The Prevalence of low T3 syndrome in chronic heart failure: A Hospital-based study

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ABSTRACT

Background: Effect of thyroid hormone on cardiac functions is mediated by biologically active T3 which binds to nuclear TR. There is increasing evidence that patients with mild thyroid dysfunctions are presenting with adverse cardiovascular manifestations which includes heart failure.

Aim: The present study aimed to determine the existence of low T3 syndrome in patients with chronic heart failure.

Material and Methods: This prospective study was conducted in the Department of General Medicine and Cardiology, KMC, and MGM Hospital, Warangal. patients with heart failure were included in the study. A total of n=100 patients were included in the study detailed physical examination was conducted to assess the patient's volume status (rales, edema, jugular venous distension), weight, height, body mass index, and orthostatic blood pressure changes. Complete blood count, blood glucose (fasting and 2 hours postprandial), Fasting serum lipid profile, blood urea, serum creatinine, and serum electrolytes were measured in all patients. Two-dimensional echocardiography was done in patients.

Results: Analysis of Echocardiography parametersCompared to patients who were alive (n=90),left ventricular end-diastolic diameter was higher in those whodied (n=10). The mean ejection fraction in died and alive groups were27.19% and 35.12% respectively. Persons who died had asignificantly lower ejection fraction than those alive.When the mean ejection fraction was compared betweenpatients with low total T_3(T3<80 ng/dl) and normal T_3, patients with low T_3 had a mean ejection fraction of 29.2% and those with normal T_3 levels had a mean ejection fraction of 34.78%. This indicates the mean ejection fraction is lower in patients with low total T_3 levels.

Conclusion: Within the limitations of the present study it can be concluded that the prevalence of low T_3 syndrome in patients with chronic heart failure is common. It was found that patients with lower T_3 levels were having a lower ejection fraction.The LVEDD diameterwas negatively correlated with total T3. Therefore, Total T_3 levels can be used as an adjunct to other parameters for risk stratification and survival estimation in chronic heart failure.

Key words: *Low T_3 Syndrome, Chronic Heart Failure,Ejection fraction, Left ventricular end-diastolic diameter*

Introduction

Thyroid hormone plays a crucial role in cardiovascular homeostasis in physiological as well as pathological conditions. Heart failure can trigger changes in metabolism and peripheral thyroid hormone concentration in euthyroid patients. In heart failure, the alteration of thyroid functions is referred to as low-T_3 (triiodothyronine) syndrome or euthyroid sick syndrome marked by a reduction in serum total $T_3$and free T_3 with normal levels of T_4 and thyrotropin. This low-T3 syndrome is an adaptive compensatory and beneficial response that decreases the energy consumption of the diseased body. Heart failure is a complex clinical syndrome that could be the result of any structural or functional cardiac disorders that impairs the ability of ventricles to fill or eject blood (reduced ejection).[1] Coronary Artery Disease (CAD) accounts for a substantial portion of patients with chronic heart failure. Survival is markedly shortened in patients with heart failure. [2]The overall 5-year rate of mortality in patients with heart failure is 50% and 1-year mortality in patients with end-stage heart failure can be as high as 75%. 2. Role of various biological and neurohormonal factors in risk assessment of chronic heart failure has been studied in various clinical studies. Noradrenaline, Angiotensin II, Atrial natriuretic peptide (ANP), and Brain Natriuretic Peptide (BNP) have been used as prognostic markers for patients with heart failure. [3]The pathophysiology of low T_3 syndrome is due to impaired peripheral deiodination of T_4 to T_3 secondary todecreased activity of type I deiodinase enzyme, whichdeiodinases T4 to T_3. Normally 20% of T_3 production comesfrom thyroidal secretion and 80% from peripheral deiodinationof T4. Though the production of T3 by the thyroid gland is normal, the peripheral production of T_3 is decreased. Production of rT3 isunchanged, while its clearance is diminished leading to raisedrT_3 levels.The syndromeaffects both sexes equally and affects people of all ages.Because of the increased incidence of chronic illness atadvanced ages the syndrome is more common in the elderly agegroup. Low T3 (triiodothyronine) levels correlate with increased mortality in chronic heart failure patients and benefits can be gained from

thyroid supplementation. [4, 5] Recent are of focus in studies have explored the use of triiodothyronine levels to predict mortality in heart failure patients. They are very few studies done in our area to determine the relation of low T^3 levels and heart failure. Therefore, we conducted the present study to determine the prevalence of low T^3 levels in heart failure and the role of Total T^3 when estimating severity in patientswith chronic heart failure as an adjunct to clinical and functionalparameters.

Material and Methods

This prospective study was conducted in the Department of General Medicine and Cardiology, KMC, and MGM Hospital, Warangal from Jan 2017 to June 2019. Institutional Ethical Committee approval was taken for the study. Written permission was obtained from all the patients of the study.

Inclusion Criteria

1. Those diagnosed with heart failure for more than 3 months
2. Ventricular ejection fraction levels < 45%
3. LV end diastolic diameter of > 56mm

Exclusion Criteria

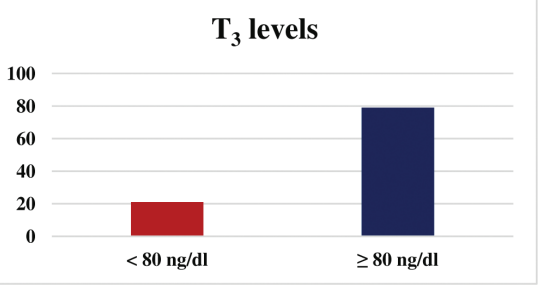
1. History of thyroid dysfunctions
2. History of revascularization procedures
3. Amiodarone therapy
4. Any other severe systemic illnesses

Based on the inclusion and exclusion criteria successive patients with heart failure were included in the study. A total of n=100 patients were included in the study. A questionnaire was prepared to note the duration,symptoms, and treatment of heart failure. Questions were asked concerning chest pain, dyspnoea, syncope, cough, smoking, andmedications. All previous clinical records of the patients were analyzed in detail. Based on the degree of effort needed to elicitsymptoms patients were assigned to NYHA (New York HeartAssociation) class I to IV.A detailed physical examination was conducted to assessthe patient's volume status (rales, edema, jugular venous distension),weight, height, body mass index, and orthostatic blood pressurechanges.Complete blood count, blood glucose (fasting and 2 hours postprandial), Fasting serum lipid profile, blood urea, serumcreatinine, and serum electrolytes were measured in all patients.Two-dimensional echocardiography was done in the cardiologydepartment of Mahatma Gandhi general hospital was reviewed for evidence of atrial enlargement, ventricularhypertrophy, evidence of antecedent myocardial infarction, andconduction blocks. Thyroid hormonemeasurements TSH, total T_3, total T_4, free T_3, free T_4 were made inall patients in the same fasting morning sample. All the above datawere obtained between two to five days of enrolment in the study.Chest X-ray posteroanterior view was done in all patients to note pulmonary congestion, pleural effusion, and to estimate cardiothoracic ratio M-mode echocardiography was used to assess the left ventricle dimensions. The left ventricle internal dimension in end-systole (LVESD) and end-diastole (LVEDD) are measured at the level of mitral valve leaflet tips in the parasternal long-axis view. Measurements are taken from the endocardium of the left surface of the interventricular septum to the endocardium of the left ventricle posterior wall. In adults, the normal range of LVEDD is 3.5 to 5.6 centimeters. The normal range of LVESD is 2 to 4 centimeters. 2-D echo imaging in apical 4 chambers, parasternal long-axis, and parasternal short-axis views were used to assess ventricular and valvular movement.All statistical analyses were performed using SPSS version 19 on Windows format.

Results

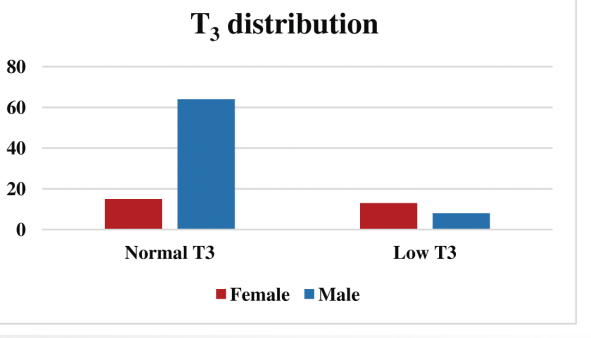
Total T_3 values of all the n=100 patients were computed. Out of the n=100 patients, n=28 were females and n=72 were male patients. The prevalence of low T_3 is found to be 21% had Total T_3 less than the lower limit of 80 ng/dl. The mean age of patients in the Low T3 group is 62.5 years which is higher than the mean age in patients with the Normal T_3 group 52.0 years.The difference of means between the two groups is analyzed using an independent T-test which is statistically significant.The mean BMI of patients in the Low T_3 group is 25.56 kg/m2which is higherthan the mean BMI in patients with the Normal T_3 group 25.10 kg/m2.Thedifference of means between the two groups is analyzed usingan independent T-test which is not statistically significant.

Figure 1: Distribution of patients according to T3 levels



N=13 out of total n=28 females were found with low T_3 levels. Similarly, in males n=8 out of total n=72 cases were found with low T_3 levels. The difference of proportions between the two groups is analyzed using the Chi-square test which is not statistically significant.

Figure 2: Sex distribution of cases according to T3 levels



Analysis of Echocardiography parametersCompared to patients who were alive (n=90),left ventricular end-diastolic diameter was higher in those whodied (n=10). The mean ejection fraction in died and alive groups were27.19% and 35.12% respectively. Persons who died had asignificantly lower ejection fraction than those alive.When the mean ejection fraction was compared betweenpatients with low total T_3(T_3<80 ng/dl) and normal T_3, patients with low T_3 had a mean ejection fraction of 29.2% and those with normal T_3 levels had a mean ejection fraction of 34.78%. Thisindicates mean ejection fraction is lower in patients with low total T^3 levels (table 1)

Table 1: Analysis of Echocardiography parameters

Variable	Group	N	Mean	SD	P-valueStudent t-test
Ejection Fraction	Died Alive	10 90	27.19 35.12	6.99 4.98	0.02*
LVEDD	Died Alive	10 90	64.04 60.84	5.75 3.22	0.01*

* Significant

N=32 out of n=100 cases were with the history of hypertension of which n=17 cases were in the low T_3 group and the rest were with normal T_3 levels. The comparison of hypertension within low T_3 was done showing the p values as 0.014 as significant given in table 2.

Table 2: hypertension distribution in cases of the study

Hypertension	Low T3	Normal T3	P values
Present	17	15	0.014*
Absent	04	64	

* Significant

A comparison between dyslipidemia, between normal T_3 and low T_3, shows the values were found to be significant. Out n=10 patients dead n=7 cases were of dyslipidemia of which n=5 cases were with low T_3 and n=2 cases were of normal T_3. As far as obesity is concerned the comparison between normal T_3 and low T_3 did not reveal any significant values. Similarly, for beta-blockers, the values were not found to be significant and smoking also did not show any significance between the normal T_3 and low T_3 levels.

Table 3: Analysis of dyslipidemia, obesity, beta-blocker use, and smoking

Variable			Low T3	P values
Dyslipidemia	Present	18	10	0.04*
	Absent	54	11	
Obesity	Present	15	07	0.998
	Absent	57	14	
Beta-blocker	Present	10	11	0.654
	Absent	05	06	
Smoking	Present	04	04	0.128
	Absent	67	17	

* Significant

The results show a significant relationship between total T_3 with ejection fraction, indicating patients who have low ejection fraction have low total T_3 levels. Total T_3 levels did not correlate with sex. There is a significant correlation betweenadvancing age and lower total T_3 levels. Using a cutof total T_3 level of 80 ng/dl (the lower limit of normal) two subgroups were identified and Kaplan-Meiersurvival analysis was compiled. Survival at 24 months in a low total T_3 group was found to be less than the group with total T_3 80 ng/dl and above.

Discussion

The results of the present study showed that the death was significantly related to low T_3 levels, low ejection fraction, and higher left ventricular end-diastolic diameter (LVEDD). Studies have shown that changes in thyroid metabolism characterized by a reduction in biologically active T_3 have been reported in HF and commonly interpreted as a compensatory mechanism.[6] In a cohort of 573 unselected cardiac patients, the probability of death was significantly higher in patients with low T_3 syndrome; free (F)T3 resulted also in a powerful independent predictor of cardiac and cumulative death.[7] Kozdag G et al;[8] found a significant correlation between low T_3 values and reduced ejection fraction. We also found a significant negative correlation of low total T_3 levels with advancing age which means as the age of patients increases the prevalence of Low T_3 increases. This contrasts with the study by Pingitore et al;[9] who did not find any correlation between low total T_3 and ejectionfraction.In the current study Kaplan-Meyer survivalcurves of patients with reduced left ventricular ejection fraction (LVEF)and total T3 showed the highest mortality when compared with thatof patients with similar LVEF but normal total T_3 which indicate that low T_3 patients are a greater risk of death. From our study, we found that age, ejection fraction, and T_3 levels are associated with high mortality. And there was a correlation of total T_3 with age and ejection fraction. Opasich et al;[10] found low T_3 syndrome was not an independent negative prognostic factor but has a definite role when used along with other parameters. Echocardiographic alterations, and mortality in patients with dilated cardiomyopathy. Hamilton et al;[11] reinforced previous data in a smaller cohort of patients showing the potential capacity of prognostic stratification of the altered THmetabolism in HF.Zargar et al;[12] studied sick euthyroid syndrome in chronic nonthyroidal illness and found a prevalence of 20.60%. There has been some evidence that HF patients have gained a small but significant benefit when treated with thyroxine. However, there are only a few studies that have tested the use of synthetic T_4 or T_3 in the treatment of cardiac dysfunction.[13, 14] However, there are also concerns of noncardiac collateral effects of hormone increasing oxygen consumption, heart rate, and negative effects on protein and fat metabolism. An alternative approach is to use TH analogs with fewer side effects such as 3,5-diiodothyropropionic acid (DITPA)with minimal effects on heart rate and metabolic activity.[15, 16] We in the present study used only a minimal dose of T_4 in cases with low T_3 syndrome. Although it proved to be beneficial in some patients, the presence of other confounding factors was responsible for the death of some patients.

Conclusion

Within the limitations of the present study, it can be concluded that the prevalence of low T_3 syndrome in patients with chronic heart failure is common. It was found that patients with lower T_3 levels were having a lower ejection fraction.The LVEDD diameterwas negatively correlated with total T_3. Therefore, Total T_3 levels can be used as an adjunct to other parameters for risk stratification and survival estimation in chronic heart failure.

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