# Thyroid Disease and the Cardiovascular System

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**KEYWORDS**

• Hypothyroidism • Hyperthyroidism • Subclinical • Thyroid hormone
• Triiodothyronine • Heart • Cardiac myocyte

**KEY POINTS**

- Thyroid dysfunction may significantly impair cardiac and cardiovascular health.
- Chronic diseases, such as heart disease, may lead to the low $T_3$ syndrome.
- More severe heart disease (NYS Heart Association classification stages 3 and 4) is associated with an increased prevalence of low $T_3$ syndrome.
- Regardless of the cause, in this context decreased serum $T_3$ levels are associated with poor prognosis, especially in heart disease.

## INTRODUCTION

There is an intimate relationship between the thyroid gland and the heart. Thyroid dysfunction, including subclinical thyroid disease, has significant effects on cardiovascular function and health. Likewise, chronic disease states, such as heart disease, may lead to reduced serum thyroid hormone levels, specifically $T_3$ (low $T_3$ syndrome) causing a synergistic negative effect on cardiac and cardiovascular function. Therefore, diagnosis and treatment of the patient with heart disease may benefit from analysis of thyroid status, including levels of serum total $T_3$.

## THYROID HORMONE REGULATION AND METABOLISM

The thyroid gland produces 2 biologically active hormones, thyroxine ($T_4$) and triiodothyronine ($T_3$). Although $T_4$ has some documented nongenomic effects, it is largely considered a prohormone. Most of $T_4$ is converted to $T_3$ by 5′-monodeiodination in the liver, kidneys, and skeletal muscle.[1,2] $T_3$ is then delivered to the circulation so that it is available for tissues and organs that rely solely or predominantly on serum $T_3$, such as the heart.

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Expression and activity of relevant monodeiodinases are also regulated in part by $T_3$.[3] Serious chronic illness, such as heart disease, is often associated with decreased serum $T_3$ levels. This is known as low $T_3$ syndrome or nonthyroidal illness and is frequently caused by impaired deiodinase activity, primarily from congestion in the liver.[1] The hepatic type 1 iodothyronine deiodinase (D1) is induced at the transcriptional level by $T_3$, but in illness, a cytokine-mediated effect blocks the induction, resulting in decreased serum $T_3$ levels.[4]

The regulation of thyroid hormone synthesis and secretion is primarily dependent on thyrotropin (thyroid stimulating hormone or TSH), synthesized and released by the anterior pituitary in a negative feedback loop. This feedback is largely driven by serum $T_4$ levels and thus, serum $T_3$ levels decline without promoting a compensatory response from the pituitary. In the low $T_3$ syndrome, however, increased $T_4$ production would not be beneficial because it is the conversion to $T_3$ that is impaired. The consequences of this and potentially significant implications for the heart and cardiovascular system are discussed.

## THYROID HORMONE ACTION AT THE CELLULAR LEVEL

The actions of $T_3$ include genomic transcriptional activation and repression and nongenomic actions targeted to specific membrane proteins, organelles, and cytoskeletal components. Membrane proteins include solute transporters for ions ($Ca^{2+}$, $Na^+$) and glucose among many others.[5] Together, the nongenomic and genomic actions of $T_3$ on cardiac myocytes and vascular smooth muscle are responsible for significant effects on the heart and cardiovascular system function.

The transcriptional actions of $T_3$ are mediated by nuclear receptor proteins that bind to specific thyroid hormone response elements in the upstream region of $T_3$ responsive genes.[6] These nuclear receptors, which include TR$\alpha$ and TR$\beta$, activate expression of positively regulated genes in the presence of $T_3$ and in the absence of $T_3$, repress transcription of negatively regulated genes. A survey of the list of $T_3$-responsive genes in the cardiac myocyte can explain why the heart is so sensitive to serum levels of $T_3$ (**Table 1**).[1,7] Our studies demonstrate that it is $T_3$ and not $T_4$ that enters the cardiac myocyte (Sara Danzi, PhD, and Irwin Klein, MD, personal communication). Measures of $\alpha$-MHC heteronuclear RNA (hnRNA), the first product of transcription (prespliced), serve as a rapid, sensitive measure of $T_3$-mediated transcription in the rodent myocyte.[8] Cardiac $\alpha$-MHC hnRNA is detectable within 30 minutes after $T_3$ administration. However, after $T_4$ administration, detectable $\alpha$-MHC hnRNA expression is delayed by almost 12 hours coinciding with rising serum $T_3$ levels. These data support the premise that $T_4$ is not transported into the cardiac myocyte, and adequate serum $T_3$ is required for maximum $\alpha$-MHC expression.

**Table 1**
**Effect of $T_3$ on cardiac-specific genes**

| Positively Regulated | Negatively Regulated |
|---|---|
| Alpha-myosin heavy chain | Beta-myosin heavy chain |
| Sarcoplasmic reticulum $Ca^{2+}$-ATPase | Phospholamban |
| $Na^+/K^+$-ATPase | Adenylyl cyclase catalytic subunits |
| Beta1-adrenergic receptor | Thyroid hormone receptor alpha-1 |
| Atrial natriuretic hormone | $Na^+/Ca^{2+}$ exchanger |
| Voltage-gated potassium channels | Thyroid hormone transporters (MCT8,10)<br>Adenine nucleotide translocase-1 (ANT1) |