The Connection between Hypothyroidism, Cardiovascular Disease, Type 2 Diabetes and Cognition

HELENA ROOTH SVENSSON MARCH 2026

This is a summary of some important research findings revealing that low T3 at the tissue level may cause cardiovascular disease, type 2 diabetes and even cognitive impairment. Based on analysis of available clinical and molecular research the time has come for a paradigm shift.

As a general practitioner I have over decades encountered many patients who described symptoms consistent with hypothyroidism despite a TSH value within the reference range. The clinical guidelines then — and still today — state that the diagnosis must be confirmed by an elevated TSH. For many years I have had a special interest concerning this group of patients. Some patients have been successfully treated based on their medical history and physical examination. Published articles on thyroid hormones and their impact on different organs are extensive. Only a few of the articles are referenced here.

Too much focus on TSH

TSH (thyroid-stimulating hormone) values have been given far too much bearing relative to the patient's medical history and physical examination. When the doctor says "your TSH is normal", meaning it is within the reference range, and the doctor equates "TSH within the reference range" with euthyroidism, it is far from the truth.

TSH stimulates the uptake of iodine and the amino acid tyrosine from the blood stream into the thyroid gland follicular cells, followed by a series of enzymatic processes catalyzed by thyroperoxidase (TPO), resulting in the synthesis of thyroxine (T4) and triiodothyronine (T3). TSH secreted from the pituitary gland does not correlate with thyroid hormones at the tissue level, yet it continues to be regarded as the sole and decisive test to evaluate whether a patient suffers from thyroid dysfunction or whether thyroid hormone substitution is adequate.

It is the thyroid hormone T3 — not TSH — that is crucial for regulating the body's metabolism, energy production, brain function and cardiovascular control. Thyroid hormones are transported into the cell by the transmembrane proteins MCT8 and MCT10. Inside the cells different deiodinase enzymes are involved in the activation or deactivation of thyroid hormone. This process is dependent on the absence of polymorphisms or genetic variants affecting genes expressing the transmenbrane proteins and deiodinases.

Here the focus will be on the connection between T3, cardiovascular disease and type 2 diabetes mellitus (T2DM) and the possibility of treating cardiovascular disease with thyroid hormones. It is also important to ask what scientific evidence supports the prevailing view that thyroid hormone replacement targeting "TSH levels below reference range" increases the risk of atrial fibrillation and cardiovascular disease.

T3 is the primary active thyroid hormone not TSH or T4. Cardiac myocytes, contracting heart muscle cells, are dependent on free T3 in the bloodstream [1]. Thyroid hormone T3 plays a central role in the cardiovascular system. There are abundant T3 hormone receptors in the heart and blood vessels. At the tissue level, thyroid hormones may vary locally regardless of blood levels. Low T3 in the heart may cause local hypothyroidism [2].

The connection between the heart and the thyroid gland is linked to a common anlage (the early embronic stage) before differentiation into two organs. This anlage explains why all components of thyroid hormone biosynthesis are expressed both in the heart and in the thyroid gland. Dysfunction in one may impact the other [3, 4].

A relatively recent article "Hypothyroidism and Cardiovascular Disease: A Review", summarizes the existing literature on the relationship between hypothyroidism and cardiovascular diseases [5].

Hypothyroidism is one of the most common endocrine disorder in the world. Together with cardiovascular diseases and type 2 diabetes they account for a significant share of the global healthcare burden. The connection between these two diseases is clarified by the knowledge of the molecular effect of T3 on the cardiovascular system. Listed below are some molecular effects due to T3 deficiency [6, 7]:

- **DECREASED eNOS** The enzyme endothelial nitric oxide synthase (eNOS) synthesizes the gas nitric oxide (NO) in the endothelium, the innermost layer in the vascular walls, modulating vascular dilator tone. Reduced NO synthesis causes increased arterial stiffness and high blood pressure. Afterload, the pressure that pumps the blood towards the aortic and pulmonary valves, increases and may lead to heart failure. Arterial stiffness can be assessed using pulse wave velocity (PWV) a method that calculates the speed of the pressure waves travel along the arteries. A higher PWV indicates increased arterial stiffness and may be a marker of elevated cardiovascular risk.

- **NO DEFICIENCY** Apart from arterial stiffness and high blood pressure nitric oxide (NO) deficiency also inhibits transcription factors that stimulate the mitochondrial biogenesis, the process of forming new mitochondria. Mitochondria are the cells' power stations that break down nutrients energy into the chemical energy molecule ATP, adenosine triphosphate. With fewer mitochondria and reduced energy production deleterious oxidative stress increases.

- **IMPAIRED MITOCHONDRIAL BIOGENESIS** T3 is necessary for the expression of transcription factors that regulate nuclear DNA and mitochondrial DNA. Both DNAs are required for the formation of new mitochondria.

- **IMPAIRED LDL RECEPTORS** Impaired genes expressing LDL (Low Density Lipoprotein) receptors reduce the liver's ability to remove LDL from the blood. LDL and the low-grade inflammation caused by hypothyroidism favors development of atherosclerosis.

- **INCREASED VASCULAR RESISTANCE** T3 has a dilating effect on smooth muscle in arteries.

- **HIGH DIASTOLIC BLOOD PRESSURE** may be caused by disturbed calcium cycling in sarcomeres. Low T3 at the cellular level decreases the expression of SERCA2, a calcium ATPase. After muscle contraction calcium ATPase pumps calcium back into the sarcoedoplasmic reticulum (SERCA). Disturbed calcium cycling impair the heart's ability to relax during diastole affecting both cardiac output and the blood pressure.

- **CARDIAC OUTPUT DECREASES** as a result of weakened muscle fiber contractility. The amount of blood pumped out with each contraction is measured as ejection fraction, EF.

- **FIBROBLAST PROLIFERATION** increases at expense of the normally T3-regulated α-myosin, a protein crucial for rapid and strong contraction of heart muscle.

- **ECG CHANGES** such as sinus bradycardia, low-voltage ECG and long QT interval which may give rise to torsade de pointes. Torsade de pointes is a special variant of ventricular tachycardia that can lead to sudden cardiac death. Extra ventricular heart beats are common in hypothyroidism, while supraventricular extra beats are more frequent in elevated metabolism due to hyperthyroidism.

- **ATRIAL FIBRILLATION** is more common at low metabolism than at elevated metabolism. A large study examining the relationship between free T4 and atrial fibrillation (AF) found that higher levels of free T4, even within the normal reference range, was associated with increased risk of AF. In contrast, AF was higher with T3 in the lower reference range and less in the upper reference range [8].

T3 Plays a Central Role in Cardiovascular Homeostasis

T3 plays a crucial role in controlling gene expression in the heart muscle. T3 stimulates both the diastolic heart relaxation and systolic contraction. T3 deficiency at the cellular level has an impact on cardiac cells and their contractility, in order to maintain the cardiac output the atria and ventricules dilate, affecting the electrical impulses of the sinoatrial node. ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide) are hormones secreted with increased degree of heart failure. There is an inverse relationship between T3 and BNP, meaning that low T3 levels are associated with high BNP levels. BNP is a biomarker of dilated heart failure and may also indicate cardiac tissue hypothyroidism[9].

Minor changes in thyroid hormone access may have an impact on the cardiovascular system. There is no correlation between TSH and cardiovascular risk factors but there is a strong correlation between T3 at tissue level and cardiovascular disease [10].

Subclinical hypothyroidism (slightly elevated TSH and T4/T3 within the reference range) is often overlooked as many doctors consider it "normal". Even in subclinical hypothyroidism there is a 20–80% increased risk of cardiovascular disease and mortality. The Rotterdam study found that women at age ≥55 years with subclinical hypothyroidism had a higher prevalence of aortic atherosclerosis. Subclinical hypothyroidism was strongly linked to increased cardiovascular disease, even more than traditional risk factors such as high blood pressure, high cholesterol, high blood glucose and smoking [11]. Listed risk factors cannot be attributed to the slightly elevated TSH. On the contrary, it is the result of low T3 at the cellular level and its consequences for the cardiovascular system. Subclinical thyroid dysfunction is associated with adverse prognosis in patients with reduced ejection fraction [12].

Muscle biopsies from subjects with subclinical hypothyroidism revealed morphological (altered shape) mitochondria and mitochondrial dysfunction. According to the author these findings should diminish the restriction to treat subclinical hypothyroid patients [13].

Low T3 syndrome, LTS, that is low free T3 but T4 and TSH within the reference range, is common in severe illness, in acute myocardial infarction and when the energy demand is low. During the period of illness the energy demand is reduced by less TRH-TSH hormone secretion from the hypothalamic-pituitary gland.

In severe illness inflammatory markers increase. One of the markers is Il-6 that blocks deiodinase 2 (D2) thereby inhibiting the conversion of T4 to T3. Also at the cellular level active T3 is transformed by deiodinase 3 (D3) to reverse T3 (rT3) causing tissue hypothyroidism. Low free T3 is a strong predictor of heart failure and cardiac death [14].

In the case of a heart attack T3 decreases. The injured area is replaced by fibrosis. As noted above cardiac myocytes have exactly the same expressing thyroid hormone genes as in the thyroid gland. Low T3 in myocytes negatively impacts cardiac function by inducing re-expression of fetal genes, while low-dose T3 substitution restores cardiac myocyte function and mitochondrial function leading to improved heart function. Low-dose T3 reduces the risk of atrial arrhythmias and improves left ventricular contractility [15, 16].

BNP a diuretic hormone, is assessed to diagnose heart failure and gauge its severity. The effect of BNP is to promote urine excretion, improve vasoreactivity and lower blood pressure. BNP is a serum marker of low T3 in the heart. Lower T3/T4 ratio may imply less conversion T4 to T3. Low ratio and elevated BNP indicates low T3 in the heart tissue. By attempting to normalize these values it may be a safe way to increase T3 beneficial for heart tissue [17].

There is a link between dilated cardiomyopathy, DCM, and low levels of thyroid hormones. DCM is characterized by slightly elevated TSH and ventricular dysfunction that frequently results in heart failure. In dilated cardiomyopathy, cardiac tissue promotes deactivation of T4 to inactive rT3, rather than conversion of T4 to active T3. [18].

According to the article "Cardioprotection and Thyroid Hormones in the Clinical Setting of Heart Failure" by Mastorci F, Sabatino L, Vassalle C and Pingitore A a low-dose T3 substitution has a cardioprotective effect that can be used in the clinic. The dose of T3 should not exceed 0.2–0.4 μg/kg per day (i.e. 15–30 μg per day) divided into two or three administrations and approximately 1 μg/kg per day for L-T4 (i.e. 50–100 μg once daily) [19].

Peripartum Cardiomyopathy, PPCM, a Diagnosis Easy to Miss

In the Swedish Medical Access no. 8-9 2021, Gunnar Nyberg has summarized parts of the doctoral thesis "Peripartum Cardiomyopathy and Heart Failure, PPCM" by Barasa A. The peripartum period includes the months before and after childbirth. Barasa was able to ascertain the impact on arterial stiffness, endothelial function and synthesis of vascular endothelial growth. The identified parameters, according to the author of the article, can be linked to low T3 at the cellular level. Arterial stiffness, measured by pulse wave velocity (PWV), may potentially be decreased by low-dose T3 therapy. Heart failure symptoms could be alleviated, heart function improved and survival likely improved.

During pregnancy and childbirth, the heart is subjected to stress. Pregnancy consumes about the same amount of energy as the equivalence of 12 kg of fat. The heart pumps every hour ~ 280 liter of blood. The total daily turnover of ATP is around 45 kg due to the recycling of every ATP molecule up to thousands of times. The human heart consists of 28 % mitochondria that produces energy in the form of ATP which is then consumed by heart muscle cells. T3 induces new mitochondria in cardiac myocytes necessary for: ATP production; stimulate maturation of myocytes; pumping capacity and for the function of ion channels in the cardiac myocyte.

Diabetes and Hypothyroidism — Two Major Public Health Diseases Globally

T3 regulate genes involved in insulin sensivity and in glucose transport proteins both necessary for transport of glucose into the cell. Dysfunction of thyroid hormone may therefore contribute to insulin resistance and is associated with a higher prevalence of type 2 diabetes. T3 also regulates the expression of the adenosine nucleotide translocator (ANT), a protein responsible for exporting ATP from the mitochondrial inner membrane. Impaired ANT expression results in reduced cellular energy and increased oxidative stress.

A comparative study of thyroid hormones in type 2 diabetics and non-diabetics found significantly lower T3 levels in the diabetic group. However, there was no major difference between the groups when it came to T4 and TSH [20].

One study examining the association between T3 and metabolic syndrome revealed that T4 and T3 —not TSH— correlated to cardiovascular disease in women with metabolic syndrome. In non-metabolic syndrome group higher T3 correlated to lower blood glucose, higher insulin levels and lower risk of cardiovascular disease [21].

Studies on rats with induced diabetes revealed low T3 levels in cardiac tissue even though TSH, T4 and T3 in the blood stream were within the reference range. T3 levels in cardiac tissue did not correlate to serum values. No less than a threefold T3 dose was required to restore the T3 level in the heart. Low-dose oral T3 restored cardiac tissue T3 levels in diabetic rats without raising serum T3 levels. Low-dose T3 replacement appears to be a safe and effective adjunct therapy [22].

Cardiovascular disease is the most common cause of death in people with diabetes. According to Gerdes A M, diabetes triggers cardiac tissue hypothyroidism that may well be the main underlying cause of cardiovascular disease in diabetics. Treatment with low-dose T3 in diabetics rats prevented the progression of heart disease. They were still diabetic, but there was no evidence of cardiovascular disease with treatment [23].

Despite antidiabetic drugs cardiovascular complications have not been averted. T3 with its beneficial effects on endothelium improves the vascular system and low-dose T3 could be an inexpensive adjunctive therapy.

Thyroid dysfunction and metabolic syndrome (i.e. abdominal obesity, high blood pressure, high blood sugar and high lipids) may amplify the cardiovascular risk with adverse effects on health outcome [24].

The common denominator is low T3 at the tissue level and is explained by the molecular effect of T3 and does not correlate to TSH level.

There is also a link between low T3 at tissue level and diabetic neuropathy. A neurophysiological examination revealed that in diabetic neuropathy the nerve conduction rate and the amplitude were low which correlated to low T3 [25]. Neuropathic pain is a rather common symptom in hypothyroidism.

Many public health diseases appear to originate from suboptimal mitochondrial function and impaired T3 signaling which increase oxidative stress and cause cellular damage. Changes in mitochondrial morphology have been associated with the pathophysiology of insulin resistance, type 2 diabetes and cardiovascular diseases [26].

Besides T3 and mitogenic agents the new obesity drugs, glucagon-like peptide 1 receptor agonists, seem to have a beneficial effect on mitochondria [27].

Cognitive Impairment

Low T3 at the cellular level and T3 in the lower or below reference range poses serious risk of cardiovascular disease and cognitive impairment. Studies have shown that when only T4 is given as hormone substitution T4 increases, while T3 and TSH decrease and that may explain insufficient recovery in some hypothyroid patients [28]. Despite standard T4 thyroxine therapy hypothyroidism remains associated with heightened risks of cognitive decline and dementia. Cognition encompasses our mental acuity as thinking, remembering, learning and paying attention which deteriorates significantly at low T3 in the brain. Cognitive decline may be due to reduced expression of brain-derived neurotrophic factor (BDNF), a protein that supports the survival, growth, and maintenance of neurons in the brain and spinal cord [29].

T3 plays a crucial role in regulating apoptosis (cell death) in the brain and exerts an inhibitory effect on amyloid-beta accumulation, the precursor of Alzheimer's plaques [30]. Interestingly, in Alzheimer's disease, T3 levels in cerebrospinal fluid are reduced, while circulating TSH and T4 levels remain within normal ranges [31].

The brain is dependent on glucose for fuel, especially for demanding tasks like thinking, learning and memory, all powered by mitochondrial ATP. T3 has a crucial role in mitochondrial energy synthesis and any impact on this may have debilitated cognitive function.

Only T4 therapy in hypothyroid patients may increase the risk of dementia and mortality since it may fail to fully restore T3 at tissue level. Supplementation with T3 (Liothyronine) in addition to T4 may help alleviate these risks [32].

Even if the patient's thyroid hormones are within the reference range and the patient still has symptoms especially related to cognitive or metabolic abnormalities, it might be due to deiodinase 2 (D2) polymorphism. This variant of D2 inhibits the T4 conversion to T3 causing hypothyroidism at the tissue level and is not revealed by traditional laboratory tests. This underlines the necessity of individualized therapy for hypothyroidism [33, 34].

An unnoticed cause of cognitive impairment is Hashimoto's encephalopathy which may occur in the presence of high titers of thyroid antibodies despite normal TSH, T4, and T3 levels. The antibodies are primarily anti-thyroid peroxidase (TPO) and anti-thyroglobulin (Tg) and their measurement can be performed alongside standard thyroid hormone testing. The diagnosis is confirmed by a combination of elevated antibody titers and exclusion of other causes of encephalopathy. The response to corticosteroid therapy is positive.

TSH within the reference range does not guarantee health because it is only one data point, a pituitary marker and cannot account for all health factors. Many physicians are not trained to recognize the clinical signs of milder cases of hypothyroidism and are therefore dependent on biochemical measurements to support diagnosis and treatment.

Ralf Gräsbeck, clinical biochemist, believed that a diagnosis should be set by the medical doctor and not by the biochemist, so true [35]. Some researchers claim that it is T3 and not TSH that should be assessed when investigating suspected hypothyroidism and when following up thyroid hormone replacement. However, T4 level must be assessed in relation to TSH, if low T4 in relation to low TSH, consider pituitary insufficiency.

Why T4 Reduces T3

The primary reason to why T4 therapy may lead to reduced T3 levels is that the peripheral conversion of T4 to T3 is time-limited with its consequence that tissues may not receiving adequate active hormone. The time depends on whether ubiquitin is connected to deiodinase 2 (D2) or not. Ubiquitin is a protein that binds to molecules and determines how long a protein remains active. At higher circulating T4 levels ubiquitin binds to D2 which then is transformed from an active dimer to an inactive monomer thereby shortening the time for conversion of T4 to T3. High T4 levels also inhibit D2 expression, leading to lower T3 levels. In hypothalamus ubiquitin does not have the inhibitory effect on D2 as in the rest of the body. This means that at the central level most T4 is converted to T3 which inhibits TRH-TSH secretion [36]. Low T3 in peripheral tissue does not correlate to regulation at the central level. T4 treatment that is intended to correct low metabolism may in some patients cause tissue hypothyroidism. To correct TSH to the reference range without taking into account any of the patients remaining symptoms will not guarantee the restoration of a patient's wellbeing.

Many hypothyroid patients treated only with T4 continue to experience symptoms and turn to hypothyroid support groups on social media for guidance. T3 should be given a more prominent role among physicians when assessing optimal thyroid function.

Time for a Paradigm Shift

According to prevailing clinical guidelines, if thyroid hormone supplementation does not maintain serum TSH within the target range, patients are at an increased risk of cardiovascular complications, including atrial fibrillation and myocardial infarction. In contrast, low cellular T3 and serum T3 within or below the reference range may contribute to cardiovascular disease and cognitive decline.

T3 is not "just" a thyroid hormone. T3 provides the conditions for life and the functions of life. It spans across all the organs and is relevant for most of the related medical disciplines. T3 measurement should not be limited to endocrinologists evaluating potential thyroid disease.

A distinction must be made between the thyroid gland and thyroid hormones at the tissue level since there may be a weak correlation between the blood and the tissue levels, particularly in borderline low thyroid dysfunction. The causal factor to many of our common public health diseases is insufficient T3 access at the tissue level — especially when it comes to cardiovascular disease, type 2 diabetes, metabolic syndrome and cognitive decline. T3 levels should therefore not be in the lower reference range, despite TSH value, but rather targeted to the middle or 3rd quartile of the reference range.

The purpose of this paper has been to emphasize the importance of T3 for the beneficial impact on our major public health diseases. It is T3, not TSH, that provides balance and health. This overview does not account for the different low-doses T3 in treatment of cardiovascular disease, which is beyond the scope of this review.

Clinical and molecular research provides the basis for a paradigm shift. Applying this knowledge is crucial. All relevant clinicians must engage with current research to prevent rising adverse health outcomes, which affect individual wellbeing as well as public health at high social costs.

Finally

Since I began my medical career as a general physician in the 1980s the guidelines for diagnosis and treatment of hypothyroidism have only been adjusted a few times, where the upper TSH reference has been lowered. This can be compared to type 2 diabetes and blood pressure medications where guidelines have been adjusted regularly with help from the pharmaceutical industry. Few general physicians in Sweden dare to combine T3 (Liothyronine) with T4 therapy since there are no clinical guidelines from the national society of endocrinology that support such approach. Unfortunately, as long as TSH is within the reference range there is no interest in optimizing the treatment of affected hypothyroid patients. With this paper I want my colleagues to gain a deeper understanding of the most widespread endocrine disorder.

I recommend "Hypothyroidism: The unsuspected illness" by Broda O. Barnes. For decades he treated patients with clinical symptoms of hypothyroidism. At that time medical history and clinical findings formed the basis for treatment with desiccated thyroid, a preparation that contained both T4 and T3. After years of treating these patients he hardly found anyone suffered from type 2 diabetes, elevated cholesterol levels, atherosclerosis or high blood pressure. This is exactly what today's molecular research has revealed, that T3 reduces the risk factors for developing cardiovascular disease.

I also want to recommend the book "Rethinking Hypothyroidism" by Professor Antonio Bianco, a former president of American Thyroid Association who runs a laboratory to study thyroid hormones. Based on recent research findings he is now more prone to consider T3 supplementation to T4 treatment.

Helena Rooth Svensson, MD
Senior Physician
Specialist in General Medicine
lak@heroscare.se

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References

1. Wang W, Guan H, Fang W et al. Free Triiodothyronine Level Correlates with Myocardial Injury and Prognosis in Idiopathic Dilated Cardiomyopathy: Evidence from Cardiac MRI and SPECT/PET Imaging. Sci Rep 6, 39811 (2016).

2. von Hafe M, Neves JS, Vale C, Borges-Canha M, Leite-Moreira A. The impact of thyroid hormone dysfunction on ischemic heart disease. Endocr Connect. 2019 May 1;8(5):R76-R90.

3. Klein I, Danzi S. Thyroid Disease and the Heart. Curr Probl Cardiol. 2016 Feb;41(2):65-92.

4. Gil-Cayuela C, Ortega A, Tarazón E, Martínez-Dolz L, Cinca J, González-Juanatey JR, Lago F, Roselló-Lletí E, Rivera M, Portolés M. Myocardium of patients with dilated cardiomyopathy presents altered expression of genes involved in thyroid hormone biosynthesis. PLoS One. 2018 Jan 10;13.

5. Zúñiga D, Balasubramanian S, Mehmood KT, Al-Baldawi S, Zúñiga Salazar G. Hypothyroidism and Cardiovascular Disease: A Review. Cureus. 2024 Jan 18;16(1).

6. Razvi S, Jabbar A, Pingitore A, Danzi S, Biondi B, Klein I, Peeters R, Zaman A, Iervasi G. Thyroid Hormones and Cardiovascular Function and Diseases. J Am Coll Cardiol. 2018 Apr 24;71(16):1781-1796.

7. von Hafe M, Neves JS, Vale C, Borges-Canha M, Leite-Moreira A. The impact of thyroid hormone dysfunction on ischemic heart disease. Endocr Connect. 2019 May 1;8(5):R76-R90.

8. Anderson JL, Jacobs V, May HT, et al. Free thyroxine within the normal reference range predicts risk of atrial fibrillation. J Cardiovasc Electrophysiol. 2020;31:18-29.

9. Wang K, Ojamaa K, Samuels A, Gilani N, Zhang K, An S, Zhang Y, Tang YD, Askari B, Gerdes AM. BNP as a New Biomarker of Cardiac Thyroid Hormone Function. Front Physiol. 2020 Jul 9;11:729.

10. Razvi, S, Jabbar, A, Pingitore, A. et al. Thyroid Hormones and Cardiovascular Function and Diseases. JACC. 2018 Apr, 71 (16) 1781–1796.

11. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 2000 Feb 15.

12. Yang G, Wang Y, Ma A, Wang T. Subclinical thyroid dysfunction is associated with adverse prognosis in heart failure patients with reduced ejection fraction. BMC Cardiovasc Disord. 2019 Apr 4;19(1):83.

13. Dunn Michael E, Hennessey James V, Cosmas Arthur C, et al. Clinical Case Report: Ultrastructural Evidence of Skeletal Muscle Mitochondrial Dysfunction in Patients With Subclinical Hypothyroidism. Thyroid Science 4(6):CLS1-8, 2009.

14. Biegelmeyer E, Scanagata I, Alves L. Reveilleau M et al. T3 as predictor of mortality in any cause non-critically ill patients. Endocr Connect. 2021 Jul 28;10(8):852–860.

15. Rajagopalan V, Zhang Y, Pol C, Costello C, Seitter S, Lehto A, Savinova OV, Chen YF, Gerdes AM. Modified Low-Dose Triiodo-L-thyronine Therapy Safely Improves Function Following Myocardial Ischemia-Reperfusion Injury. Front Physiol. 2017 Apr 12;8:225.

16. Rajagopalan V, Gerdes AM. Role of thyroid hormones in ventricular remodeling. Curr Heart Fail Rep. 2015 Apr;12(2):141-9.

17. Gerdes AM. Cardiac remodeling in heart disease and the importance of thyroid hormones. American Journal of Physiology-Heart and Circulatory Physiology 2025 328:4.

18. Gil-Cayuela C, Ortega A, Tarazón E, Martínez-Dolz L, Cinca J, González-Juanatey JR, Lago F, Roselló-Lletí E, Rivera M, Portolés M. Myocardium of patients with dilated cardiomyopathy presents altered expression of genes involved in thyroid hormone biosynthesis. PLoS One. 2018 Jan 10;13.

19. Mastorci F, Sabatino L, Vassalle C, Pingitore A. Cardioprotection and Thyroid Hormones in the Clinical Setting of Heart Failure.Front Endocrinol (Lausanne). 2020 Jan 28;10:927.

20. Islam S, Yesmine S, Kahn SA et al. A comparative study of thyroid hormone levels in diabetic and non-diabetic patients. Southeast Asian J Trop Med Public Health 2008 Sep 39(5).

21. Luna-Vazquez F, Cruz-Lumbreras R, Rodríguez-Castelán J et al. Association between the serum concentration of triiodothyronine with components of metabolic syndrome, cardiovascular risk, and diet in euthyroid post-menopausal women without and with metabolic syndrome. Springerplus. 2014;3:266.

22. Weltman NY, Ojamaa K, Schlenker EH, Chen YF, Zucchi R, Saba A, Colligiani D, Rajagopalan V, Pol CJ, Gerdes AM. Low-dose T3 replacement restores depressed cardiac T3 levels, preserves coronary microvasculature and attenuates cardiac dysfunction in experimental diabetes mellitus. Mol Med. 2014 May 1;20(1):302-12.

23. Gerdes AM. New York Institute of Technology. ”Restoring thyroid hormones in heart may prevent heart disease from diabetes.” ScienceDaily. ScienceDaily, 30 June 2014.

24. Pingitore A, Gaggini M, Mastorci F, Sabatino L, Cordiviola L, Vassalle C. Metabolic Syndrome, Thyroid Dysfunction, and Cardiovascular Risk: The Triptych of Evil. Int J Mol Sci. 2024 Oct 2;25(19):10628.

25. Zhu FF, Yang LZ. The Association Between the Levels of Thyroid Hormones and Peripheral Nerve Conduction in Patients with Type 2 Diabetes Mellitus. Exp Clin Endocrinol Diabetes, 2018 Sep;126(8):493–504.

26. García-Peña LM, Abel ED, Pereira RO. Mitochondrial Dynamics, Diabetes, and Cardiovascular Disease. Diabetes. 2024 Feb 1;73(2):151-161.

27. Old VJ, Davies MJ, Papamargaritis D, Choudhary P, Watson EL. The Effects of Glucagon-Like Peptide-1 Receptor Agonists on Mitochondrial Function Within Skeletal Muscle: A Systematic Review. J Cachexia Sarcopenia Muscle. 2025 Feb;16(1).

28. Werneck de Castro JP, Fonseca TL, Ueta CB, McAninch EA, Abdalla S, Wittmann G, Lechan RM, Gereben B, Bianco AC. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. J Clin Invest. 2015 Feb;125(2):769-81.

29. Cortés C, Eugenin E, Aliaga E, Carreño LJ, Bueno SM, Gonzalez PA, Gayol S, Naranjo D, Noches V, Marassi MP, Rosenthal D, Jadue C, Ibarra P, Keitel C, Wohllk N, Court F, Kalergis AM, Riedel CA. Hypothyroidism in the adult rat causes incremental changes in brain-derived neurotrophic factor, neuronal and astrocyte apoptosis, gliosis, and deterioration of postsynaptic density. Thyroid. 2012 Sep;22(9):951-63.

30. Belakavadi M, Dell J, Grover GJ, Fondell JD. Thyroid hormone suppression of β-amyloid precursor protein gene expression in the brain involves multiple epigenetic regulatory events. Mol Cell Endocrinol. 2011 Jun 6;339(1-2):72-80.

31. Dolatshahi M, Salehipour A, Saghazadeh A, Sanjeari Moghaddam H, Aghamollaii V, Fotouhi A, Tafakhori A. Thyroid hormone levels in Alzheimer disease: a systematic review and meta-analysis. Endocrine. 2023 Feb;79(2):252-272.

32. Beltrão FEL, Carvalhal G, Meneghini V, Matos DAR, Beltrão DCA, Andrade BARM, Beltrão FNL, Ramos HE, Ribeiro MO, Golovko G, Ettleson MD, Bianco AC. Treatment of Hypothyroidism that Contains Liothyronine is Associated with Reduced Risk of Dementia and Mortality. J Clin Endocrinol Metab. 2025 Jun 20.

33. Ettleson MD, Bianco AC. Individualized Therapy for Hypothyroidism: Is T4 Enough for Everyone? J Clin Endocrinol Metab. 2020

34. Mazza AD. Personalized Approaches to Hypothyroidism: The Role of Triiodothyronine (T3) in Thyroid Hormone Replacement. Cureus. 2025 Aug 21;17(8),

35. Gräsbeck, R. Health and Disease from the Point of View of the Clinical Laboratory. In: Nordenfelt, L., Lindahl, B.I.B. (eds) Health, Disease, and Causal Explanations in Medicine. Philosophy and Medicine, vol 16,1984.

36. Werneck de Castro JP, Fonseca TL, Ueta CB, McAninch EA, Abdalla S,Wittmann G, Lechan RM, Gereben B, Bianco AC. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. J Clin Invest. 2015 Feb;125(2):769-81.