

Thyroid Supplementation in Patients with Heart Failure

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1. Background

Heart failure is a chronic condition which affects nearly 5.7 million Americans, attributed to costs of up to \$37.2 billion, and is mentioned on 1 in 8 death certificates.¹ In a clinical study, a correlation between hypothyroidism and coronary disease was shown in 11.5% of patients.² Hypothyroidism is related to heart failure in the way that its characteristics, such as dyslipidemia and hypertension, increase the risk of atherogenesis.^{3,4} Atherogenesis leads to atherosclerosis and subsequently coronary artery disease, that may further lead to myocardial infarction, which results in systolic dysfunction or decreased contraction. The most common causes of heart failure originate from systolic and diastolic dysfunction.⁵ Signs and symptoms of hypothyroidism include fatigue, dry coarse skin, depression, impaired memory, cold intolerance, tenderness and stiffness, and bradycardia, among other health issues. If left untreated, symptoms can get worse and can even be life-threatening.⁶

2. Heart Failure and Hypothyroidism

Other similarities also exist between heart failure and hypothyroidism. Hypothyroidism results in decreased myocardial oxygen demand by creating a negative chronotropic and inotropic state. β -Adrenergic receptors in the heart activate downstream events that are responsible for inotropic and chronotropic effects. Like hypothyroidism, a negative chronotropic and inotropic can be observed in heart failure. In the non-failing human heart, the left or right ventricles have a β_1/β_2 ratio of 70 to 80/30 to 20. However, 35-40% of β -receptors in the failing human heart are β_2 secondary to down regulation of the β_1 receptor subtype.⁷ It has been noted by Liggett et al. that β_2 receptor subtype overexpression attenuates cardiac function, which is made manifest secondary to depressed systolic function and a cardiomyopathy phenotype.⁸ Cardiotoxic concentrations of norepinephrine are found in the failing heart and bind preferentially to β_1 -receptors up to 10-30 fold compared to that of the β_2 -receptor subtype.⁹ Therefore, achieving a euthyroid state, i.e. normal levels of TSH, T_3 , and T_4 , may potentially result in positive outcomes in patients with decreased thyroid levels and heart failure

3. β_1 -receptor Upregulation

Beta blockers are now a critical component of standard therapy in heart failure because of numerous trials showing decreased morbidity and mortality in many patients with heart failure.^{10,11} Another purported benefit of beta blocker use is resultant up-regulation of β_1 -receptors in the failing heart, which restores inotropic and chronotropic responsiveness of the myocardium, that further leads to improvement in cardiac function.¹² It then could be theorized that fewer deleterious cardiac effects of β_2 -receptor stimulation would be observed because of preferential binding of norepinephrine to the β_1 -receptor.

Thyroid supplementation also results in up-regulation of β_1 -receptors, thus serving as a potential therapeutic option, alternatively to or in conjuncture with beta blocker therapy. In a murine study, T_3 has been noted to up-regulate β_1 -receptor mRNA up to four-fold within 30 minutes, while having minimal changes on β_2 -receptor up-regulation. Once β_1 -receptor mRNA increases, downstream β_1 -receptors increase up to three-fold, which may last up to 48 hours.¹³

4. Thyroid Supplementation in Heart Failure

For the diagnosis and management of heart failure, the ACCF/AHA guidelines, recommend thyroid function tests.¹⁴ Screening for thyroid dysfunction is critical since it is manifested in different forms of heart disease, both in men and women. Treatment of hypothyroidism with thyroid supplementation remains uncontested.

However, treatment of subclinical hypothyroidism is controversial as it is asymptomatic, and outcomes are equivocal, in an otherwise healthy individual.¹⁵ Subclinical hypothyroidism is defined as serum thyroid stimulating hormones in the range of 4.5 to 19.9 mIU per L, with normal levels of T₄ and T₃.¹⁶ Limited data are available on the treatment of subclinical hypothyroidism. In patients below 70 years and with TSH levels greater than 10 mIU/L, treatment with levothyroxine has been recommended, although at lower TSH levels such treatment still remains controversial.¹⁷

However, treatment of subclinical hypothyroidism may result in positive outcomes, especially in patients with cardiac deficiencies that are associated with heart failure. It has been reported that patients with a failing heart have decreased T₃ concentrations, which is directly proportional to the extent of heart failure.¹⁸ T₄ supplementation is associated with decreased diastolic dysfunction.¹⁹⁻²³ In a reported study, patients with subclinical hypothyroidism exhibited a poor exercise capacity. However, when a euthyroid state was achieved, the negative changes associated with subclinical hypothyroidism reverted back to normal.²⁴

It is also important to make to note that in illness not secondary to thyroid dysfunction, low T₃ levels with normal TSH and T₄ levels have been observed.²⁵ This differs from subclinical hypothyroidism, where T₃ and T₄ levels are normal, but TSH levels are increased. This phenomenon may be observed in heart failure patients. In a randomized placebo-controlled study of patients with heart failure and low T₃ levels, it was suggested that T₃ replacement reduces the activation of the neuroendocrine system as well as notable improvements in left ventricular stroke volume.²⁶

In another reported study, two hours after administration of a single bolus of 0.058 mg of T₃, an increase in cardiac output as well as a decrease in systemic vascular resistance was observed, with no deleterious adverse effects, such as myocardial ischemia.²⁷ Also, several studies were conducted, which displayed that the administration of 0.1 mg T₄ per day improved cardiac and exercise performance in patients with idiopathic dilated cardiomyopathy.^{28,29} Improvements were also noted in cardiac output and heart rate, most likely secondary to up-regulation of β_1 -receptors.

5. Conclusion

Although patients with heart failure may be screened for thyroid and observed to exhibit levels low levels of T₃ or subclinical hypothyroidism, thyroid supplementation may not be initiated, as treatment is controversial. However, several studies suggest that achieving a euthyroid state may result in increased heart function, which may be especially beneficial to a patient with a failing heart.

In the ACCF/AHA/AMA-PCPI 2011 HF performance measurement set, heart failure outcomes are listed, such as reduced patient hospitalizations, symptoms, and readmission rates.¹ Such outcomes may result from thyroid supplementation in patients with subclinical hypothyroidism or decreased T₃ levels in heart failure. As stated by the AHA, there is a need to assess outcomes associated with thyroid supplementation because of limited studies for its use in treating heart failure.²⁵ Secondary to a need for clinical studies and purported benefits, thyroid supplementation may have a potential therapeutic role in patients with heart failure.

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