

Original Research Article

A study of association between serum TSH levels and severity of heart failure in subclinical hypothyroidism

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ABSTRACT

Background: Cardiovascular diseases account for most common cause of death in India and world so far. One of the established risk factors for HF is subclinical hypothyroidism. Our study aimed to study the relationship between TSH levels in subclinical hypothyroidism and the clinical severity of HF in patients with pre-existing HF.

Methods: This cross-sectional study was conducted in the hospitals attached to Bangalore medical college and research Institute. 51 patients with HF who had subclinical hypothyroidism who satisfied the inclusion criteria were included, Data was collected in the form of history, clinical examination and relevant investigations. Statistical analysis was performed using SPSS software, $p < 0.05$ was considered significant.

Results: Out of 51 patients, 70.6% were males and 29.4% were females and majority of the patients (33.3%) were aged 40 to 50 years. 35.3% patients had LV global hypokinesia, 31.4% had LV diastolic dysfunction and 21.6% had RWMA. Chi-square test showed statistically significant association between TSH and RWMA ($p=0.00$). Out of the 51 patients, NYHA Class-1 were 9.8%, Class-2 were 31.4%, Class-3 were 27.5% and Class-4 were 31.4%. Chi-square test showed no statistically significant association between TSH levels and NYHA class ($p=0.32$).

Conclusions: There was significant association between features suggestive of cardiac compromise on 2D-echocardiography with subclinical hypothyroidism, but there was no significant association between the severity of HF assessed clinically by NYHA class with subclinical hypothyroidism. Hence, our study couldn't establish an association between severity of subclinical hypothyroidism on clinical severity of existing HF.

Keywords: Subclinical hypothyroidism, Heart failure, Thyroid stimulating hormone

INTRODUCTION

Thyroid hormones have wide effects on the body and play a crucial role in the homeostasis of cardiovascular system.¹ While the number of cardiovascular morbidity and deaths have been on the rise, patients with hypothyroidism are found to have an increased risk of cardiovascular abnormalities, such as accelerated atherosclerosis, dyslipidemia, hypertension etc.² Subclinical hypothyroidism refers to patients who have an elevated TSH levels and a normal free thyroxine (T4) level.³

Subclinical hypothyroidism is becoming increasingly recognized because the performance of thyroid function tests has substantially increased in primary care settings.⁴ It is an easily treatable condition. It has been observed to be associated with both systolic and diastolic cardiac dysfunction, pericardial effusion, brady arrhythmias etc. and hence, resultant cardiac morbidity. Some studies have shown that thyroxine replacement improved measurements of cardiac function in such patients.⁵ However, there have also been studies that have shown no effect. As the number of hospitalizations for HF has

greatly increased, examining a common and easily treatable potential risk factor for HF is warranted.⁶ Moreover, data on cardiovascular outcomes in patients with subclinical hypothyroidism are limited.⁷ It is generally accepted to treat the abnormal free thyroxine levels of overt thyroid dysfunction but the indications and threshold TSH for treatment of subclinical hypothyroidism are areas of clinical controversy.⁸ No evidence exists to support an association between clinical severity of heart failure and a TSH level of less than 10.0 mIU/l. Again, most studies were performed in overt hypothyroidism and studies that were performed in patients with SCH, did not categorize the severity of HF for degrees of TSH elevation, and hence, data remains insufficient for a TSH level less than 10 mIU/l while there is strong evidence of increasing severity of HF for a TSH level greater than 10 mIU/l or for overt hypothyroidism.⁹

Studies are needed to establish a definitive cut off of TSH value in SCH beyond which treatment is warranted in patients for HF if at all there is a significant association between elevating TSH levels and clinical severity of HF. This study will be aimed at analyzing the relationship between different levels of serum TSH values and clinical severity of heart failure.

METHODS

Study population

The study was conducted on In-patients with heart failure with subclinical hypothyroidism admitted in Department of Internal Medicine of hospitals attached to Bangalore medical college and research Institute, Bangalore, from November 2018 to May 2020, 51 adult population with age more than 18 years with heart failure according to Framingham's heart criteria with sub clinical hypothyroidism.

Inclusion criteria

Patients who are willing to participate in the study and give informed written consent. With age more than 18 years. Patients with heart failure according to Framingham's heart criteria with sub clinical hypothyroidism were included.

Exclusion criteria

Patients who are not willing to participate in the study and not willing to give informed consent. Patients with overt hypothyroidism, on antithyroid medications or Amiodarone. Critically ill patients like patients with shock septicemia, multi organ dysfunction etc. Patients with valvular heart diseases and patients with anemia Patients with acute or chronic respiratory disorders like pneumonia, chronic obstructive pulmonary disease or interstitial lung diseases or bronchial asthma. Patients with end stage renal disease or cirrhotic liver disease were excluded.

Data collection

Written informed consent was taken from the patients. Data was collected by detailed relevant history, clinical examination and investigations. Data of all the patients satisfying the inclusion and exclusion criteria was collected. For the purpose of the study, the following operational standard criteria/definitions were used: questionnaire regarding basic demographic data, clinical history and examination. Patients were diagnosed to have Heart failure based on the Framingham criteria for the diagnosis of heart failure.

Framingham criteria for congestive heart failure

Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. Major criteria: Paroxysmal nocturnal dyspnea, Neck vein distention, Rales, Radiographic cardiomegaly (increasing heart size on chest radiography), Acute pulmonary edema, S3 gallop, Increased central venous pressure (>16 cm H₂O at right atrium), Hepato jugular reflux, Weight loss >4.5 kg in 5 days in response to treatment. Minor criteria: Bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by one third from maximum recorded, tachycardia (heart rate >120 beats/min.). Minor criteria are acceptable only if they cannot be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome). The Framingham heart study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.

These patients were subjected to thyroid function tests which include TSH and free T₄ and patients with sub clinical hypothyroidism was identified, Subclinical hypothyroidism (SCH) is defined as a serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine when thyroid function has been stable for weeks or more, the hypothalamic-pituitary-thyroid axis is normal, and there is an absence of recent or ongoing severe illness. TSH levels will be classified into 3 classes as follows: TSH A: 4.6 mIU/l to 7 mIU/l, TSH B: 7.1 mIU/l to 10mIU/l 90, TSH C: greater than 10 mIU/l. The severity of the heart failure will be assessed as per the New York Heart Association (NYHA) classification and the class of severity will be correlated with the TSH levels.¹³

Statistical analysis

Statistical analysis was performed using SPSS software. Data was analyzed by descriptive statistics. Student's t-test was used for significant difference between two means. Pearson correlational analysis/Spearman's rank correlation was used to assess the correlation between NYHA class and TSH levels.

RESULTS

The present study was conducted in the department of internal medicine, Bangalore medical college and research institute. A total of 51 cases of heart failure with subclinical hypothyroidism were taken according to the proforma as detailed in the methodology and the data obtained were analyzed and the results obtained were as follows: Out of 51 (100%) patients, 17 (33.3%) patients were aged between 40 to 50 years followed by 16(31.4%) patients aged between 51 to 60 years; 11 (21.6%) patients aged 61 to 70 years and 7 (13.7%) patients aged above 70 years (Table 1).

Table 1: Age wise distribution of the patients.

Age (years)	N	%
40 to 50	17	33.3
51 to 60	16	31.4
61 to 70	11	21.6
Above 70	7	13.7
Total	51	100.0

Out of 51 (100%) patients, 24 (47.10%) were TSH A, 21 (41.20%) were TSH B and 6 (11.8%) were TSH C. Chi-square test showed no statistically significant association between TSH classes and age (p=0.63) (Table 2).

Table 2: Correlation of age with TSH.

Age (years)	TSH			Total
	A	B	C	
40 to 50	N 8	8	1	17
	% 15.70	15.70	2.00	33.30
51 to 60	N 8	6	2	16
	% 15.70	11.80	3.90	31.40
61 to 70	N 4	4	3	11
	% 7.80	7.80	5.90	21.60
Above 70	N 4	3	0	7
	% 7.80	5.90	0.00	13.70
Total	N 24	21	6	51
	% 47.10	41.20	11.80	100.00
Chi-square value=4.29				
P value=0.63				

Out of 51 (100%) patients, 36 (70.6%) were males and 15 (29.4%) were females. Out of 51 (100%) patients, 36 (70.6%) were males and 15 (29.4%) were females. Out of 15 (29.4%) females, majority were in TSH B whereas out of 36 (70.6%) males, 21 (41.2%) belonged to TSH A. Chi-square test showed statistically significant association between TSH classes and gender (p=0.042) (Table 3). Chest pain was seen more in patients with TSH A- 15 (29.4%) whereas breathlessness- 18 (35.3%), palpitation- 1 (2%), Syncope/giddiness-3 (5.9%), Fatigue-18 (35.3%) and abdominal pain-4 (7.8%) was seen more in TSH B. Chi-square test showed statistically significant association with respect to chest pain (p=0.042), fatigue (p=0.034) and abdominal pain (p=0.004) Out of 28(54.9%) patients who

had diabetes mellitus, 14 (27.5%) were in TSH A. Similarly, out of 26 (51%) patients having Hypertension, 13 (25.5%) patients were in TSH A.

Table 3: Correlation of gender with TSH.

Gender	TSH			Total
	A	B	C	
Female	N 3	9	3	15
	% 5.9	17.6	5.9	29.4
Male	N 21	12	3	36
	% 41.2	23.5	5.9	70.6
Total	N 24	21	6	51
	% 47.1	41.2	11.8	100.0
Chi-square value=6.36				
P value=0.042				

Chi-square test was applied to compare the co-morbidities with TSH. Chi-square test showed no statistically significant association with respect to DM (p=0.89) and HTN (p=0.65). Out of 23 (45.1%) patients who had smoking habit, 15 (29.4%) were in TSH A. Out of 8 (15.7%) patients having alcohol habit, 5 (9.8%) patients were in TSH B. Chi-square test showed statistically significant association with respect to smoking (p=0.03) and not with alcohol.

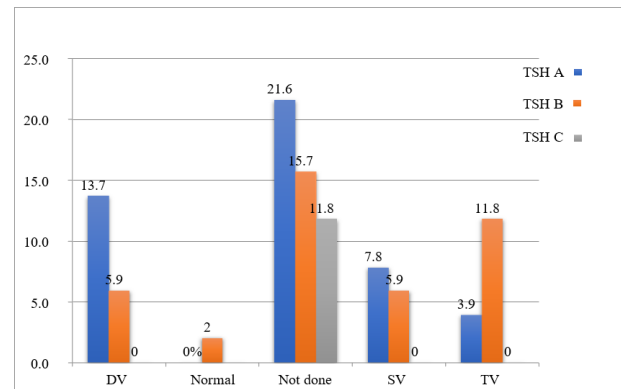


Figure 1: Correlation of coronary angiogram results with TSH levels.

Out of 51 (100%) patients, 50 (98%) had sinus and 1 (2%) subject had atrial fibrillation. Out of 51 (100%) patients, 17 (33.3%) had poor R wave progression, 13 (25.5%) had t wave inversions in V5.V6., 3.9% had malignant ectopics, 5.9% had low voltage qrs in all leads, 9.8% had poor r wave progression with t wave inversions, 2% had RBBB and 13.7% had LVH. Chi-square test showed statistically significant association between TSH and 2decho findings of RWMA and PAH (p=0.00, PAH (p=0.001) (Table 4). Coronary angiogram was done in 26 patients out of which, it was found that 10 (19.6%) patients had DVD, 7 (13.7%) patients had SVD and 8 (15.7%) patients had TVD. 1 patient however, had normal coronaries. Chi-square test showed that there was no statistically significant association (p=0.121) (Figure 1). Out of the 51 patients, 9.8% belonged to NYHA class 1, 31.4% belonged to

NYHA class 2, 27.5% belonged to NYHA class 3 and 31.4% belonged to NYHA class 4. Majority of the patients i.e., 24 (47.05%) belonged to TSH-A, 21 (41.17%) belonged to TSH-B and 6 patients (11.76%) belonged to TSH-C. Out of 24 patients in TSH A, 9 (37.5%) had NYHA 3. Out of 21 patients having TSH B, 7 (33.3%) each had NYHA 2 and 4. Chi-square test showed no statistically significant association between TSH and NYHA ($p=0.32$) (Figure 2).

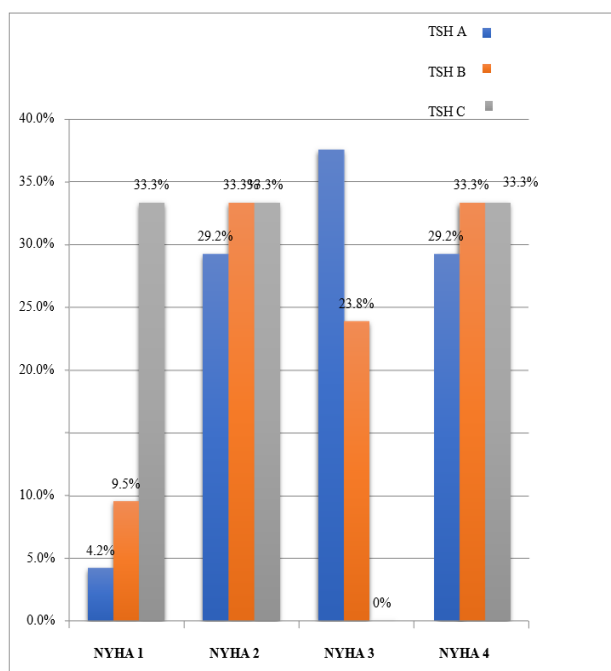


Figure 2: correlation of NYHA classes and TSH levels.

DISCUSSION

We in the modern era have evidence-based medicine for majority of the established co-morbid illnesses including heart failure. However, despite several data, heart failure still continues to be a main cause of cardiovascular mortality. Hence, more studies are required to explore and understand the risk factors that cause and worsen heart failure, one of those being SCH discussed in our study. The severity of SCH as evidenced by increasing levels of TSH was correlated with NYHA class of heart failure.

Age

In this study, out of 51 (100%) patients, majority of the patients 17 (33.3%) were aged between 40 to 50 years followed by 16 (31.4%) patients aged between 51 to 60 years; 11 (21.6%) patients aged 61 to 70 years and 7 (13.7%) patients aged above 70 years. However, in general, it is hypothesized that as the aging process leads to a hypothyroid status termed “physiological aging” resulting in a reduction of the basal metabolism.¹⁴

Gender

Out of 51 patients, 36(70.6%) were males and 15(29.4%) were females. Similar data was obtained in a study conducted by Kuchulakanti et al, SCH was seen in 58.5% (38) males and 41.5 females.¹⁵ This could likely be possible because the incidence of heart failure is higher in males compared to females. Chi-square test showed statistically significant association between TSH classes and gender ($p=0.042$). It was noted that males were on the lower end of TSH as compared to females that was consistent with Zhang et al where males showed lower TSH but higher FT3 and FT4 than women.¹⁶

Co-morbidities

Out of 51 patients in our study, 28 (54.9%) patients had Diabetes Mellitus, and 26 (51%) patients had hypertension.

Clinical features

Amongst complaints, majority had breathlessness. Incidence of PND was most common i.e., 27.5% followed by neck vein distension which was 21.6%. The incidence of s3/s4 was 11.8%, hepatojugular reflex was 7.8%, murmurs was 2.0%, basal crepitations was 15.7%, acute pulmonary edema was 15.7%, pedal edema was 17.6%, and nocturnal cough was 25.5%. Chi-square test showed statistically significant association between TSH and neck vein distension ($p=0.012$), Hepatojugular reflex ($p=0.045$), pedal oedema ($p=0.02$), nocturnal cough ($p=0.00$) and PND ($p=0.002$). while majority of patients belonged to both NYHA class-2 and 3, 31.4%, the least number of patients belonged to class-1(9.8%).

Lipid profile

Our study showed a significant association between TG and SCH while there was no significant association found between HDL-C or LDL-C. As evidenced by Efstathiadou et al on the contrary, patients with SCH had significantly higher levels of TC, LDL-C, Apo B and Lipoprotein (a), thus displaying a more atherogenic lipid profile when compared with healthy individuals. Also, supplementation of thyroxine had no impact on improving lipid profile.¹⁷

Electrocardiogram abnormalities

Generally, SCH is associated with sinus bradycardia, pan low voltage QRS-complexes. In Davie et al, where a total of 96 patients with echocardiographic proven left heart failure were taken. Major ECG abnormalities (atrial fibrillation, previous myocardial infarction, left ventricular hypertrophy, bundle branch block or left axis deviation) were identified in 90 patients. Out of 51 (100%) patients in our study, 17 (33.3%) had poor R wave progression, 13 (25.5%) had t wave inversion in V5.V6, suggestive of LV-failure and ventricular strain pattern. Majority of our patients had coronary artery diseases leading to ischemic cardiomyopathy.

Echocardiographic findings

Our study had a majority of patients with lv global hypokinesia (35.3%) followed by LV diastolic dysfunction (31.4%) followed by RWMA (21.6%). Chi-square test showed statistically significant association between TSH

and 2d echo findings of RWMA and PAH (p=0.00) suggesting that there was a significant association between SCH and IHD in the form of RWMA and PAH (p=0.00) suggesting that there was a significant association between SCH and IHD in the form of RWMA.

Table 4: Correlation between 2d echo cardiography findings and TSH levels.

Parameters		TSH-A, B, C			Total	Chi- square value	P value	
		A	B	C				
2d echo	LV global hypokinesia	N	2	13	3	31.56	0.00	
		%	3.9	25.5	5.9			18
	LV global hypokinesia, dilated RA, LA and RV	N	1	1	0			2
		%	2.0	2.0	0.0			3.9
	LVDD	N	16	0	0			16
		%	31.4	0.0	0.0			31.4
	RWMA	N	3	5	3			11
		%	5.9	9.8	5.9			21.6
	RWMA, dilated LA, LV	N	2	2	0			4
		%	3.9	3.9	0.0			7.8
PAH	Mild	N	5	5	0	22.22	0.001	
		%	9.8	9.8	0.0			10
	Moderate	N	0	3	3			6
		%	0.0	5.9	5.9			11.8
	No	N	19	8	3			30
		%	37.3	15.7	5.9			58.8
	Severe	N	0	5	0			5
		%	0.0	9.8	0.0			9.8
Pericardial effusion	Minimal	N	0	2	3	13.57	0.001	
		%	0.0	3.9	5.9			9.8
	No	N	24	19	3			46
		%	47.1	37.3	5.9			90.2

In Rodondi et al, the risk of HF was not increased among the high proportions of older adults with TSH levels between 4.5 and 9.9 mIU/l while those with TSH \geq 10.0 had a higher peak E velocity at baseline, an echocardiographic measurement of diastolic function that was associated with higher incident HF in their cohort sample.¹⁸ Accordingly, Biondi et al, demonstrated a marked increase in Left ventricular mass in patients with endogenous subclinical hyperthyroidism.¹⁹

Coronary angiogram

Total 50.9% (26) of the patients had undergone CAG of which 1 patient had normal coronaries. Although SCH is associated with increased risk of atherosclerosis, in our study, where majority of the patients had DVD followed by TVD followed by SVD, Chi-square test showed no statistically significant association between SCH and coronary angiogram. A greater sample size would be needed to establish whether or not a definitive association is there since our study only involved 26 patients with CAG (p=0.121).

Severity of heart failure

The severity of heart failure was assessed objectively by the NYHA classification in our study. The main objective was to compare the severity of heart failure to the severity of SCH as evidenced by elevating levels of TSH and to find association as to whether heart failure severity increased with increasing severity of SCH. For this, we compared the TSH levels which were classified into 3 classes i.e., TSH-A, TSH-B and TSH-C with NYHA classes 1 to 4. It was observed that out of 24 patients in TSH A, 9 (37.5%) had NYHA 3. Out of 21 patients having TSH B, 7 (33.3%) each had NYHA 2 and 4.

Chi-square test showed no statistically significant association between TSH and NYHA (p=0.32) suggesting that there was no definitive relationship between severity of heart failure and SCH. While there are new data supporting improved outcomes in younger (<70 years) CHD patients treated with T4.²⁰ On the other hand, a Cochrane review from 2007 assessed 12 RCTs of T4 replacement in patients with SCH and concluded that replacement therapy for SCH did not result in improved

survival or decreased CV morbidity.²¹ Hence, further studies with larger sample sizes are needed to establish the definitive effect of SCH on HF and the impact of treatment on HF.

CONCLUSION

Cardiovascular diseases account for most common cause of death in India and world so far. It is important to establish the risk factors for the same and to prevent their occurrence and treat those as a part of primordial and primary prevention. Sub clinical hypothyroidism is known to be associated with cardiovascular risk factors. However, the relationship between Subclinical hypothyroidism and severity of heart failure still remains understudied. Our study aimed to study the relation between serum TS levels in SCH and the severity of HF in patients with pre-existing HF. Our study showed significant relationship between TSH levels in SCH and hypertriglyceridemia, which in itself is a risk for heart failure. Also, there was a significant association between features suggestive of cardiac compromise on 2D echocardiography with TSH levels in SCH. However, there was no significant association seen between the clinical severity of heart failure assessed by NYHA class with TSH levels in sub clinical hypothyroidism. Hence, our study reinforced the findings from several other studies that subclinical hypothyroidism was associated with risk factors of heart failure but couldn't establish an association between severity of SCH on clinical severity of existing HF. Our study however throws light on the fact that SCH needs early detection and treatment of the same in order to control cardiovascular risk factors and hence cardiovascular compromise and hence cardiovascular morbidity.

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