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REVIEW ARTICLE

Functional Relationship between Thyroid Dysfunction and Heart: From Mechanism to Manifestation

Richa Kahol[1,2] , Atul Kathait[1] , Sunil Kumar Mishra[2] , Anil Bhan[3], Naresh Trehan[3]
[1] School of Biosciences, Apeejay Stya University, Gurugram, Haryana, India.
[2] Division of Endocrinology and Diabetes, Medanta The Medicity Hospital, Gurugram, Haryana, India.
[3] Department of Cardiothoracic and Vascular Surgery, Medanta The Medicity Hospital, Gurugram, Haryana, India.
*Email: richabiotech03@gmail.com

ABSTRACT
Thyroid shares a close relationship with cardiac system therefore, thyroid hormone significantly impacts it. Deficiency or excess of thyroid directly effects the cardiovascular hemodynamic and regulations. These effects are executed by genomic method (mediated by nuclear receptors) or non-genomic method (mediated by ion channels). In case of existing cardiac diseases, thyroid is overlooked. This is because subtle symptoms of thyroid are presumed to be signs of cardiac discomfort. Current study is a narrative literature review. Many experimental research papers, review articles and case studies were searched on databases such as Medline, Pubmed, Google scholar etc. with terms such as cardiovascular system, heart failure, hyperthyroid, hypothyroid, thyroid hormones. Relevant information from them was researched, retrieved, analysed and compiled. It is reaffirmed that there is a strong functional relation between thyroid dysfunction and heart. We found that hypothyroid is more common in comparison to hyperthyroid among cardiac disease cases. Among hypothyroid, specifically subclinical hypothyroid is further more common. This review provides an up to date version thyroid hormone perturbations to the physicians working with cardiac diseases, and suggests that pre thyroid test shall be made mandatory for all cardiac procedure.
Keywords: *cardiovascular-system, heart failure, hyperthyroid, hypothyroid.*

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INTRODUCTION

Cardiovascular disease (CVD) are globally the biggest reason of death [1] partiularily Heart Failures (HF) with a rising occurrence rate of 10/1000 person years [2]. Parallel to this, there has been an increase in the number of thyroid cases worldwide. This simultaneous rise indicate a strong relation between the heart and thyroid gland. Medical literature has also cited a common embryologic origin of both the organ [3]. Hence, endocrine hormones are physiopathologically associated to the cardiac system [4]. Mildest alteration in the normal thyroid level, either excess (termed as hyperthyroid) or deficiency (termed as hypothyroid) may lead to manifestation of cardiac diseases, progressing to heart failure. This adds to the risk of CVD [2]. These manifestations are conveyed by two mechanisms: genomic and non-genomic. Genomic methods included nuclear receptors regulating expression of target genes. Non-genomic methods are also known as extranuclear methods because they are executed nuclear receptors. Sometimes, there is also a combined effect of both the mechanisms [1]. Since thyroid has recorded a high prevalence rate of about 16% [5], it is strongly recommended to investigate endocrine hormones and preclude thyroid dysfunction in all subjects with risk of CVD, irrespective of reported HF history [2]

This review recapitulates the relationship of thyroid disorders in heart diseases, ranging from the functional mechanism to their clinical manifestations, with special emphasis on involvement of hypothyroidism and hyperthyroidism in heart failures.

Chronicle:

The interconnection between endocrine and cardiac system was first reported in 1786. An English physician, Caleb Hillier Parry proposed the relation between enlarged thyroid gland and the heart as he observed one of his female patients having goiter and palpitation, describing it as "every systole shook the full thorax" [3]. Since a long time, thyroid hormone concentrates spearheaded as a potential treatment of myxedema [6]. This was experimentally proven in 1891 by George Murray, an English pathologist. He administered a shot of sheep thyroid extract subcutaneously to a 46 years old myxedema patient. His patient survived for 30 years [7-8]. Later, in 1914, Kendall materialized thyroid hormone thyroxine (T4) and Harington and Barger gave its chemical structure in 1927. Around 1934, pitt-rivers and Gross identified Triiodothyronine (T3) [10].

Initial Research:

It has been accounted earlier that thyroid gland and the heart have developed from the same embryologic ancestor but, mutual correlation between the two organs were proven later.

During extensive analysis of post-mortem reports of heart attack mortalities, thyroid deficiency was found as a common factor. So, researchers recommended to include thyroid hormone therapy among CVD treatment therapeutics [11]. During initial days of TH therapy trials, subjects with known angina had complaints of ingestion, which was rectified by gradually increasing the prescribed thyroid extract dose [6].

Biochemical Pathway of TH mechanism:

Proper functioning of thyroid gland is imperative for metabolism as well as growth and development of the body. It is maintained by a trio-coalition of hypothalamus- pituitary and thyroid through a feedback loop mechanism. Firstly, thyroid releasing hormone (TRH) is released from the hypothalamus. Then thyroid stimulating hormone (TRH) is released from the anterior pituitary. TRH works on thyroid gland to secrete Thyroid hormones, Thyroxine (T4) and triiodothyronine (T3). Among the two key hormones of this mechanism, T4 is a biologically pro-hormone and T3 is hyper active. Deiodinase (DIO) enzymes play a key role in TH metabolism, DIO type I and DIO type II catalyse the conversion of T4 into T3. DIO II also participates in T3 production. DIO III is responsible for catabolism and termination of thyroxine and triiodothyronine [1, 6].

Functional impact of TH on Cardiac System:

Thyroid hormone effects cardiovascular system in multiple ways (figure 1). These include effects which occur either directly on the genomic level or non- genomic and also as a combined effect. Genomic effects are mediated by the nuclear receptor signaling that leads to the target gene expression within cardiomyocytes. Non-genomic effects are extranuclear methods and are ion channel dependent. The participating ion channels are specifically situated in the cell membrane of cardiac cells. The combined action of both the mechanisms affects the peripheral circulation [12].

Genomic (Direct/Delayed) mechanism: This mechanism is mediated by TH nuclear receptors of cardiomyocytes. TH binds to thyroid hormone receptors (TR) which further binds to thyroid hormone response elements (TRE) in the promoter region of the TH responsive gene. The gene response majorly depends on the availability of TH because its binding promotes the expression of the specific genes and inhibits the transcription of other genes. As compared to T4, T3 has 10 times more affinity towards TR, hence it binds to the receptor quickly. There are two main TRs located in cardiomyocytes, TRα (highly expressed) and TRβ, which finally bind to the target gene [1,6,13]. Table1 enlists cardiac gene mediated by T3.

Additional to this, T3 also plays a role in optimizing cardiac myocyte contraction and relaxation, mainly by increasing Calcium cycling. Myocardial contractility is Myosin Heavy Chain (MHC α/ β) dependent function and sarcoplasmic/ endoplasmic reticulum calcium ATPase 2 (SERCA2) pumps out calcium into sarcoplasmic reticulum space. T3 upregulates MHC-α and SERCA2 as they increase calcium cycling in the sarcoplasmic reticulum space and down regulates MHC-β beta and phospholamban (PLB) which are inhibitory counterparts of MHC-α and SERCA2 respectively [1, 6, 14].

Non-Genomic (Extranuclear/Rapid) mechanism: This mechanism is mainly based on ion channels. It includes accelerating of Na+/K+ ATPase activity, stimulating Ca2+ ATPase activity, inactivating sodium channels and membrane Na+/H+ antiport (NHE). Availability of TH through these channels determines the myocardial excitation and action potential [1]. Non-genomic mechanism also includes integrin receptors interactions that are responsible for cytoplasmic signalling pathways [15] and phosphorylation-activation of kinase pathways. TH dependent pathways are essential for metabolism, growth and development of body [16]. Besides this, Few cardioprotective effects on the ischaemic animal hear are also listed under the non-genomic mechanism [17,18].

Combined effect: Genomic and non- genomic mechanisms are in-differentiable mechanisms. TH exerts a combined effect on the heart firstly by controlling the expression of β1- adrenergic receptor signally. Secondly by, influencing chronotropy through sodium, potassium and calcium channels.

Hyperthyroidism in relation to CVD

When thyroid gland secretes thyroid hormone excessively, it is termed as hyperthyroidism. it's prevalence ranges between 0.3% to 3%. Its occurrence depends on a number of factors such as iodine intake, presence of comorbidities, age, sex etc. [19]. Hyperthyroidism strongly effects the heart function. Broadly, it causes atrial fibrillation (AF), hypercoagulability, high heart rate, decreased systemic vascular resistance and increased preload in heart patients [13, 19, 20]. Increased cardiac mass is the most common observation whereas, increased pulmonary artery pressure is a recently reported symptom of cardiac manifestations of hyperthyroidism [3].Usual signs of hyperthyroidism can be classified as physical, psychological and hemodynamic. Physical symptoms include menstrual abnormalities, increased appetite but weight loss, muscle weakness with tremors, hypersensitivity to heat, mild hyperhidrosis and fatigue; psychological symptoms include frequent nervousness and hyperactive reflexes. Hemodynamic alterations include increased resting heart rate and blood volume. These symptoms subsequently lead to cardiac manifestations of hyperthyroidism, which are, palpitations, angina, tachycardia, increased stroke volume, atrial fibrillation and also congestive heart failure [21]. Hyperthyroidism has been a potential cause of alteration in the cardiovascular hemodynamics and arterial wall structure [22]. Increased risk of cardiac mortalities among elderly people might be due to hyperthyroidism, as they experience tachycardia and AF due to increased oxygen demand, which the aged heart cannot satisfy in presence of excessive TH [21]. At the molecular level, symptoms of increased TH are similar to high adrenergic condition. Endocrine hormones have no direct effect on adrenergic signal pathways but epinephrine and TH together gives a synergic impact. Catecholamine (neurohormone) and ß-adrenergic blockers (sympatholytic agent) are found effective in reversing adverse influence of hyperthyroidism in CVD [21, 23]. In case of hyperthyroidism ß1-adrenergic receptors is up-regulated and other adrenergic components are down-regulated to maintain the effect on heart [24, 25, 26].

Hyperthyroidism is broadly of two types, Subclinical (milder) and overt (severe). Subclinical hyperthyroidism is characterised with normal TH and low TSH values. It is often associated with systolic hypertension plus diastolic dysfunction. Overt hyperthyroidism is characterized with suppressed TSH and increased free hormone [22]. This is the least prevalent form of thyroid. Young *et al*, in a Study have reported an association overt hyperthyroidism and increased CV mortality. About 5-10% subjects with AF have overt hyperthyroid [27]. Albeit both, overt and subclinical hyperthyroidism are linked to cardiac risk factors and mortalities, But still, their probability of being an independent risk factors that causes CV events or mortality remains a question for research [19, 22].

Hypothyroidism in relation to CVD:

When thyroid gland secretes less thyroid or it is under-reactive, the condition is known as hypothyroidism. Madariaga *et al* cited the prevalence of hypothyroidism as .6% (0.3% overt and 4.3% subclinical) based on a survey conducted by NHNES III with 13,344 people [28]. In hypothyroidism the cardiac output declines from 30 to 50% due to rise in systemic vascular resistance [3]. Hypothyroid causes severe changes in cardiac structure and function depending on the duration of TH deficiency [4]. It is found to be related [3, 4]. Cardiac manifestations of hypothyroidism include cold intolerance, bradycardia, reduced pulse rate, mild diastolic hypertension and fatigue, these are the results of low TH action on both the heart as well as peripheral vasculature. Low pulse rate is a common symptom, caused due to increased diastolic and decreased systolic pressure in hypothyroidism. Along with this, low TH alters ion channel expression and function of the heart, decreases heart rate and prolongs sinus node recovery time [4].

Hypothyroidism can be milder, with raised serum TSH is and normal TH, known as Subclinical Hypothyroidism is diagnosed. This is the most common form of hypothyroid, overall prevalence ranges from 4 to 15% [1] and 80% of hypothyroid patients suffer from it [13]. Left ventricular diastolic dysfunction is a commonly observed cardiac abnormality in cases of subclinical hypothyroidism. It arises due to impaired early ventricular filling and relaxation [13].

Overt hypothyroidism is the severe form of hypothyroidism where serum TSH is elevated and circulating TH are low. It is less prevalent as compared to subclinical form. It's prevalent amongst approximately 3% of the adult female population age [4]. Typical heart related symptoms include reduced cardiac output, diastolic dysfunction and increased peripheral vascular resistance. Along with this modifiable atherosclerotic risk factors like diastolic hypertension, hypercholesterolemia, alteration in intimal media thickness are also noticed [13].

Role of Thyroid Dysfunction in Heart Failure:

The relationship between the thyroid and heart failure is a gradational process (Figure 2) which has been extensively researched. Any deviation from normal TH levels results in functional impairments in cardiac system [29].Since, T3 has cardioprotective properties, around 15% to 30% cases of HF show low T3 syndrome, though this incidence rate might change with disease severity[13]. In both acute and chronic HF (with ischemic or non-ischemic LV dysfunction), alterations in TH are associated with poor outcomes. For instance, subjects with lowered Left Ventricular Ejection Fraction (LVEF) with low T3 reported higher number of deaths as compared to cases with similar LVEF and normal T3 levels [13]. Besides this, it is observed that subjects suffering from HF or any cardiac surgery usually have altered TH metabolism and lowered T3, which further worsens the clinical outputs [30]. The American College of Cardiology, in latest guidelines for HF, has recommended screening for thyrotropin levels in all new cases of HF [31].

Hypothyroidism- a risk of Heart Failure:

Even mild (subclinical) hypothyroidism can increase the incidence of Heart Failure and diastolic dysfunction [31]. Acute hypothyroid and HF display some similar symptoms such as, low cardiac output and contractility. It also alters gene expression profile [4]. Lack of TH reduces thermogenesis in tissues and increases peripheral arterioles resistance by the direct action of on vascular smooth muscles. In hypothyroidism cardiac preload decreases (due to disrupt diastolic function and decreased blood volume) and Cardiac afterload increases. Final cardiac output is lowered as inotropic and chronotropic effects are reduced [32, 33]. Table 2 summarizes various factors that lead to heart failure in hypothyroidism.

During diastolic phase the chronic response and cardiac muscle tension relies upon appropriate T3 expression in cardiocytes and it stimulation on Na+-K+-ATPase and Ca2+-ATPase in the endoplasmic reticulum. At the time of isovolumetric relaxation of diastolic function slacks down leading to chamber dilation and inadequate myocardial blood flow [23]. Figure 3 is a pictorially represents components leading to heart failures in hypothyroidism.

Many cohort studies have extensively studied the risk factors causing heart failures. Hypothyroidism, even if it is subclinical has been associated with HF causing medical ailment [34]. With an aim to study the participation of hypothyroidism in heart failures, many clinical studies have been conducted with different age groups [35]. A 2012 study, that was conducted with aged subjects concluded that if high TSH levels (>10 mIU/L) persist for more than 6 months, chances of HF increase, irrespective of past CVD [36, 37]. Additionally, 13 longitudinal studies have reported hypothyroidism as a common factor in all cause mortalities in cases of HF [38]. With the progression of age, heart gets sensitive towards fluctuating TH levels. Hypothyroidism (even subclinical) can be an indicator of ailing condition in cases of HF [39, 40]. Comprehensively, these studies indicate a multifactorial adverse effects of thyroid which depends on age, working status of heart and degree and duration of hypothyroidism [41]. Although, a study by Hernando *et al* stated low probability of HF in subjects with hypothyroidism. Holmager *et al* conducted a randomized trail wherein T3 was administered to subjects having chronic HF, results showed no benefits. Contradictory to this, few studies have observed improvement in neuroendocrine and systolic-functions in subjects with levothyroxine [2, 42]. Still, recommendation of thyroid replacement as a cardiomyopathy medication remains a matter of discussion [43, 44].

Hyperthyroidism- a risk of Heart Failure:

HF is the most common side effect of hyperthyroidism in context of cardiac diseases [45]. In people with hyperthyroidism, low output HF is common in old age and high output HF with Graves' disease at younger age [45]. Such people experience breathlessness at rest, pulmonary arterial hypertension (PAH) and pleural effusion. The most common and an early symptom of developing HF in hyperthyroid patients is exercise intolerance, it is because the heart cannot accommodate the sudden increase in cardiac demands during intense physical activities [45-51].

Another common cardio-related complication observed with hyperthyroid is atrial fibrillation (AF). It is observed in 7-8% among middle aged people and 10-20% in older people [52] but it is reversible, if euthyroid status is maintained and toxic, if left untreated [53]. Following AF, arrhythmias and tachycardia are also commonly observed. Hyperthyroid is also considered as an independent prognosis feature of mortality in HF cases [54, 55]. Figure 4 pictorially represents the components leading to heart failures in hyperthyroidism.

In cases with no history of heart disease, hyperthyroid and HF show similar signs of discomfort. At the cellular level, hemodynamic changes caused by hyperthyroid lead to further decrease in the peripheral vascular resistance which eventually activates RAAS signalling pathway causing sodium ion retention [48, 56]. At the transcriptional level, Ca^{+} circulation in sarcoplasmic reticulum and phosphorylation of phospholamban is controlled by TH. Its non- transcriptional effects are mediated by the ion channels [57]. These effects consequently lead to a state of "high output heart failure" which is marked by cardiac index

>3.9 L/min/m2 [58]. It is suspected to be a result of "tachycardia mediated cardiomyopathy" (TMC), so it is reversible when tachycardia is under control [58]. The root cause of cardiomyopathy in hyperthyroid patients is not clear, but it is controlled by thyroid medication [23]

In a study done by Siu *et al*, involving 591 hyperthyroid subjects of an average age of 45 years, 6% reported HF [60]. Nanchen *et al* concluded that subjects with mild signs of hyperthyroid are at higher risk of developing HF as compared euthyroid subjects. In this study length of hospitalization was also prolonged in hyperthyroid cases [61]. Similar results were given by a pool analysis study that included 25,000 particpants. The researchers also found strong correlation between rising HR and TSH levels, at TSH > 0.1, HR was equal to1.3 and at TSH < 0.1, HR was equal to 1.9 [62]. HF is also observed in cases with overt hyperthyroidism, such conditions gives rise to 'high-output HF' [63, 64]. Likewise, Rotterdam studied 10,000 individuals, who were above 45 years of age and conclude that over a follow-up of 9.1 years, individuals with high FT4 and normal TH had increased risk of sudden heart attack deaths [65].

Table 1: Cardiac Genes That Are Regulated By T3

Positively regulated	**Negatively regulated**
Sarcoplasmic reticulum Ca^{2+} ATPase	Phospholamban (SERCA2 inhibitor)
α myosin heavy chain	β myosin heavy chain
Voltage gated K^+ channels	Na^+/Ca^+ exchange channels
Na^+/K^+ ATPase	Adenylyl cyclase type V,VI
G_S Guanine nucleotide binding protein (increase adrenergic effect)	G_i Guanine nucleotide binding protein (decrease adrenergic effect)
β1-Adrenergic receptor	Thyroid hormone receptor α-1
Adenine nucleotide translocase (ANT1)	Thyroid hormone transport (MCT8,10)

Table 2: Components Leading To Heart Failure In Hypothyroidism.

Bradycardia	Impaired systolic function
Decreased cardiac preload	Impaired diastolic function
Increased systemic vascular resistance	Impaired left ventricular diastolic filling
Increase in left ventricular mass	Pericardial effusion

Fig 1: Action of TH on cardiomyocytes. (from Salman Razvi review 2019)

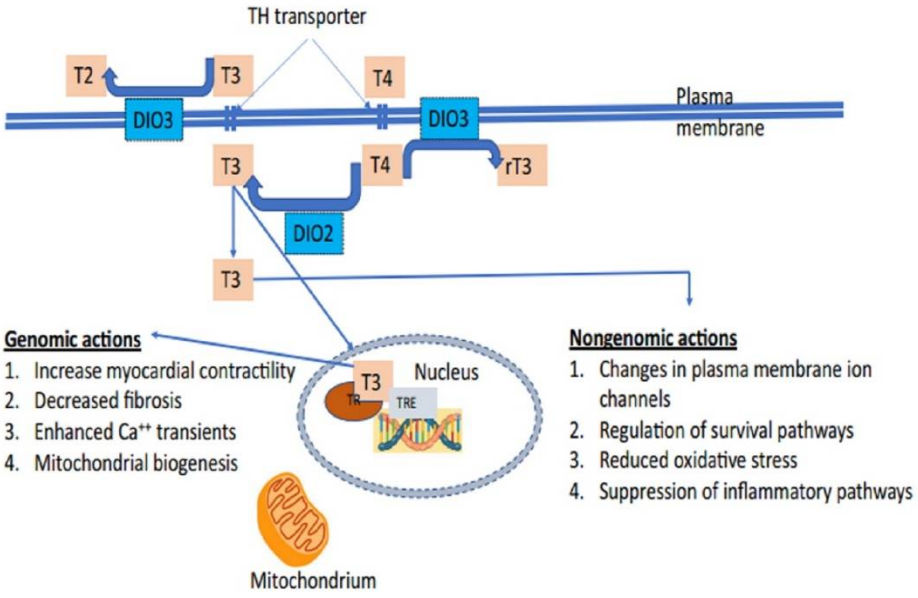


Figure 2: Thyroid Disease progression towards Heart Failure.

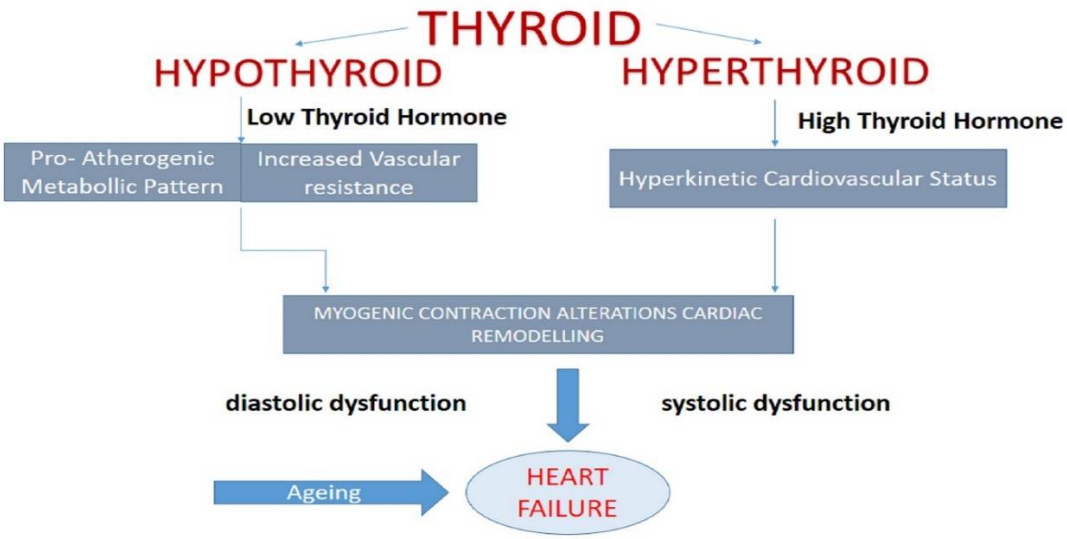


Figure 3: Progression of Hypothyroid in Heart Failure.

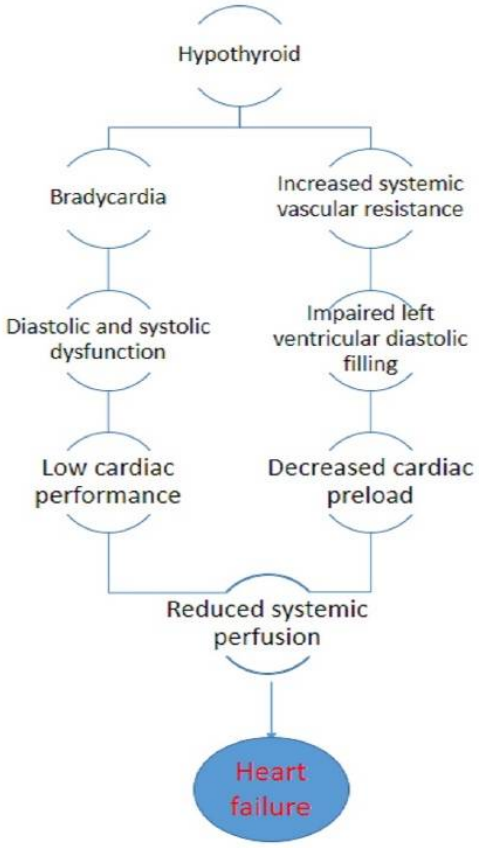
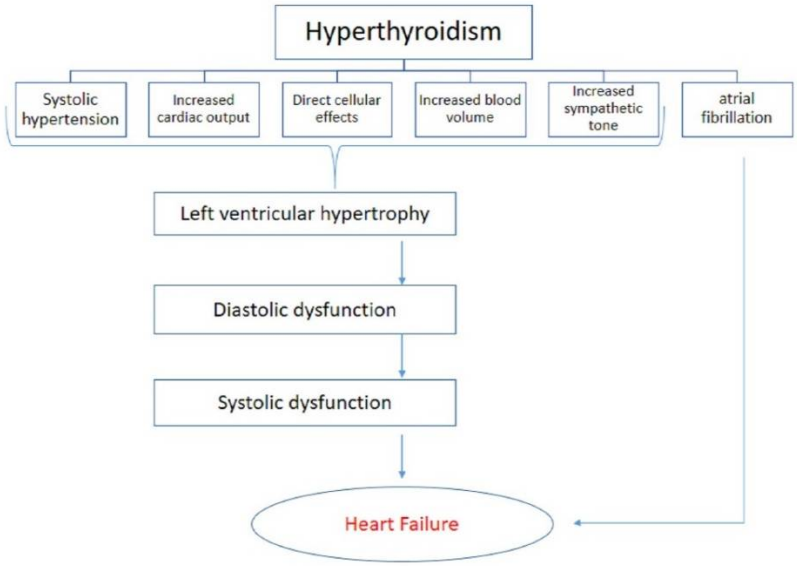


Figure 4: Progression of Hyperthyroid in Heart Failure.



Conclusive remarks:

Deranged thyroid levels cause cardiovascular complexities, these may be mild or severe depending on various factors such as age, existing cardiac complications etc. Often the presence of thyroid goes unidentified in subjects with cardiac issues because either it is asymptomatic or symptoms are similar to the cardiac manifestations. Therefore, it is strongly recommended to have a pre-test of thyroid before proceeding for any form of cardiac surgery because thyroid also impacts post-surgical outcomes

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REFERENCES

1. Navid Ahmadi, Faisal Ahmadi, Masehullah Sadiqi, Katarzyna Ziemnicka, Andrzej Minczykowski. (2020). Thyroid gland dysfunction and its effect on the cardiovascular system: a comprehensive review of the literature. Endrokrynol Pol; 71(5):466-478. DOI: 10.5603/EP.a2020.0052
2. G. Pasqualetti, F. Niccolai, V. Calsolaro, G. Bini, N. Caraccio, F. Monzani. (2017). Relationship between throid dysfunction and heart failure in older people. JGG. 65: 184-191.
3. Irwin Klein, Sara Danzi. (2016). Thyroid Disease and the Heart. Curr Probl Cardiol.;41(2):65-92. Doi: 10.1016/j.cpcardiol.2015.04.002
4. Stanciu AE, Anton AZC, Stanciu MM, Gheorghe DC, (2017). Impact of Thyroid Disease on Heart Failure, chapter 8, INTECH. http://dx.doi.org/10.5772/66283.
5. Arindam Bose, Norman Sharma, Nanda Hemvani, Dhananjay S Chitnis. (2015). A Hospital Based Prevalence Study on Thyroid Disorders in Malwa region of Central India. Int.J.Curr.Microbiol. App. Sci; 4(6): 604-61
6. Salman Razvi. (2019). Novel uses of thyroid hormones in cardiovascular conditions. Endocrine. (66): 115-123. https://doi.org/10.1007/s12020-019-02050-4.
7. G.R. Murray. (2010). Note on the treatment of myxoedema by hypodermic injections of an extract of the thyroid gland of a sheep. Br. Med. J. 1891;2: 796–797. https://doi.org/10.1136/bmj.2.1606. 796 8.
8. G.R. Murray, (1920). The life-history of the first case of myxoedema treated by thyroid extract. Br. Med. J. 13: 359–360. https:// doi.org/10.1136/bmj.1.3089.359
9. J. Lindholm, P. Laurberg, (2011). Hypothyroidism and thyroid substitution: historical aspects. J. Thyroid Res. 809341. https://doi.org/10.4061/2011/809341
10. J. Gross, R. Pitt-Rivers,(1952). The identification of 3:5:3 -L-triiodothyronine in human plasma. Lancet ; 439–441. https:// doi.org/10.1016/s0140-6736(52)91952-1
11. I.A. Gaspar, (1968). Postmortem observations on the thyroid in atherosclerosis. J. Am. Geriatr. Soc. ;16:686–695. https://doi.org/ 10.1111/j.1532-5415.1968.tb01278.x
12. Avais Jabbar, Alessandro Pingitore, Simon H S Pearce, Azfar Zaman, Giorgio Iervasi, Salman Razvi. (2017). Thyroid hormones and cardiovascular disease. *Nat. Rev. Cardiol.* 14:39-55. doi: 10.1038/nrcardio.2016.174.

13. Salman Razvi, Avais Jabbar, Alessandro Pingitore , Sara Danzi , Bernadette Biondi, Irwin Klein, *et al*. (2018). Thyroid Hormones and Cardiovascular Function and Diseases. J Am Coll Cardiol. 71(16): 1781–1796, doi: 10.1016/j.jacc.2018.02.045, indexed in Pubmed: 29673469.
14. Khaled D Algarni. (2020). The effect of hyperlactatemia timing on the outcomes after cardiac surgery. The cardiothoracic surgeon.28:18. https://doi.org/10.1186/s43057-020-00029-w.
15. Cheng SY, Leonard JL, Davis PJ. (2010). Molecular aspects of thyroid hormone actions. Endocr Rev. 31(2): 139–170, doi: 10.1210/er.2009-0007
16. Xia Cao , Fukushi Kambe, Lars C Moeller, Samuel Refetoff, Hisao Seo. (2005). Thyroid hormone induces rapid activation of Akt/protein kinase B-mammalian target of rapamycin-p70S6K cascade through phosphatidylinositol 3-kinase in human fibroblasts. Mol Endocrinol. 19(1): 102–112, doi: 10.1210/me.2004-0093
17. Kahaly GJ, Dillmann WH. (2005). Thyroid hormone action in the heart. Endocr Rev. 26(5): 704–728, doi: 10.1210/er.2003-0033.
18. Robert M Mentzer Jr, Robert D Lasley, Andreas Jessel, Morris Karmazyn. (2003). Intracellular sodium hydrogen exchange inhibition and clinical myocardial protection. Ann Thorac Surg. 75(2): S700–S708, doi: 10.1016/s0003-4975(02)04700-8.
19. Seo Young Sohn, Eunyoung Lee, Min Kyung Lee, Jae Hyuk Lee. (2020). The Association of Overt and Subclinical Hyperthyroidism with the Risk of Cardiovascular Events and Cardiovascular Mortality: Meta-Analysis and Systematic Review of Cohort Studies. Endocrinol Metab; 35:786-800. https://doi.org/10.3803/EnM.2020.728
20. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015;36: 1163–70.
21. Charles R. Albrecht III Steven R. Gambert. (2002). Cardiovascular Manifestations of Thyroid Disease. Heart Drug;2:312–32. DOI: 10.1159/000069666.
22. Vidli G, Delitala A, Manetti R. (2021). Subclinical Hyperthyroidism: the cardiovascular point of view, European Review for Medical and Pharmacological Sciences, 25: 3264-3271
23. Hernando Vargas-uricoechea, Anilsa Bonelo-Perdomo, Carlos Hernan Sierra-Torres. (2014). Effects of thyroid hormones on the heart. Clin Invest Arterioscl. 26(6): 296-309.
24. Levey GS, Klein I. (1990). Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. Am J Med;88:642–646.
25. Hoit BD, Khoury SF, Shao Y, Gabel M, Liggett SB, Walsh RA. (1997). Effects of thyroid hormone on cardiac beta-adrenergic responsiveness in conscious baboons. Circulation;96:592–598.
26. Ojamaa K, Klein I, Sabet A, Steinberg SF. (2000). Changes in adenylyl cyclase isoform as a mechanism for thyroid hormone modulation of cardiac beta-adrenergic receptor responsiveness. Metabolism;49:275–279
27. Serafino Fazio, Emiliano A. Palmieri, Gaetano Lombardi, Bernadette Biondi. (2004). Effects of Thyroid Hormone on the Cardiovascular System. Recent Porg Horm Res. 59:31-50. doi: 10.1210/rp.59.1.31.
28. Ane Garmendia Madariaga , Silvia Santos Palacios, Francisco Guillén-Grima, Juan C Galofré. (2014). The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis. J Clin Endocrinol Metab. 99(3):923-31. doi: 10.1210/jc.2013-2409. Epub 2014 Jan 1.
29. Martinez F. (2016). Thyroid hormones and heart failure. Heart Fail Rev. 21(4): 361–364, doi: 10.1007/s10741-016-9556-5, indexed in Pubmed: 27098905.
30. Iordanis Mourouzis, Francesca Forini, Constantinos Pantos, Giorgio Iervasi. (2011). Thyroid hormone and cardiac disease: from basic concepts to clinical application. J Thyroid Res. 958626, doi: 10.4061/2011/958626, indexed in Pubmed: 21765997
31. Clyde W Yancy, Mariell Jessup, Biykem Bozkurt, Javed Butler, Donald E Casey Jr, Monica M Colvin *et al*. (2017). ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 136(6): e137–e161, doi: 10.1161/CIR.0000000000000509
32. Rhee CM, Curhan GC, Alexander EK, Bhan I, Brunelli SM. (2013). Subclinical hypothyroidism and survival: the effects of heart failure and race. JCEM.98:2326-36.
33. Gerdes AM, Iervasi G. (2010). Thyroid replacement therapy and heart failure. Circulation. ;122:385-93.
34. Vincenzo Triggiani, Vito Angelo Giagulli, Giovanni De Pergola, Brunella Licchelli, Edoardo Guastamacchia, Massimo Iacoviello. (2016). Mechanisms explaining the influence of subclinical hypothyroidism on the onset and progression of chronic heart failure. Endocr Metab Immune Disord Drug Targets;16:2-7.
35. Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, *et al.* (2012). Thyroid Studies C. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation; 126: 1040- 1049.
36. Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S, *et al.* (2012). Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab ; 97: 852-861.
37. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins j, Fried LP,*et al*. (2008). Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol;52 (14):1152-9
38. Ning N, Gao D, Triggiani V, Iacoviello M, Mitchell JE, Ma R, *et al*. (2015). Prognostic role of hypothyroidism in heart failure: a meta-analysis. Medicine (Baltimore). 94:e1159. doi:10.1097/MD.0000000000001159

39. Boekholdt SM, Titan SM, Wiersinga WM. *et al*. (2010). Initial thyroid status and cardiovascular risk factors: the EPICNorfolk prospective population study. Clin Endocrinol (Oxf). 72:404-10.
40. Rodondi N, Aujesky D, Vittinghoff E, Cornuz J, Bauer DC. (2006). Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. Am J Med;119:541-51.
41. Tognini S, Marchini F, Dardano A, Polini A, Ferdeghini M, Castiglioni M, *et al*. (2010). Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. Age Ageing ;39: 46-50.
42. Holmager P, Schmidt U, Mark P, Anderson U, Dominguez H, Raymond I, *et al*. (2015). Long-term L-Triiodothyronine (T3) treatment in stable systolic heart failure patients: a randomised, double-blind, cross-over, placebo-controlled intervention study. Clin Endocrinol (Oxf) ;83:931-7
43. Triggiani V, Iacoviello M, Monzani F, Puzzovivo A, Guida P, Forleo C, *et al*. (2012). Incidence and prevalence of hypothyroidism in patients affected by chronic heart failure: role of amiodarone. Endocr Metab Immune Disord Drug Targets.12: 86-94.
44. Sabih D, Inayatullah M. (2013). Managing thyroid dysfunction in selected special situations. Thyroid Res. 6:2.290
45. Biondi B, Cooper DS. (2008). The clinical significance of subclinical thyroid dysfunction. Endocr Rev;29: 76-131.
46. Brandt F, Green A, Hegedu¨s L, Brix TH. (2011). A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. European Journal of Endocrinology 165491–497. doi:10.1530/EJE-11-0299
47. Collet TH, Gussekloo J, Bauer DC, Elzen WPD, Cappola AR, Balmer P, *et al*. (2012). Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Archives of Internal Medicine ;172799–809. doi:10.1001/archinternmed.2012.402.
48. Biondi B. How could we improve the increased cardiovascular mortality in patients with overt and subclinical hyperthyroidism? European Journal of Endocrinology 2012;167:295–299. doi:10. 1530/EJE-12-0585
49. Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Archives of Internal Medicine. 2004;164: 1675–1678. doi:10.1001/archinte. 164.15.1675
50. Lin HC, Yang LY, Kang JH. Increased risk of pulmonary embolism among patients with hyperthyroidism: a 5-year follow-up study. Journal of Thrombosis and Haemostasis.2018;8: 2176–2181. doi:10.1111/j.1538-7836.2010.03993.x
51. Pearce SHS, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S,*et al*. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J. 2013;2(4): 215–28.
52. Ross DS, Burch HB, Cooper DS, Greenlee CM, Laurberg P, Maia LA, *et al*. American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343-421
53. Jankauskas SS, Morelli MB, Gambardella J, Lombardi A, Santulli G. Thyroid hormones regulate both cardiovascular and renal mechanisms underlying hypertension. J Clin Hypertens. 2021;23:373–381. doi: 10.1111/jch.14152
54. Gencer B, Collet TH, Virgini V, Auer R, Rodondi N. Subclinical thyroid dysfunction and cardiovascular outcomes among prospective cohort studies. Endocr Metab Immune Disord Drug Targets. 2013;13(1):4-12.
55. Wang W, Guan H, Gerdes AM, Iervasi G, Yang Y, Tang YD. Thyroid status, cardiac function, and mortality in patients with idiopathic dilated cardiomyopathy. J Clin Endocrinol Metab. 2015;100(8):3210-3218.
56. Galli E, Pingitore A, Iervasi G. The role of thyroid hormone in the pathophysiology of heart failure: clinical evidence. Heart Fail Rev. 2010:155-69
57. Schindhelm RK, Boekel E, Heima NE, Schoor NMV, Simsek S. Thyroid hormones and erythrocyte indices in a cohort of euthyroid older subjects. Eur J Intern Med. 2013;24:241-4
58. Gopinathannair R, Sullivan R, Olshansky B. Tachycardia mediated cardiomyopathy: recognition and management. Curr Heart Fail Rep. 2009;6: 257-64.
59. Klein I, Ojamaa K. (2001). Thyroid hormone and the cardiovascular system. NEJM.344:501-9.
60. Siu CW, Yeung CY, Lau CP, Kung WCA, Tse HF. (2007). Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. Heart;93:483-7. doi: 10.1136/hrt.2006.100628.
61. Nanchen D, Gussekloo J, Westendorp RG, Stott DJ, Jukema JW, Trompet S. (2012). Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab; 97: 852-861.
62. Dekkers OM, Puhó EH, Cannegieter SC, Vandenbroucke PJ, Sørensen HT, *et al*. (2016). Acute cardiovascular events and all-cause mortality in patients with hyperthyroidism: population-based cohort study. Eur J Endocrinol;176:1-9.
63. Laulund AS, Nybo M, Brix TH, Abrahamsen B, Jørgensen HL, Hegedüs L. (2014). Duration of Thyroid Dysfunction Correlates with All-Cause Mortality. The OPENTHYRO Register Cohort. PLoS ONE. 9(10): e110437. https://doi.org/10.1371/journal.pone.0110437
64. Alasrawi Samah, Rahim RA, Alhalabi Rawan. (2021). The Association between Thyroid Dysfunction and Heart Diseases. MAR Cardiology. 2:4
65. Chaker L, Berg MEVD, Niemeijer MN, Franco OH, Dehghan A, Hofman A.(2016). Thyroid Function and Sudden Cardiac Death: A Prospective Population-Based Cohort Study. Circulation;134:713-22.