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Sick Euthyroid Syndrome as a Prognostic Marker and Therapeutic Target in Heart Failure: A Literature Review

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ABSTRACT

Heart failure (HF) is a significant disease burden and mortality worldwide and is often accompanied by endocrine changes that affect the disease course. One of these is Sick Euthyroid Syndrome (SES), or Non-thyroidal Illness Syndrome (NTIS) which is a decrease in serum levels of triiodothyronine (T3) in the absence of any thyroid disease. This literature review will review the current evidence of the role of SES as a prognostic marker and its role as a therapeutic target in patients with heart failure. A thorough literature review was done with the predefined search terms of heart failure, SES, thyroid hormone dysfunction, prognosis, and thyroid hormone replacement therapy, in major databases. Relevant clinical studies were reviewed and synthesized narratively to examine clinical thyroid function, clinical outcomes, and therapeutic interventions. The evidence on hand is consistently associated with the association between low T3 levels with increased severity of disease, impaired cardiac function, hospitalisation and mortality. Free T3, reverse T3, the FT3/FT4 ratio and NT-proBNP also seem to be useful biomarkers in risk stratification. The results of thyroid hormone replacement in selected hemodynamic and functional parameters in different experimental and small

clinical studies have been inconclusive and need further study before it can be recommended as a routine therapy. SES is a clinically relevant indicator of poor prognosis in patients with heart failure and it highlights the intricate relationship between thyroid hormone metabolism and heart failure pathophysiology. More good clinical studies are needed to better define its therapeutic value and clarify its role in the therapy of heart failure patients.

Keywords: Heart failure, Sick Euthyroid Syndrome, Non-thyroidal Illness Syndrome, Low T3 Syndrome, Thyroid hormones.

INTRODUCTION

Heart failure (HF) is a significant public health challenge in the world and the prevalence of HF is increasing even further, primarily due to population ageing, especially in developed countries (1). Cardiovascular disease is the leading cause of death in the world, causing more than 17 million deaths a year in the developed and developing world. The studies have reported that up to 23% of patients attending with myocardial infarction develop Sick Euthyroid Syndrome (SES) which has been shown to have potential as a prognostic marker in cardiovascular disease(2).

To ensure the development and maintenance of normal cardiac structure and function, several endocrine pathways are involved in cardiovascular regulation, thyroid hormones being one of the most important ones. Thyroid hormone metabolism changes are very common in the setting of advanced heart failure, and may be associated with subnormal levels of circulating triiodothyronine (T3) and thyroxine (T4) despite normal intrinsic thyroid function. The changes are accompanied by alteration in the regulation of thyroid-stimulating hormone (TSH), and this combination is known as Sick Euthyroid Syndrome or Non-thyroidal Illness Syndrome (NTIS). One suggested mechanism is a decrease in the activity of type 1 deiodinase (D1) and an increase in the expression of type 3 deiodinase (D3) which results in a reduced conversion of T4 to the active T3 in the periphery (3).

The other suggested mechanism suggests oxidative stress is involved in heart failure. During HF, increased production of reactive oxygen species (ROS) leads to nitric oxide synthase uncoupling, lipid peroxidation, endothelial dysfunction, vascular smooth muscle proliferation, increased inflammatory signaling, oxidative DNA damage and platelet activation. These pathological processes could also affect deiodinase activity, which further leads to SES (3).

Thyroid hormones play crucial roles in myocardial tissue and in the vascular endothelium via thyroid hormone receptors. They control cardiocontractility, heart rates, vascular resistance, blood pressure and thrombogenic pathways, thus contributing to the cardiovascular homeostasis. The decreased T3 levels seen in SES therefore have implications for clinical practice. Increased S.V.R., decreased cardiac output and impaired cardiac contractility have been described as part of low thyroid hormone levels, which lead to worsening heart failure (HF) (1).

Non-thyroidal Illness Syndrome or Sick Euthyroid Syndrome or Low T3 Syndrome is found in about 30% of heart failure patients. There is a low level of T3 and T4 and a high level of reverse T3 (rT3) in the serum. Thyroid hormone abnormalities have been found to be independent mortality predictors in heart failure, with the cardioprotective and antiapoptotic effects of thyroid hormones on myocardial cells (1). This work has stimulated the growing interest in using SES as a prognostic biomarker in patients with heart failure.

In the last 20 years, much evidence has emerged revealing the importance of thyroid hormones in cardiac function. Therefore, Sick Euthyroid Syndrome has been found to predict disease progression, worsen clinical outcomes and mortality in patients with heart failure (4,2). This relationship could also have therapeutic significance; if there is a relationship, targeted interventions, designed to correct thyroid hormone abnormalities could be offered to these patients.

Although the evidence is accumulating, there are still several gaps in the understanding of the heart failure–Sick Euthyroid Syndrome association. These conditions often occur together, but the mechanisms by which these conditions are connected and the therapeutic implications of thyroid hormone modulation are not fully understood. Thus, a thorough assessment of the evidence is required to determine the prognostic relevance of SES and as a therapeutic target in heart failure patients.

The purpose of this literature review is to look at the existing evidence on the role of Sick Euthyroid Syndrome (SES), which is also referred to as Non-thyroidal Illness Syndrome (NTIS) or Low T3 Syndrome, in heart failure patients as a prognostic marker and therapeutic target.

METHODOLOGY

Major databases were used for a comprehensive literature search to identify studies that assessed the prognosis and therapeutic effect of Sick Euthyroid Syndrome (SES) in patients with heart failure. To ensure the maximum number of eligible studies were identified, a combination of Medical Subject Headings (MeSH), keyword combinations and manual screening of the reference lists of the relevant articles was used. The search strategy used the words: "heart failure" AND "sick euthyroid syndrome," "low T3 syndrome" AND "heart failure prognosis," "thyroid hormone replacement" AND "heart failure," and "non-thyroidal illness syndrome" AND "cardiovascular disease" in addition to "triiodothyronine therapy" AND "heart failure.The search terms comprised: "heart failure" AND "sick euthyroid syndrome," "low T3 syndrome" AND "heart failure prognosis," "thyroid hormone replacement" AND "heart failure," and "non-thyroidal illness syndrome" AND "cardiovascular disease," as well as "triiodothyronine therapy" AND "heart failure. Only studies which were freely available in full-text were included.

Studies were included if they studied patients with heart failure and Sick Euthyroid Syndrome or Non-thyroidal Illness Syndrome or Low T3 Syndrome. Where available, parameters of thyroid

function included free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) and reverse triiodothyronine (rT3) and outcomes assessed were mortality, hospitalization, disease severity, cardiac function, prognosis, or response to thyroid hormone therapy. Randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and cross sectional studies published in English were included.

Studies were excluded if the primary focus was on intrinsic thyroid disorders such as hypothyroidism, hyperthyroidism, thyroiditis or thyroid malignancy, or if the study did not measure thyroid hormone levels, or if heart failure was combined with other critical illnesses in a single analysis. Case reports, editorials, letters to the editor, conference abstracts without full-text publication, review articles, expert opinions and studies published in other languages besides English were not included.

Data from each eligible study were gathered and included study design, number of patients, patient characteristics, type of heart failure, measurements of thyroid function, clinical outcomes, treatment interventions, and main conclusions. The studies that were selected were synthesized narratively to assess whether thyroid hormone replacement therapy can be used to treat heart failure and to explore thyroid hormone replacement as a prognostic tool in the disease.

DISCUSSION

Heart Failure Pathophysiological Overview

Heart failure (HF), or congestive heart failure (CHF), is a complex clinical syndrome resulting from structural or functional changes that compromise the filling and/or ejection of blood by the heart. The most common causes are ischaemic heart disease, myocarditis, hypertension (HTN) and valvular diseases (5).

HF is initiated by injury to myocardial tissue, which reduces cardiac output. This then triggers the compensatory mechanisms of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), causing an increase in heart rate, vasoconstriction and sodium & water retention. Chronic stimulation of these mechanisms results in myocardial hypertrophy, fibrosis, remodelling and apoptosis of myocytes. As cardiac function further decreases, ventricular pressure increases, and blood accumulates in the pulmonary and systemic circulation, causing congestion. This decreases renal perfusion, further increasing fluid retention in a vicious circle, worsening HF and finally leading to decompensation (6).

Two categories of HF exist according to ventricular ejection fraction: heart failure with preserved ejection fraction (HFpEF; LVEF ≥ 50%) and heart failure with reduced ejection fraction (HFrEF; LVEF ≤ 40%). In HFrEF, the heart undergoes eccentric hypertrophy and weakness with decreased pumping ability. In HFpEF, the heart undergoes concentric hypertrophy and stiffness, which causes impaired relaxation and filling with increased pressure. HFpEF is related to aging and several chronic diseases, such as HTN, type 2 diabetes mellitus (T2DM), obesity, renal insufficiency, and liver diseases. HFrEF is primarily related to myocardial infarction (7).

Chronic systemic inflammation and metabolic dysregulation are the key players in HF progression. In HF, chronic inflammation is characterised by the release of pro-inflammatory cytokines, oxidative stress and endothelial dysfunction, which in turn impair cardiac function and cause adverse cardiac remodelling. Metabolic disorders, including insulin resistance, obesity, diabetes and altered energy metabolism, impair heart efficiency and increase disease progression. This vicious cycle exacerbates the severity of HF and worsens clinical outcomes (8).

Thyroid Hormones and Cardiovascular Physiology

Thyroid hormones (TH) have cardiac effects which are primarily mediated via interaction with nuclear based thyroid hormone receptors, which change the expression of certain cardiac proteins. The effects of the active form of TH, triiodothyronine (T3), on cardiac functions like heart rate, contractility and cardiac output are closely regulated. Normally, T3 increases peripheral oxygen consumption and substrate requirement, which in turn causes an increase in cardiac contractility; it also has direct effects on cardiac myocytes. T3 decreases systemic vascular resistance (SVR) by vasodilating the blood vessels. It is due to direct effects of T3 on vascular smooth muscle cells through releasing nitric oxide (NO) and promoting vasodilation. This decrease in SVR reduces the arterial filling volume, which would lead to stimulation of the RAAS system, releasing renin and sodium reabsorption, leading to water retention and increasing plasma volume. Thyroid hormone also stimulates erythropoietin secretion. This combined effect would increase blood volume and preload, which further increases cardiac output, heart rate and myocardial oxygen consumption (9).

The effects of THs at the cardiac intracellular level are divided into genomic and non-genomic pathways. In the genomic response, the TH binds to the thyroid hormone receptor in the cardiomyocyte nucleus, upregulating the expression of genes encoding sodium/potassium-transporting ATPases (Na^+/K^+ ATPase), α-myosin heavy chain and sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) and downregulating transcription of β-myosin heavy chain and phospholamban. This increases calcium concentrations in cardiomyocytes and enhances systolic contraction. Whereas in the non-genomic response, several plasma-membrane ion transporters, such as Na+/K+-ATPase, Na^+/Ca^{2+} exchanger and voltage-gated potassium channels, are regulated at both the transcriptional and post-transcriptional levels by thyroid hormone (10).

Dysregulation of the thyroid state leads to considerable alterations in energy balance; indeed, the importance of the THs-mediated homeostatic control of energy metabolism is evident in patients with thyroid dysfunction. Hyperthyroidism, a clinical syndrome that causes an excess of TH, promotes a hypermetabolic state characterised by increased energy expenditure at rest, weight loss despite increased food intake, reduced cholesterol levels, increased lipolysis and gluconeogenesis. By contrast, hypothyroidism is associated with hypometabolism characterised by decreased metabolic rate, weight gain despite reduced food intake, increased cholesterol levels, reduced lipolysis and decreased gluconeogenesis (11).

Pathophysiology of Sick Euthyroid Syndrome in Heart Failure

Sick Euthyroid Syndrome (SES) or Non-thyroidal Illness Syndrome (NTIS) is characterised by abnormal thyroid hormone levels in acute and chronic systemic illness patients despite having proper thyroid gland function. The hallmark finding is low T3 levels with normal or low normal T4 and TSH levels. Its causes could be external systemic metabolic adaptations like inflammation, neurohormonal activation, hypoperfusion and oxidative stress (2,12).

In normal physiological conditions, the conversion of T4 to T3 is mediated by the iodothyronine deiodinase enzyme, mainly D1 and D2, located in the liver, kidneys, skeletal muscle, brain, and myocardium. Normally D1 is responsible for synthesising T3 by converting T4 into active T3. It also metabolises reverse T3 (rT3) into inactive metabolites, preventing its accumulation. D2 is responsible for ensuring there are adequate intracellular thyroid hormones necessary for local tissue metabolism. D3 is more active during fetal development but remains active in adult myocardium. D3 converts T4 into rT3 and converts active T3 into biologically inactive T2, thereby reducing thyroid hormone activity. In heart failure, because of inflammatory cytokines (IL-6 and TNF-α), oxidative stress and tissue hypoxia, these D1 and D2 enzymes are suppressed and D3 is enhanced, which leads to a decrease in the conversion of T4 to T3 but an increase in the production of reverse T3 (rT3). This results in functional tissue hypothyroidism despite normal thyroid gland function. Although rT3 itself does not impair cardiac function, its accumulation indicates reduced intracellular T3 levels, which diminishes mitochondrial energy production, decreased oxygen utilisation and impaired myocardial metabolism (13,2,12).

The reactive oxygen species (ROS) created in HF damage deiodinase enzymes responsible for peripheral T3 production. ROS reduces ATP production and promotes opening of the mitochondrial permeability transition pore, leading to mitochondrial swelling and apoptosis, which damages myocardial contraction and relaxation, leading to reduced cardiac function and progressive HF. This oxidative stress in turn releases a lot of inflammatory cytokines and further suppresses T3 production and worsens cardiac function. This reciprocal relationship between inflammation and oxidative stress amplifies thyroid hormone abnormalities observed in sick euthyroid syndrome (2,13).

In HF, when cardiac output decreases, several compensatory mechanisms get activated to maintain blood pressure and organ perfusion. These include the RAAS and the sympathetic nervous system. When the sympathetic system gets activated, a lot of catecholamines get released into the bloodstream, which stimulates β-adrenergic receptors, which initially enhances heart rate and contractility. But eventually causes receptor downregulation, increased oxygen consumption, calcium overload, apoptosis and ventricular remodelling. When there is less renal perfusion, the RAAS system gets activated and causes an increase in angiotensin II, which promotes vasoconstriction, oxidative stress, cytokine release and myocardial hypertrophy and fibrosis. All these mechanisms worsen ventricular remodelling and further suppress thyroid hormone metabolism through increased inflammation and oxidative injury (2,13).

The overall decrease in T3 reduces SERCA activity and β-adrenergic responsiveness, impairs calcium handling, reduces ATP production and increases myocardial fibrosis. In the heart this results in low ejection fraction, decreased exercise tolerance and increased mortality. Therefore, low T3 is both a marker and mediator of poor prognosis in chronic heart failure (2,14).

Prevalence and Clinical Characteristics

Many clinical studies have shown that SES is highly prevalent in patients with HF. Although it varies with patient population, diagnostic criteria, disease severity and study design, approximately 15-35% of patients with CHF show signs of SES. Among hospitalised patients with advanced or decompensated HF, the prevalence may exceed 40-50%, showing the impact of acute systemic illness on thyroid hormone metabolism (15).

SES can occur in both acute and chronic HF. In acute HF, sudden changes in haemodynamic status, tissue hypoxia, inflammation and neurohormonal activation alter the peripheral thyroid hormone metabolism. In chronic HF, prolonged thyroid hormone dysfunction leads to progressive impairment of myocardial function, ventricular remodelling, endothelial dysfunction and worsening exercise intolerance (2,15).

SES has also been associated with higher concentrations of brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), biomarkers that indicate ventricle wall stress (seen in patients with HFrEF). Patients who exhibit low T3 levels show the highest BNP levels, which indicates greater myocardial dysfunction and increases intracardiac filling pressure. Older HF patients have physiological reduction in thyroid reserve together with multiple comorbidities like chronic inflammation, malnutrition, renal dysfunction, etc. These age-related factors reduce the conversion of T4 to T3, making them prone to SES. Multiple studies also show that patients with SES experience high rates of recurrent hospitalisation due to worsening HF compared with euthyroid patients (15).

The hallmark laboratory finding of SES is low T3, resulting from reduced D1 and D2 deiodinase enzyme activity and increased D3 activity, which converts T4 into rT3. In this state, TSH usually remains normal or slightly reduced because inflammatory cytokines block the hypothalamic-pituitary-thyroid axis (2,15). These hormonal changes cause overall dysfunction in myocardial contractility, ventricular remodelling and higher mortality, highlighting the importance of thyroid function assessment for risk stratification in patients with heart failure (15).

SES as a Prognostic Marker in Heart Failure

An observational cohort study in 2018 developed for ICU patients with a population of age 20-29 ; 83 females and 17 men ; 100 adult patients with unknown endocrine disorders. But the median age for death was 48 and 97.5% of them have euthyroid sick syndrome prevalence was higher in males (94%) and the main cause was sepsis, shock, and heart failure. Based on this study they found out

free triiodothyronine had greater sensitivity and reverse triiodothyronine had greater specificity to predict mortality (FT3 levels, with a median of 1.5pg/mL for those who died) (rT3 there was a higher value ; with a median of 0.56ng/mL for those who died and 0.35ng/mL for those who survived). But sampling bias existed as large women and less male population present (16).

Table 1: Prognostic value shown to know the importance of thyroid markers in terms of heart failure (16)

Marker	Finding	Prognostic Value
TSH	Lower levels associated with death	Moderate
fT3	< 2.9 pg/mL	Best sensitivity and accuracy
rT3	> 0.2 ng/mL	Best specificity
ESS	Present in 97.5% of deaths	Strong predictor of mortality

Prospective cohort study from 2015 to 2017 showed Low triiodothyronine syndrome and selenium deficiency where 59 consecutive patients hospitalized due to decompensated heart failure reduced ejection fraction NYHA III or IV and grouped as [A] low free t3(9) and [B] normal free t3 (50): prevalence of low T3 syndrome was 15.3% ($n = 9$) while the prevalence of selenium deficiency was 74.6%; Patients with low T3 syndrome had a lower body mass index and systolic blood pressure. They also more frequently suffered from peripheral edema and required inotropic drugs. Patients with low fT3 presented: low fT3/ft4 ratio, higher levels of NT-proBNP and hsCRP. They couldn't identify any significant correlation between selenium and fT3 levels. Study population relatively small and further investigation for selenium deficiency need to done as it negatively impact thyroid hormone metabolism by decrease the synthesis of thyroid hormone by decrease the function of iodothyronine deiodinase (form of selenoproteins) responsible for T4 to T3 conversion and calcium flux causing increase in atherogenesis and oxidative stress (3).

December 2017 to January 2019, there was a prospectively performed observation in 2 hospitals which studied about N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a useful marker for predicting death. 594 euthyroid patients hospitalized with acute decompensated HF; 27 patients died during hospitalization and 100 deaths were identified in patients discharged alive during one year follow-up This study showed 28.3 % of euthyroid patients with acute decompensated HF had Low Triiodothyronine Syndrome (LT3S).

In multivariable regression analysis, they found that variables, which partially reflect the status of nutrition (hemoglobin, albumin), liver (albumin) and kidney function (blood urea nitrogen), and

volume overload (NYHA functional class, systolic blood pressure), have a significant effect on LT3S. But was weak to provide additional prognostic value for in-hospital mortality (17).

So from the above given studies its proved that there are are some prognostic markers; low fT3 low fT3/ft4 ratio, higher levels of NT-proBNP and hsCRP and Free triiodothyronine had greater sensitivity and reverse triiodothyronine had greater specificity to predict mortality.

Therapeutic Potential of Thyroid Hormone Supplementation

A large clinical trial reported a group receiving parenteral nutrition within 48 h of admission to the ICU supplement insufficient enteral nutrition at the start and a parenteral nutrition group that did not start with a feeding regimen before day 8 in the ICU. Results showed that the toleration of a nutritional deficit during the first week of critical illness resulted in fewer complications and accelerated recovery as it proved that to have parenteral intake at 8 days was beneficial. This also showed a subanalysis ; that feeding late enhanced the changes in circulating concentrations of serum TH showing peripheral TH metabolism is clearly affected by decreased nutritional intake during acute critical illness. The subanalysis also suggested that the inactivation of T3 to rT3, as part of the fasting response ; might be a beneficial adaptation during acute illness because reduced amount of circulating active T3 could be interpreted as an attempt for the body to decrease the metabolic rate, reduce energy expenditure, and prevent protein breakdown, thereby promoting survival (18).

Randomised case control study that tells about the relationship between T3 supplementation and prognosis in two pilot groups of patients in the acute and chronic phase of septic shock with ESS. A total of 95 reported as septic shock patients with ESS were divided according to values of the thyroid hormones into low T3 and low T3T4 groups. Among 48 patients with low T3, 24 (50%) were randomized for 4 days with T3 supplementation and 24 (50%) to placebo. In the low T3 group, mortality was significantly higher in the T3 receiving group compared to the placebo receiving group In the low T3T4 group, mortality was significantly lower in the T3 receiving group compared to the placebo receiving group.

It also included analysis for a 28 days chart on primary outcome and laboratory analysis along with hemodynamics as secondary outcome. As this report suggested that T3 hormone supplementation for the first 4 days of the treatment of late phase of septic shock in patients with low serum levels of T3 and T4; it improves survival, shortens duration for mechanical ventilation and vasopressors requirement and helps in recognizing the inflammatory response in terms of lower platelets - lymphocytic ration (PLR),Neutrophil-lymphocytic ration (NLR), Modified glasgow prognostic score (mGPS) and Perfusion index (PI) scores compared to the placebo groups. The results showed a better survival rate during the chronic phase compared to acute case who was supplemented with T3. During chronic phase along with T3 supplementation, a lower incidence of anemia and hypoalbuminemia with better hemodynamic stability was also observed. Also they observed 4-day oral T3 hormone supplementation in septic shock patients was associated with a significant reduction

in 28-day mortality in the low T3T4 ESS group, while in the low T3 ESS group it was associated with a higher incidence of mortality. In addition, T3 treatment in the low T3T4 group enabled better maintenance of mean arterial pressure (MAP) with positive results of blood gas analysis.

The finding highlighted the importance of phenotyping thyroid hormone in septic shock and not universally beneficial and patients selection is based on a specific pattern of thyroid dysfunction (19).

So RCT studies investigating TH therapy in postoperative cardiac patients have yielded mixed findings. High- and low-dose intravenous T3 improved cardiac index for post-coronary artery bypass surgery, without any significantly affected mortality. Studies indicate that cardiopulmonary bypass can lead to a decrease in serum T3 levels, potentially contributing to postoperative hemodynamic dysfunction but this improved hemodynamic performance and reduced arrhythmia incidence. Although routine T3 administration is not recommended for cardiac surgery patients, it may be beneficial as a rescue agent for patients struggling to wean from cardiopulmonary bypass despite maximal inotropic support (20)

NTIS is also frequently observed in patients with COVID-19 and has been associated with disease severity. It is suggested that reduction in serum T3 levels have been a potential biomarker for severe illness in COVID-19. Experimental evidence shows that T3 could help prevent tissue hypoxia in sepsis. In order for this, a double-blind, placebo-controlled trial was designed to evaluate T3 administration in severe COVID-19 patients but the study was halted prematurely due to changing treatment protocols (20).

The choice of whether to administer T4 or T3 presents a challenge due to reduced T4-to-T3 conversion during critical illness and the potential mismatch between serum hormone levels and tissue availability. Timing is another key issue, as metabolic needs differ between the acute and chronic phases of illness.

Current Clinical Challenges and Knowledge Gaps

As NTI occurring in the acute phase of critical illness is to a large extent explained by concomitant fasting, and as acute NTI likely brings about being part of adaptive responses, the acute phase of critical illness is not that should be further investigated but patients in the prolonged phase of critical illness who are fully fed via the enteral or the parenteral route, who present with low plasma T4 and T3 concentrations who show symptoms and signs that could be compatible with (non-iatrogenic) hypothyroidism may be different and these patients should be included as patients of risk groups and show eligibility for inclusion in RCTs to assess the effect of treatment (21).

The acute stress or critical illness-induced alterations happening within the thyroid axis as these occur in the first days of critical illness are studied least in part by the concomitant macronutrient deficit. However, the NTI that occurs in prolonged critically ill patients, who continue to be dependent on ICU for weeks or months, may have a different stage of illness, in its origin, in its

impact and outcome. So further studies should perhaps target this specific and selected patient population at risk; after excluding iatrogenic drug changes and investigate the effect on outcome of treatment with hypothalamic releasing factors with strong RCTs studies.

As a potential challenging factor, serum TSH may be relatively low in critically ill patients with concomitant hypothyroidism as a result of a variety of drugs, like dopamine that inhibits TSH release, use of anticonvulsants and glucocorticoids should be noted, since these agents can lower (F)T4 (13).

Diagnosis for severe case of primary hypothyroidism in critically ill patients with NTIS made preferred loading dose of 300–500 μg intravenous of T4 which restored about 50% of circulating levels of T4 to euthyroid value, followed by 50–100 μg of intravenous LT4 daily until oral medication can be given. If clinical improvement is not seen within 24 to 48 h after the onset of intravenous LT4 treatment, T3 may be considered where 10 μg given intravenously within intervals of 4 h or 25 μg given intravenously every 8 hours. An unresolved issue; although some studies related to use of TH treatment with heart failure, some reports gave positive results. A small RCT in patients suffering with dilated cardiomyopathy shows positive results with use of levothyroxine treatment for 3 months with good prognosis on cardiac performance. The mechanism of ESS is still not fully understood. Idiopathic etiology that causes abnormalities in the production, transport, and metabolism of thyroid hormones, which can lead to ESS. Often, ESS is accompanied by changes in other endocrine systems, such as decreased gonadotropin hormone and increased serum ACTH (13).

A 2020 study included 956 patients with acute heart failure, and ESS occurred in 511 cases. Therefore Brain Natriuretic peptide (BNP), platelets (PLT) and albumin (ALB) became indicators for the early detection and identification of ESS. but there are no similar studies or reports related to this, so study requires further investigation (22).

There are many limitations; First, the number of research samples is relatively small. The distribution of disease types is quite diverse and different types of patients were analyzed together. For further research on the incidence of SES in ICUs, it is necessary to expand the size of samples between different hospitals. Second, the data collected in this research were obtained upon admission to the ICU, and no dynamic monitoring was performed. Finally, the variables included in this study's multivariate regression analysis meaning fixed predictors and variables are included and so many exclusion criteria are also included and further research is needed which also includes the exclusion criteria.

It is difficult to distinguish persistent hypothyroid symptoms with the typical HF symptoms and EES causing heart failure because of this studies need to be additionally explored in better-designed randomized clinical trials with rigorous selection criteria. The effect of therapeutic options could be assessed to see if there are any changes in LVEF, LVDD and NT-proBNP levels or through HF symptom alleviation, and correlated with TH improvement so dynamic monitoring is needed. Even though therapeutic interventions appear helpful and apt for disease, not always positive results can be seen in patients as different patients have different (1).

Future Directions and Clinical Implications

Studies consistently demonstrated that low t3 is causing increased mortality and also predicts cardiovascular mortality independent of traditional risk factors. NTIS also correlated with NYHA functional class, lower exercise capacity, ventricular remodeling. Elevated NT-proBNP levels there is also an enhanced risk stratification incorporated with other risk models include free T3, Total T3, FT3/FT4 ration, Reverse T3, NT-proBNP, troponins, renal function, Left ventricular ejection fraction as these models appears to improve prediction of mortality (10).

Standardized biomarkers currently available have strong correlation and HF severity and prognosis. There should be dynamic monitoring of patients as studies just relay on single thyroid hormone measurement like ; serial FT3 measurement, T3 replacement therapy showed significant benefits in heart contractility, reduced systemic vascular resistance, diastolic function improvement but evidence for these are inconsistent as no large scale RCT studies were made (13).

Screening recommendation for which heart failure population to be tested and frequency of monitoring should also be increased. Prognostic biomarkers along with HF risk prediction are set therapeutic recommendation of thyroid hormone supplementation along with efficacy and adverse effects of drugs, nutritional and selenium based intervention should be further studied but lack of large RCT is a major barrier for guideline recommendation (3).

Future studies related for selenium supplementation, correction of micronutrient deficiency, and personalized approaches with patient of persistent low T3,elevated reverse t3 and specific deiodinase abnormalities as these groups may benefit from targeted hormone intervention than unselected heart failure population (3). Large multi center randomized trails, validation of FT3 AND FT3/FT4 ratio for prognostic biomarker, precision medicine studies for phenotyping heart failure further to be researched (13).

Future studies should determine if NTIS behaves differently in heart failure reduced ejection fraction(HFrEF), heart failure mildly reduced ejection fraction(HFmrEF), heart failure preserved ejection fraction(HFpEF), acute decompensated stage HF and advance end stage HF along with development of integrated risk score combination (17).

CONCLUSION

Sick Euthyroid Syndrome (SES), also known as Non-thyroidal Illness Syndrome (NTIS) or Low T3 Syndrome is becoming a more well known clinically relevant endocrine change in HF patients. The findings in this literature review are consistent and indicate decreased levels of triiodothyronine (T3) in the circulation are associated with more severe heart failure, less cardiac function, greater hospitalizations and mortality. The changes in SES are not just an isolated hormonal defect, but they are a result of the complex interaction of inflammation, oxidative stress, neurohormonal activation and altered thyroid hormone metabolism occurring in the course of progressive cardiac dysfunction.

Current literature corroborates the idea of low T3 being an important prognostic marker in heart failure. The use of biomarkers like free T3, reverse T3, FT3/FT4 ratio and the interaction of these with known biomarkers like NT-proBNP gives information about disease severity and patient outcomes. Together, these results indicate that measurement of thyroid hormone status could be used to supplement traditional clinical assessment to identify patients with increased risk for cardiovascular outcomes and disease course.

Whether thyroid hormone replacement is therapeutic, though, is unclear. Although improvements in cardiac performance and hemodynamic parameters have been reported in experimental studies and in a few small clinical trials, there is still some variability in the data, with different patient groups, different treatment regimens, and small numbers of patients. Therefore, there is a lack of data to support routine thyroid hormone replacement in patients with heart failure and SES.

The overall conclusion from the available data is that Sick Euthyroid Syndrome is not a mere biochemical reaction to the severity of the disease but is a significant part of the disease process in heart failure. It has strong association with clinical outcomes, thus it could be a valuable tool for prognosis, but it must be interpreted carefully in the context of the clinical situation. An improved understanding of thyroid hormone dysregulation and cardiovascular disease will further optimize the management of patients with heart failure and aid in understanding of this complex endocrine–cardiac interaction.

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