroidism, an endocrine condition, occurs when the thyroid gland underperforms, disrupting homeostasis and normal bodily functions. It is diagnosed through clinical symptoms and measurement of thyroid hormone levels in the blood.

Objective: This abstract aims to detail the morphological and physiological changes in the cardiovascular system caused by hypothyroidism and elucidate the intracellular and extracellular mechanisms of thyroid hormones.

Methods: A comprehensive analysis of the physiological interplay between the thyroid gland and the circulatory system was conducted, focusing on how hypothyroidism affects cardiovascular health. The impacts on hemodynamics, myocardial structure, and function were reviewed, alongside considerations of hypertension and vascular health.

Results: Hypothyroidism influences cardiovascular health through altered hemodynamics, myocardial dysfunction, and vascular changes. The condition is associated with congestive heart failure, hypertension, and compromised blood vessel integrity. Both clinical hypothyroidism and subclinical thyroid dysfunction are identified as significant risk factors for developing cardiovascular disorders.

Conclusion: Hypothyroidism exerts a profound effect on cardiovascular function through direct and indirect mechanisms. Understanding these relationships is crucial for identifying and managing cardiovascular complications associated with thyroid dysfunction.

KEYWORDS: heart disease, cardiovascular disease, thyroxine, triiodothyronine, hypothyroidism.

INTRODUCTION:

Hypothyroidism is a disorder characterized by a thyroid hormone shortage; its description is primarily biochemical because of the various forms and the general lack of particular symptoms. The change can occur at the thyroid gland level (primary hypothyroidism) or be more widespread because of a reduction in hypothalamic-pituitary stimulation (secondary hypothyroidism ***free-low (FT4)). Geographically speaking, the prevalence of hypothyroidism varies; it is between 0.2% and 5.3% in Europe and between 0.3% and 3.7% in the United States. It is more common in regions with severely deficient or high iodine intake. Women, being older (over 65), being Caucasian, having autoimmune disorders (such as type 1 diabetes), gastric atrophy, celiac disease, Down syndrome, and Turner syndrome are among the most common risk factors (Quintanilla Ferrufino et al., 2020).

Women, being older (over 65), being Caucasian, having autoimmune disorders (such as type 1 diabetes), gastric atrophy, celiac disease, Down syndrome, and Turner syndrome are among the most common risk factors. Thyroid-stimulating hormone, or thyrotropin (TSH), is increased while thyroid hormone levels are normal, indicating subclinical hypothyroidism, an illness in which most patients have no symptoms. However, there are significant side effects as well, like myxedema coma, which is characterized by extended, severe hypothyroidism, organic malfunction, and a decline in mental status; the diagnosis can be made without the presence of myxedema (skin and soft tissue oedema) or coma. Different forms of hypothyroidism have other causes, such as peripheral hypothyroidism (extrathyroid hypothyroidism) brought on by abnormal production of the enzyme deiodinase 3, which is found in tumour tissues and is in charge of deactivating thyroid hormone (Abdel-Moneim et al., 2020).

The prevalence of subclinical hypothyroidism varies depending on the population being studied. For instance, in a study conducted in the Indian Kashmiri ethnic group, subclinical hypothyroidism was found to be 18% prevalent in adults, with a higher prevalence in women (24% compared to 11% in men). According to the US III National Health and Nutrition Examination Survey findings, blood TSH, T4, anti-thyroglobulin antibodies, and thyroid peroxidase antibodies were measured in 13,344 individuals with thyroid illness that had not previously been diagnosed. As a result of the investigation, 4.6% of people had hypothyroidism (0.3% of clinical cases and 4.3% of subclinical instances). The physiology of the heart and the peripheral vascular system (PVS) is significantly influenced by thyroid hormones (Ahmadi et al., 2020).

In addition to causing hemodynamic changes and decreasing peripheral vascular resistance (PVR), T3 activates the cardiac sarcolemma, which has an inotropic and vasodilatory effect on the cardiomyocyte through gene expression. Because of those above, low cardiac index and significant increases in peripheral vascular resistance are hallmarks of hypothyroidism. We will briefly explain the pathophysiology of this disease, its connection to changes in the cardiovascular system, its clinical manifestations and sequelae, and its role as a risk factor for some cardiovascular manifestations (Danzi & Klein, 2022).

METHODS OF RESEARCH INFORMATION:

Data were gathered from the HINARI, ScienceDirect, PubMed, and Google Scholar databases. Using the following Boolean operators: "hypothyroidism AND cardiovascular disease," "hypothyroidism AND cardiovascular disease," "subclinical hypothyroidism AND cardiovascular

disease," and the following terms: hypothyroidism, clinical hypothyroidism, hypothyroidism, and cardiovascular disease. Articles meeting the following inclusion criteria were included: they had to be published in English or Spanish in the adult population (less than 18 years old), experimental, observational studies, and bibliographic reviews, and they had to be published within the last five years (searches were extended to earlier years if the most recent references were not available). The articles had to analyze the relationship between cardiovascular alterations and clinical and subclinical hypothyroidism. Articles that satisfy the inclusion criteria and are qualitative studies fall under the exclusion criteria. The articles with the most recent information were chosen from thirty-one articles (Vidili et al., 2021).

ANALYSIS:

HEART

Thyroid hormone (TH) receptors are in the heart and vascular endothelial tissues. They interfere with the circulating TH's homeostasis, which is required to control end-organ function. Figure 1 illustrates how slight variations in TH content can hurt the cardiovascular (CV) system. There is a 20–80% higher risk of vascular morbidity and mortality when there is thyroid dysfunction (Hoshi et al., 2020).

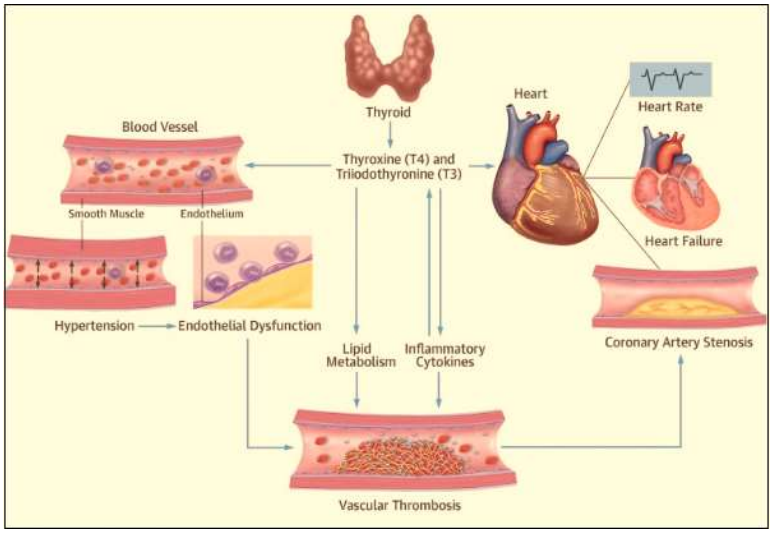

Figure 1: Thyroid hormones and the cardiovascular system's interaction.

Either hyperthyroidism or hypothyroidism can bring on cardiovascular dysfunction. Increased total and LDL cholesterol, diastolic hypertension, arterial stiffness, thrombogenicity through as-yet-undisclosed processes, endothelial degradation due to dependent vasodilation, and left ventricular systolic and diastolic dysfunction are all caused by the latter (Kaushik & Agrawal, 2023).

MYOCARDIOCYTE ALTERATIONS CAUSED BY HYPOTHYROIDISM

Receptors located in the TH nucleus at the intracellular compartment regulate the genomic effects of TH. Receptor proteins found in the α and β isoforms (TRα and TRβ) bind triiodothyronine (T3) with a higher affinity (>10) than thyroxine (T4). These receptors couple to response elements in the TH promoter regions, promoting the expression of genes positively modulated by T3 and repressing it when TRa and TRb genes are absent. Research has demonstrated that the TRα isoform is essential for expressing cardiac genes, ruling out T3 as a thyroid hormone biologically significant for

cardiac myocytes. This is because T3 enhances the force and speed of systolic contraction as well as the speed of diastolic relaxation. Besides raising coronary arteriolar angiogenesis and lowering vascular resistance (Hashimoto, 2022).

T3 interacts with nuclear thyroid hormone receptors (RT3) after it enters the myocyte. Sarcoplasmic reticulum calcium ATPase (SERCA2), phospholamban, and myosin heavy chains are among the regulatory and structural proteins linked to contractile function that are encoded when T3 binds to these receptors and optimally transcriptionally transcribes particular DNA sequences. T3 controls the positive and negative regulation of myosin heavy chains (MHC), a and b (a-MHC and b-MHC), or fast and slow myosin, respectively. Comorbidities such as arterial hypertension and atherosclerosis are frequently observed in patients with clinical and subclinical hypothyroidism because these conditions are linked to reversible phases of endothelial impairment. Premature ventricular filling and a decline in the rate of myocardial relaxation cause a decrease in left ventricular diastolic performance with time (Smedegaard et al., 2020).

Heart contractility and output both decrease with a drop in thyroid function. These changes result in reduced SERCA2 activity and increased phospholamban. T3 positively regulates SERCA2, which pumps calcium ions (Ca2Í) back to the sarcoplasmic reticulum during the relaxation phase of myofilament contraction. Phospholamban controls SERCA2 activity. Heart diastolic function is altered due to these variations in protein concentrations (Griadil et al., 2021).

PERMANENT HEART FAILURE

Ion channel activation (Naþ, Kξ, and Ca2þ) and the control of particular signal transduction in the phosphatidylinositol kinase 3-kinase and serine/threonine kinase activation pathway are among the effects of TH at the cardiac level (Figure 2). which, via its effects on vascular smooth muscle cells, induces the synthesis of endothelial nitric oxide, which lowers systemic vascular resistance. On the other hand, it has also been demonstrated that hypothyroid individuals with reduced endothelium function get better with TH replacement therapy. This is because thyroid hormones reduce myocardial damage and reverse positive left ventricular remodelling, which causes evolution to occur either slowly or not at all. In the direction of permanent post-ischemic heart failure (Đenić & Vidić, 2020).

Experiments on adult hamsters with subclinical hypothyroidism suggest that a reduction in myocardial cells, weakening of the myocardial artery, and widespread fibrosis are likely the biological processes via which thyroid hormones influence diastolic function. A thyroid hormone shortage may cause increased hyaluronic acid in the cardiac interstitium, impeding diastolic filling, and impaired calcium absorption into the sarcoplasmic reticulum during diastole. Diastolic hypertension, dyslipidemia, and endothelial dysfunction are additional possible processes in hypothyroidism that may contribute to heart failure by promoting atherogenesis and coronary artery disease (Aringazina et al., 2023).

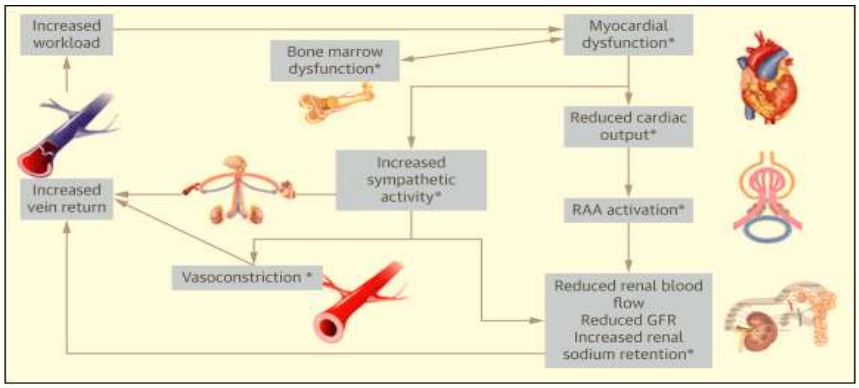

Figure 2: The pathophysiology of the heart and the role of thyroid hormones.

Moreover, it lengthens the QT interval and action potential, which increases the risk of ventricular hypertonicity and, in rare instances, torsade points. Low QRS complexes and varying degrees of atrioventricular block could be observed. Because T3 stimulation encourages the liver's manufacture of renin substrates, hypothyroidism also affects the renin-angiotensin-aldosterone pathway. As a result, there will be a drop in renin and a rise in diastolic blood pressure, leading to diastolic hypertension, which is typically sodium-sensitive (Urgatz & Razvi, 2023).

Hypothyroidism's Precardial Effect

The degree and length of the hypothyroidism condition determine the appearance and extent of pericardial effusion. Pericardial effusion, which is frequent in patients with primary hypothyroidism, affects up to 25–30% of these patients. Nonetheless, considering its modest size, this can potentially be asymptomatic and does not impact hemodynamics. The aetiology of these mild pericardial effusions is a steadily growing capillary leak and pericardial distention. Large pericardial effusions are uncommon in hypothyroid patients. They are linked to a severe and advanced form of the disease that may need immediate pericardiocentesis, whether or not cardiac tamponade is present. The pericardial effusion disappears a few weeks or months after beginning T4 therapy (Jadhav & Kammar, 2020).

To avoid future cardiac tamponade or recurrence, patients presenting with a significant pericardial effusion should be suspected of primary hypothyroidism. Pericardial fluid may have a golden hue due to cholesterol crystals. The mechanism underlying the excessive appearance of fluid rich in polysaccharides and proteins in the pericardial space is similar to myxedema. It is caused by volume retention due to increased capillary permeability, increased albumin volume of distribution, and inadequate and compromised lymphatic drainage (Kumar et al., 2022).

Changes at the level of the blood vessel

By generating Nitric Oxide (NO), the endothelium defends itself against inflammatory and atherogenic processes. NO is also regarded as a trustworthy marker of the early stages of endothelial dysfunction, vascular tone abnormalities, and vascular ageing. The parameters of thermal hyperemia, whose alteration was dependent on anomalous nitric oxide values, led to an increase in mortality secondary to cardiovascular components; Kruger et al. showed that the reduction of NO in endothelial dysfunction determines a decrease in anti-migratory, antiproliferative, and anti-inflammatory-functions-. These findings were contrasted with those of a different study that involved patients with subclinical hypothyroidism and a control group and revealed a more notable deterioration in hypothyroid individuals. Through specific biochemical pathways in impacted endothelial cells, increased generation of NO, and enhanced breakdown of vasodepressant intermediates, subclinical hypothyroidism may directly exacerbate endothelial failure (Moutzouri et al., 2021).

EMPs, or circulating endothelium-derived microparticles, are a diverse group of vesicles generated during cell fission and vesiculation. of the endothelial cell membrane, which is produced by apoptotic or activated endothelial cells and is essential for vascular remodelling, tissue injury repair, and endothelial repair. EMPs that are integrated into endothelial cells via interactions with surface-expressed alpha4 and beta1 integrins either directly stimulate the cells or transmit surface receptors to the cells, which has a biological effect. It is unclear, therefore, what causative impact the EMP pattern plays in people with subclinical hypothyroidism. Decreased thyroid function may result in

dysregulation of cell-to-cell recognition, cooperation, and information transfer by reducing the expression of proteins, signalling molecules, endothelial nitric oxide synthase, and surface receptors cells. It is still unclear if the phenotypic deterioration results from pre-existing endothelium damage or if it develops as the disease progresses (Bacelova et al., 2023).

Thyroid function can be altered in patients with congestive heart failure (CHF), as evidenced by the study "Pattern of circular endothelial-derived microparticles among Chronic Heart Failure Patients with Dysmetabolic Comorbidities: The Impact of Subclinical Hypothyroidism" (Berezin & Berezin, 2024). EMPs produced from activated endothelial cells, a model of circulating EMPs, may be essential for angiogenesis and endothelial repair. On the other hand, endothelium-derived microparticles that come from endothelial cells that have undergone apoptosis are thought to be a direct cause of vascular injury. Whether endothelial dysfunction compromises the ratio of apoptotic to active endothelial cell microparticles remains unanswered. In light of these events, the altered pattern of circulating EMPs can be interpreted as a sign of endothelial dysfunction and damage and potentially a novel CV risk factor (Papadopoulou et al., 2020).

Hypothyroidism is linked to other cardiovascular disease risk factors, such as excessive homocysteine levels and impaired glomerular filtration. Authors like Orzechowska-Pawilojc et al. describe homocysteine as an amino acid oxidized in the plasma to make homocysteine and homocysteine thiolactone. Free radicals and hydrogen peroxide are also produced during this process, which results in endothelial lesions. Based on their research, they concluded that thyroid hormone levels determine blood homocysteine concentrations. Increased homocysteine levels are associated with a higher likelihood of artery intima thickness, a factor in asymptomatic cardiovascular disease. According to this correlation, high blood homocysteine levels are prevalent in the early stages of atherosclerosis and precede acute cardiovascular events (Dell'Aquila et al., 2024).

Coagulation Of Disorders And Hypothyroidism

Hemostasis is modulated by thyroid hormones, which also control the action of coagulation factors. Thyroxine appears to affect the synthesis of proteins that modify liver hemostasis and is associated with the release of Von Willebrand factor from endothelial cells. Because of this, a shortage of thyroxine in hypothyroidism is related to a lack of several coagulation factors (factors VII, IX), X, and XI, Unlike hyperthyroidism, when atherosclerotic and thrombotic illnesses predominate, clinical hypothyroidism is characterized by hypercoagulable conditions (Khabibovna et al., 2023).

Research on coagulation in overt hypothyroidism has produced inconsistent findings. For example, one study comparing patients with euthyroid controls who had moderate or severe hypothyroidism found that the former had decreased fibrinolytic activity and was more prone to clot formation. In contrast, the latter had greater fibrinolysis and minor tissue plasminogen activator antigens. Another study found that patients with subclinical hypothyroidism had decreased antithrombin III activity and increased fibrinogen levels and that plasminogen activator inhibitor antigen in subclinical hypothyroidism may account for a possible hypercoagulable state (Chawda et al., 2022).

Atherosclerosis

Increased LDL oxidation is linked to hypothyroidism and contributes to atherogenesis. Reduced LDL receptors lead to decreased hepatic cholesterol clearance and seven alpha-hydroxylase activity, which is TH-activated, causing hyperlipidemia in hypothyroidism. There is proof that subclinical hypothyroidism increases the risk of atherosclerosis, coronary heart disease, and heart attacks in direct proportion to TSH levels. The existence of dyslipidemia, hypertension, coagulation problems, elevated homocysteine and CRP in serum, and endothelial dysfunction are cardiovascular

risk factors that could account for this. According to a Peruvian study, middle-aged women with TSH levels ≥ 2.5 uIU/mL had higher lipid plaques and carotid intima-media thickness (CIMT) than women with lower TSH levels (Anderson, 2020).

Extension Of The Arterial Due To Hypothyroidism

Thyroid hormones typically improve cardiac output by promoting the expression of proteins that increase myocardial contractility and decrease peripheral vascular resistance through vasodilation, encouraging venous return. These mechanisms are described above. Hypothyroid patients experience signs and symptoms of heart failure, such as fatigue, dyspnea, constipation, cold intolerance, bradycardia, etc., since a decrease in cardiac output results from the absence or reduction of all these effects, which are controlled by thyroid hormones that are insufficient in hypothyroidism. Recognizing that subclinical hypothyroidism does not cause symptoms in its patients. Bradycardia and arterial hypertension are the most prevalent physical manifestations of hypothyroidism in the cardiovascular system (Panday et al., 2021).

Insufficient thyroid hormone results in both genetic and non-genomic changes in the cardiomyocyte. These changes affect the cardiomyocyte's ability to contract and raise peripheral vascular resistance. The decreased ventricular relaxation that follows produces diastolic dysfunction, which is a prevalent condition in hypothyroidism. While genomic alterations are typified by reducing or increasing the production of regulatory and structural proteins, non-genomic alterations involve the modification of sodium, potassium, and calcium channels. The specific changes observed in a given thyroid condition are explained by the critical role thyroid hormones play in the vasoconstriction of vascular myocytes. Because low serum T3 levels inhibit the generation of nitric oxide and endothelium-derived relaxing factors (EDRF), which cause arterial stiffness, peripheral vascular resistance can rise by as much as 30% (Pradeep Kumar, 2020).

Decreased cardiac output, a slower pulse wave, longer circulation times, and reduced tissue perfusion are all caused by increased total vascular resistance (TVR). Ex vivo studies show increased nitric oxide-dependent vasodilation in L-thyroxine-treated patients with subclinical hypothyroidism (Balli et al., 2022).

DISCUSSION:

Thyroid hormone deficit is the cause of hypothyroidism, which is more common in populations with high intake or severe iodine deficiency. It is more prevalent in white persons, women, those over 65, patients with autoimmune disorders (especially those who are part of multiple autoimmune endocrinopathies), people with Down syndrome, and people with Turner syndrome. The primary categorization of the pathology is determined by the organ responsible for hypothyroidism, which is split into Primary hypothyroidism, which involves thyroid gland change; secondary hypothyroidism, which involves decreased thyroid stimulation at the pituitary gland level; and tertiary hypothyroidism involves decreased thyroid stimulation at the hypothalamus level. Similarly, it can be divided into two categories: subclinical hypothyroidism, which is characterized by high levels of TSH combined with normal levels of T3 and T4 and is typically asymptomatic, and clinical hypothyroidism, which occurs when there is an increase in TSH combined with low levels of free thyroxine (FT4) and symptoms (Lisco et al., 2020).

About the interaction of thyroid hormones with the heart and PVS, it is established that these hormones cause hemodynamic changes, mediate effects on the cardiomyocyte, and initiate various cellular and biochemical processes that result in a cardioprotective impact. We recall that cardiovascular dysfunction, elevated total, and LDL cholesterol, diastolic hypertension, endothelial deterioration, left ventricular systolic and diastolic dysfunction, congestive heart failure, torsion of tip,

and pericardial effusion with or without cardiac tamponade are among the main cardiovascular conditions that hypothyroidism, both clinical and subclinical, can cause. Thyroid function tests (TSH, T3, T4), blood tests, and physical examinations are performed to ensure a proper diagnosis. The kind, severity, and interaction of hereditary and sociodemographic factors will determine how hypothyroidism is treated (Tandia & Tandia, 2024).

CONCLUSION:

Since thyroid hormones and the heart are closely related, they have a definite cardioprotective effect. T3 enters the cardiac myocyte and attaches itself to its nuclear receptor, which causes the encoding of proteins that control the heart's contraction. Thus, an elevation in this hormone's concentration would increase cardiac output and contractility. On the other hand, in hypothyroidism, the myocardium reduces its cardiac production and power of contraction, leading to an increase in residual volume and, ultimately, diastolic dysfunction. This is one of the starting points for developing several cardiac diseases.

Similarly, thyroid hormones trigger the production of endothelium-derived relaxing factors and nitric oxide, two substances that support peripheral vasodilation. Peripheral vascular resistance rises in hypothyroidism due to their decline, which may account for their association with arterial hypertension and other vascular changes brought on by endothelial degradation. Because of this, abnormalities in the cardiovascular system are intimately linked to some clinical signs of this condition, including fatigue, cold intolerance, dyspnea, and bradycardia. Thus, hypothyroidism must be taken into account in patients who have cardiac pathologies, such as pericardial effusion, cardiac tamponade, heart failure, high blood pressure, or even coagulation disorders.

Thyroid dysfunction is thus associated with an increased risk of cardiovascular disease. This poses a risk to public health and highlights the need to understand how thyroid hormones and the circulatory system interact to avoid consequences.

REFERENCES:

Abdel-Moneim, A., Gaber, A. M., Gouda, S., Osama, A., Othman, S. I., & Allam, G. (2020). Relationship of thyroid dysfunction with cardiovascular diseases: updated review on heart failure progression. *Hormones*, *19*(3), 301-309.

Ahmadi, N., Ahmadi, F., Sadiqi, M., Ziemnicka, K., & Minczykowski, A. (2020). Thyroid gland dysfunction and its effect on the cardiovascular system: a comprehensive review of the literature. *Endokrynologia Polska*, *71*(5), 466-478.

Anderson, B. (2020). Subclinical Hypothyroidism and its Relation to Cardiac Dysfunction.

Aringazina, R. A., Abenova, N., & Bhat, S. A. (2023). Subclinical Hypothyroidism and Functional Hemodynamics of the Heart. *West Kazakhstan Medical Journal*, 95–100-195–100.

Bacelova, M., Popova, M., & Alakidi, A. (2023). Hypothyroidism and subclinical hypothyroidism and their influence on autonomic cardiovascular regulation and metabolism. *Fiziologichnyi Zhurnal (Physiological Journal)*, *69*(1).

Balli, M., Köksal, F., Söylemez, N., Ertürk, E., Aydinli, B., Özkan, B., & Vurgun, V. (2022). Subclinical hypothyroidism and its relationship with therapy failure in patients who underwent cardiac resynchronization therapy. *European Review for Medical & Pharmacological Sciences*, *26*(23).

Berezin, A. E., & Berezin, A. A. (2024). Extracellular vesicles in heart failure.

Chawda, N., Jain, S., & Solanki, B. (2022). A study of cardiovascular manifestations in hypothyroidism. *Series Endo*.

Danzi, S., & Klein, I. (2022). Thyroid abnormalities in heart failure. *Cardiology clinics*, *40*(2), 139-147.

Dell'Aquila, M., Rossi, C. S., Caldonazo, T., Cancelli, G., Harik, L., Soletti, G. J., An, K. R., Leith, J., Kirov, H., & Ibrahim, M. (2024). Subclinical Hypothyroidism and Clinical Outcomes after Cardiac Surgery–A Systematic Review and Meta-analysis. *JTCVS Open*.

Đenić, A., & Vidić, N. (2020). Disorders of cardiovascular function and echocardiographic parameters of the heart in overt and subclinical hypothyroidism. *Medicinski glasnik Specijalne bolnice za bolesti štitaste žlezde i bolesti metabolizma'Zlatibor'*, *25*(77), 37-46.

Griadil, T. I., Chopey, I. V., Chubirko, K. I., & Feysa, S. V. (2021). The clinical presentation of subclinical hypothyroidism in patients with type 2 diabetes mellitus associated with obesity, its impact on cardiovascular risk, and ways of its correction. *Wiadomości Lekarskie*, 2634.

Hashimoto, K. (2022). Update on subclinical thyroid dysfunction. *Endocrine Journal*, *69*(7), 725-738.

Hoshi, R. A., Santos, I. S., Dantas, E. M., Andreão, R. V., Mill, J. G., Duncan, B. B., Schmidt, M. I., Lotufo, P. A., & Bensenor, I. (2020). Diabetes and subclinical hypothyroidism on heart rate variability. *European Journal of Clinical Investigation*, *50*(12), e13349.

Jadhav, V., & Kammar, K. F. (2020). Electrocardiographic changes in subclinical hypothyroidism. *National Journal of Physiology, Pharmacy and Pharmacology*, *10*(06).

Kaushik, A., & Agrawal, M. (2023). Relationship between subclinical hypothyroidism and the risk of cardiovascular complications. *Cureus*, *15*(1).

Khabibovna, Y. S., Alisherovna, K. M., Nizamitdinovich, K. S., & Totlibayevich, Y. S. (2023). Features of heart failure in patients with thyrotoxicosis. *Journal of New Century Innovations*, *29*(1), 89-97.

Kumar, A., Prabhu, M. M., Bhat, N., & Stanley, W. (2022). A study of cardiovascular profile in patients with primary hypothyroidism. *Biomedicine*, *42*(4), 766-770.

Lisco, G., De Tullio, A., Iacoviello, M., & Triggiani, V. (2020). Congestive heart failure and thyroid dysfunction: the role of the low T3 syndrome and therapeutic aspects. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *20*(5), 646-653.

Moutzouri, E., Lyko, C., Feller, M., Blum, M. R., Adam, L., Blum, S., Aeschbacher, S., Fischer, U., Roten, L., & Del Giovane, C. (2021). Subclinical thyroid function and cardiovascular events in patients with atrial fibrillation. *European journal of endocrinology*, *185*(3), 375-385.

Panday, P., Franchini, A. P. A., Iskander, B., Anwer, F., Oliveri, F., Kakargias, F., Hamid, P., & Fotios, K. (2021). Subclinical hypothyroidism in geriatric population and its association with heart failure. *Cureus*, *13*(4).

Papadopoulou, A.-M., Bakogiannis, N., Skrapari, I., Moris, D., & Bakoyiannis, C. (2020). Thyroid dysfunction and atherosclerosis: a systematic review. *in vivo*, *34*(6), 3127-3136.

Pradeep Kumar, S. (2020). *A Study of Cardiovascular Changes in Newly Diagnosed Hypothyroid Patients* Government Vellore Medical College, Vellore].

Quintanilla Ferrufino, G. J., Medina Guillen, L. F., Erazo, L. C., Medina Guillen, M., & Shafick Asfúra, J. (2020). Cardiovascular disorders are caused by clinical and subclinical hypothyroidism. *Revista Científica Ciencia Médica*, *23*(1), 52-60.

Smedegaard, S. B., Riis, A. L., Christiansen, M. K., & Linde, J. K. S. (2020). Subclinical hyperthyroidism and the risk of developing cardiovascular disease-a systematic review. *Dan Med J*, *67*(11), A12190701.

Tandia, G., & Tandia, K. (2024). A CLINICAL STUDY OF CARDIOVASCULAR CHANGES IN HYPOTHYROIDISM. *Pakistan Heart Journal*, *57*(1), 122-126.

Urgatz, B., & Razvi, S. (2023). Subclinical hypothyroidism, outcomes and management guidelines: a narrative review and update of recent literature. *Current Medical Research and Opinion*, *39*(3), 351-365.

Vidili, G., Delitala, A., & Manetti, R. (2021). Subclinical hyperthyroidism: the cardiovascular point of view. *European Review for Medical & Pharmacological Sciences*, *25*(8).