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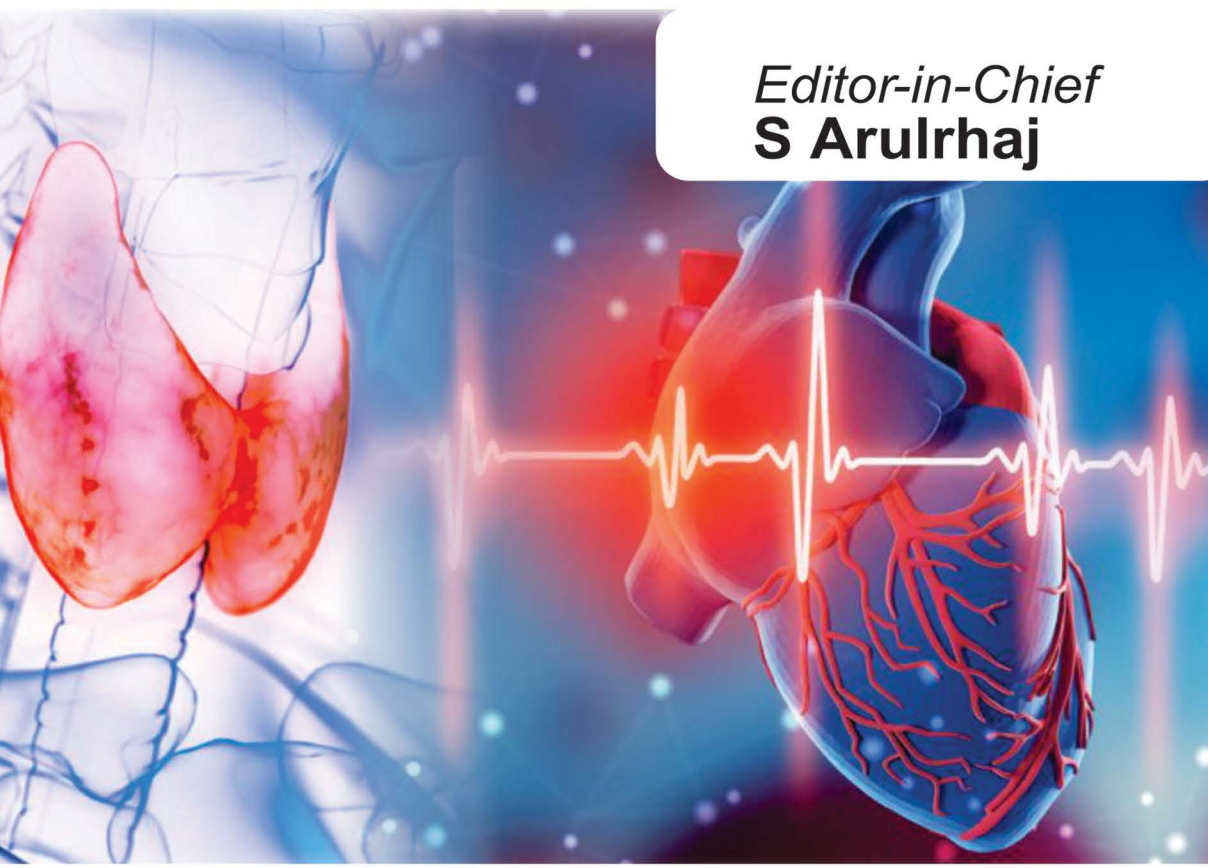
Clinical Update
Thyro-Cardiovascular Medicine



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CHAPTER

Cardiometabolic Implications of Thyroid Dysfunction

Muthu Kumaran Jeyapal

LEARNING OBJECTIVES

- Understand the effects of thyroid hormone on cardiovascular homeostasis
- Learn the cardiometabolic alterations in overt and subclinical hypothyroidism
- Discover the studies investigating cardiovascular risks in subjects with hypothyroidism
- Highlight the impact of thyroid hormone therapy on cardiovascular health

GENE REGULATION OF CARDIAC PROTEINS BY THYROID HORMONES

Table 1 shows gene regulation of cardiac proteins by thyroid hormones.

TABLE 1: Gene regulation of cardiac proteins by thyroid hormones.

Positive regulation	Negative regulation
• Alfa myosin heavy chain • Sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2) • β1-adrenergic receptors • Na^{+}/K^{+}-ATPase • K voltage-dependent channels • Atrial natriuretic peptide	• Beta myosin heavy chain • Phospholamban • Adenylyl cyclase types V, VI • T3 nuclear receptor alpha-1 • Na^{+}/Ca^{2+} interchanger • Thyroid hormone transporters (MCT8, 10) • Adenine nucleotide translocase-1 (ANT1)

(ATPase: adenosine triphosphatase; MCT: monocarboxylate transporter)

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VASODILATATORY ACTION OF THYROID HORMONE

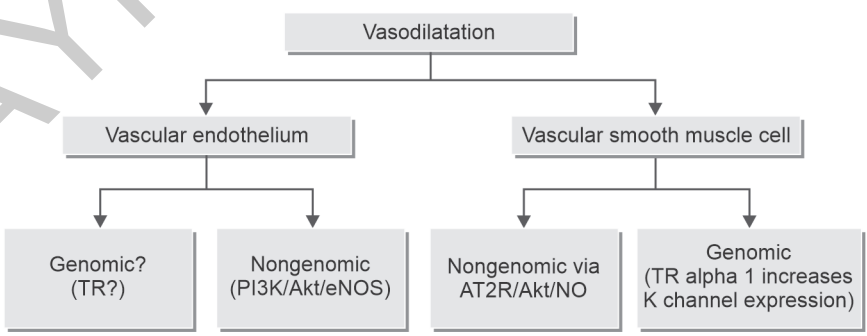
Overt hypothyroidism has been found to be associated with accelerated atherosclerosis and increased risk of cardiovascular disease (CVD) (**Flowchart 1**).

HYPERTENSION AND SUBCLINICAL HYPOTHYROIDISM

Thyroid hormones have several well-recognized effects on the cardiovascular system, including decreased systemic vascular resistance (SVR) and increased resting heart rate, left ventricular contractility, and blood volume. It has long been known that some of the most characteristic and common signs and symptoms of thyroid dysfunction are those that result from the profound effects of thyroid hormones on the heart and peripheral vasculature. Overt hypothyroidism (OH), with its accompanying dyslipidemia and hypertension, has been known to be associated with CVD. In these patients, increased SVR in association with decreased arterial compliance results in elevated diastolic blood pressure (DBP) (**Figs. 1 and 2 and Flowchart 2**).

LIPID PROFILES IN OVERT HYPOTHYROIDISM

Serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), lipoprotein (a) [Lp(a)], oxi-LDL, ApoB, remnants of very-low-density lipoprotein (VLDL), and chylomicron (CM) levels are increased in OH, while serum levels of triglyceride, high-density lipoprotein cholesterol (HDL-C), and VLDL are normal or slightly increased. All of the lipid abnormalities in OH are reversible with levothyroxine (L-T4) therapy unless the patient has underlying hyperlipidemia. In OH, thyroid hormone effects on LDL receptor expression and cholesterol absorption outweigh the effects of decreased hepatic cholesterol synthesis, leading to high serum levels



FLOWCHART 1: Vasodilatory action of thyroid hormone.

(TR: thyroid hormone receptor; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; PI3K: phosphoinositide 3-kinase)

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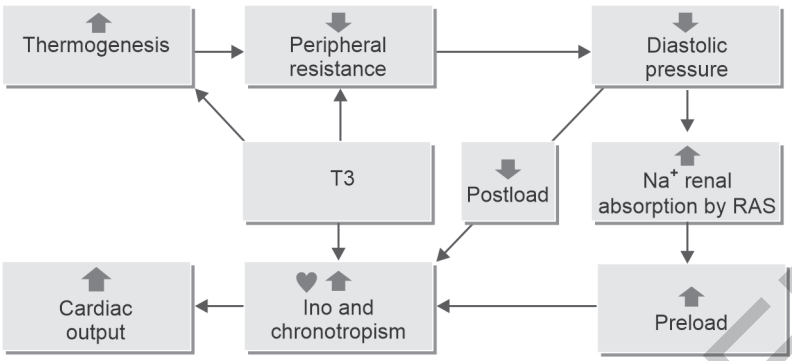

FLOWCHART 2: Effect of T3 on renin–angiotensin–aldosterone system (RAAS) mechanism in hypertension.

(RAS: renin–angiotensin system)

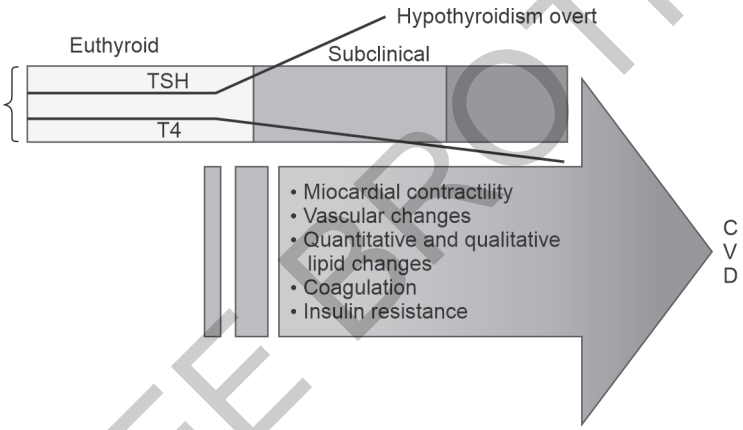

FIG. 1: Hypothyroidism and cardiovascular risk factors.

(CVD: cardiovascular disease; TSH: thyroid-stimulating hormone)

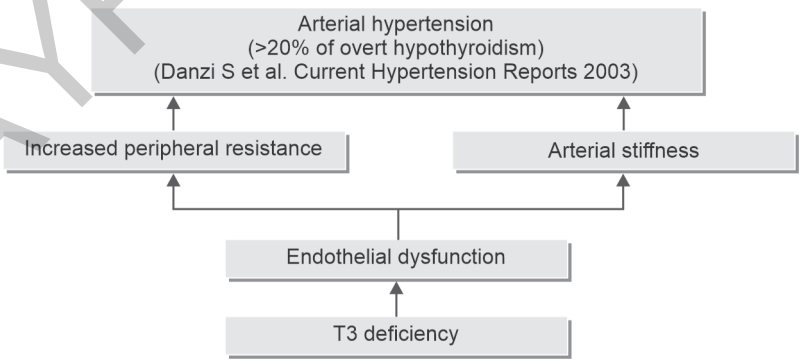

FIG. 2: Hypothyroidism and hypertension relationship.

Source: Modified from Brenta G. Hipotiroidismo y sistema cardiovascular. Rev Fed Arg Cardiol. 2006;35: 164-75.

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of LDL, intermediate density lipoprotein cholesterol (IDC), and TC levels. Additionally, lipoprotein lipase (LPL) activity is decreased in hypothyroidism, resulted in higher level of VLDL-triglyceride (TG). Studies showed that Lp(a) levels are increased in patients with OH and decrease after L-T4 treatment. Lp(a) is a complex of LDL in which apolipoprotein (apo) B-100 is linked to apo(a) by a disulfide bridge. Lp(a) promotes foam cell formation and deposition of cholesterol, resulting in increased atherosclerotic and thrombogenic potential. The mechanism may be related to the decreased clearance of LP(a) mediated by the LDL-R degradation pathway. The levels of apolipoprotein (B) are higher in both overt and subclinical hypothyroidism (SCH) and have been shown to decrease after L-T4 treatment.

HEART FAILURE AND SUBCLINICAL HYPOTHYROIDISM

It is well known that thyroid hormones act on the heart and vasculature and, as a result, the impact of subclinical thyroid dysfunction on the CV system has recently become an important topic of research. SCH can lead to impaired systolic and diastolic cardiac function and symptomatic SCH patients often complain of reduced exercise tolerance during effort. This same study found that a slowed rate of left ventricular relaxation might critically impair ventricular filling during exercise and result in left ventricular systolic dysfunction. Older people with SCH and a high CV risk appear to be at an increased risk of incident heart failure and SCH was found to affect left ventricular dysfunction, although this abnormality may be reversed by T4 substitutive therapy. Likewise, a recent cardiac magnetic resonance spectroscopic study demonstrated that early cardiac bioenergetic impairments in SCH patients are reversible with T4 therapy.

RECOMMENDATION 16 AMERICAN THYROID ASSOCIATION/AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGIST (ATA/AACE)

Treatment based on individual factors for patients with thyroid-stimulating hormone (TSH) levels between the upper limit of a given laboratory's reference range and 10 mIU/L should be considered particularly if patients have symptoms suggestive of hypothyroidism, positive thyroid peroxidase antibody (TPOAb) or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases. Grade B, BEL 1.

RECOMMENDATION 13 LATS

For patients with mildly increased serum TSH levels (4.5–10 mU/L), treatment should be considered for those patients younger than 65 with

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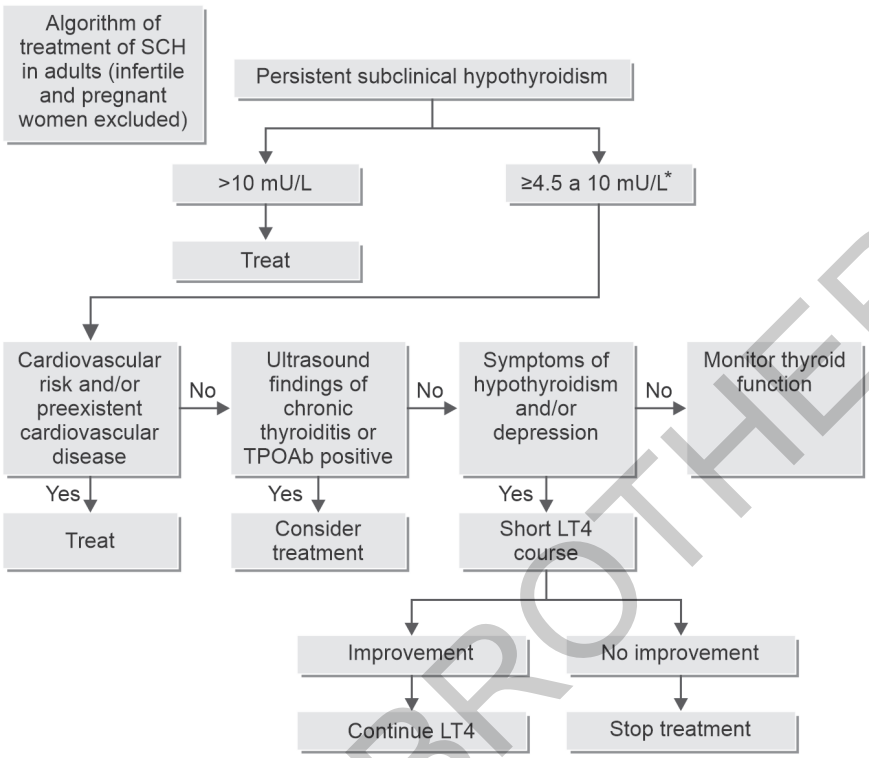

* In patients above 65 years of age this algorithm should be applied on an individual basis.

FLOWCHART 3: Guidelines for the management of subclinical hypothyroidism.

(TPOAb: thyroid peroxidase antibody)

Source: Brenta G, Vaisman M, Sgarbi JA, Bergoglio LM, Andrada NC, Bravo PP, et al. Clinical practice guidelines for the management of hypothyroidism. Arq Bras Endocrinol Metabol. 2013;57(4):265-91.

increased cardiovascular risk (e.g., previous cardiovascular disease, diabetes, dyslipidemia, hypertension, metabolic syndrome), particularly when TSH level is persistently >7 mU/L. Grade A **(Flowchart 3)**.

TREATMENT OF HYPOTHYROIDISM

In patients with previous CVD or in elderly patients:

- Start slow and go slow
- Initial dose of 25 μg of levothyroxine with increments of 25 μg every 3–4 weeks until total replacement is achieved.

CONCLUSION

- Hypothyroidism is associated with cardiovascular alterations that vary according to the degree of thyroid dysfunction and the age of patients.
- Overt and SCH patients exhibit qualitative and quantitative lipid changes.

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- Observational studies show an increase in cardiac mortality in patients with SCH.
- Evidence is stronger in patients <65 years of age and with TSH > 7 mU/L.
- Different guidelines agree on treating this particular set of patients with levothyroxine.

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Clinical Update
Thyro-Cardiovascular Medicine

Salient Features

- A monogram covering all the components of thyroid and cardiovascular disease (CVD)
- Contributed by faculties with expertise on thyroid cardiovascular disease (TCVD)
- A quick reference on "thyro-cardiovascular disease" for young physicians, and postgraduates

S Arulrhaj MD PhD FRCP (Glasgow and London) MBA is a distinguished Professor (Hony) at Dr MGR Medical University, Chennai, Tamil Nadu, India. He is a Dr BC Roy National Awardee, the highest professional award in India and the Founder Chairman, Chief Physician, and Intensivist of Sundaram Arulrhaj Hospitals, Tuticorin and Founder and Chairman for "ARULS Group". He has been the National President of Indian Medical Association and Association of Physicians of India (API). Prof Dr S Arulrhaj is the Founder Chairman of the Commonwealth Medical Association Trust and Commonwealth Medical eVarsity, UK. He is the Founder and Past Chairman of Commonwealth Health Professions Alliance, UK; Founder and Chairman of Indo Global Cardio Diabetes Academy, India, Past President of the Commonwealth Medical Association, Honorary National Professor of Medicine, IMA and IMACGP, India, and Chief Patron of IMACGP and IMA eVarsity, India. He has published Diabetes Update 2011, Clinical Medicine Update Book 2016, Cardiodiabetes Medicine 2017 and 2018. He is regularly contributing for Medicine Update, and API over 20 years. He is a postgraduate teacher in Internal Medicine over 20 years—DNB Medicine and has addressed acute medicine on various national and international platforms. Dr Arulrhaj's medical interests are nonintensive cardiology and intensive care. His public health interests are prevention and control of noncommunicable diseases, cardiodiabetic medicine, digital health, rural health, and prehospital trauma and emergency care. He has organized several conferences—national, international and state API, IMA, and conferences of GCDC and ISECON.

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