RELATIONSHIP BETWEEN THYROID FUNCTION AND CORONARY ARTERY DISEASE SEVERITY IN TERTIARY CARE HOSPITAL, KANCHIPURAM

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Abstract

This study aimed to assess the relationship between thyroid function and coronary artery disease severity. Cardiovascular disease and related mortality have emerged as a major health burden worldwide with atherosclerosis being the major cause. Thyroid dysfunction results in changes in blood pressure. The correlation between irregular thyroid function and coronary artery disease is studied by many researchers. This is a randomized, double-blinded parallel arm study with a total of 300 patients diagnosed with coronary artery disease and thyroid dysfunction. Patients were block randomised based on third-party allocation (1:1). Concealment was done through SNOSE (Sequentially Numbered Opaquely Sealed Envelope). The presence of overt hypothyroidism was significantly more in the high-risk syntax score of 28.1% compared to the intermediate risk of 17 %. The presence of subclinical hypothyroidism was significantly more in the high-risk syntax score of 18.8% compared to the intermediate risk of 11.4 %. The presence of euthyroid was significantly higher in low risk at 85.6% compared to intermediate risk at 71.6% and high risk at 53.1 %. The present study showed that Free T4 was more strongly associated with CAD and the severity of atherosclerosis than TSH in the entire study population. We conclude that Overt and Subclinical hypothyroidism patients had more severe Coronary atherosclerosis than the Euthyroid study population.

Keywords: Free T4, Free T3, TSH, CAD and Euthyroid.

1. INTRODUCTION

Cardiovascular Disease (CVD) and related mortality have emerged as a major health burden worldwide with atherosclerosis being the major cause. Coronary artery disease (CAD) accounts for the major share of the CVD burden in India and is in epidemic proportions1. The Registrar General of India reported that Coronary heart disease (CHD) led to 17% of total deaths and 26% of adult deaths in 2001-2003, which increased to 23% of total and 32% of adult deaths in 2010-2013. In India, studies have reported increasing CHD prevalence over the last 60 years, from 1% to 9%-10% in urban populations and <1% to 4%-6% in rural populations2. Some studies from India noted the regional variation in CAD and reported a higher prevalence in southern India than in other regions of the country 2.

Thyroid hormone has many effects on the cardiovascular system3. Thyroid dysfunction results in changes in cardiac contractility, cardiac output, myocardial oxygen consumption, systemic vascular resistance, and blood pressure4. The prevalence of Overt hypothyroidism, subclinical hypothyroidism, Overt hyperthyroidism and subclinical hyperthyroidism in India is 10.95%, 8.2%, 0.6% and 1.3% respectively5. The relationship between abnormal thyroid function and coronary artery disease has been recognized for a long time, especially in hypothyroidism status due to the associated hypercholesterolemia and hypertension6. Even subclinical hypothyroidism7 and subclinical hyperthyroidism8 have been related to increased risk of CHD and mortality, although still controversial9.

Few studies have examined the relationship between thyroid function and CAD in euthyroid individuals within the Reference

range population. The HUNT study, a prospective population-based cohort study in Norway, found that low thyroid function within the clinically normal range was associated with increased mortality from CHD in women during 12-year follow- up10. However, they found no association between thyroid function with the risk of being hospitalizedwith myocardial infarction10. Therefore, the morbidity finding of the HUNT study does not confirm the suggestion that thyroid function in the normal range is associated with the risk of CHD.

To the best of our knowledge, the relationship between different thyroid functions, including both normal thyroid function and thyroid dysfunction, and the presence of CAD and the severity of coronary atherosclerosis according to SYNTAX Score, in a population undergoing coronary angiography is not well studied so far. Hence this study is an attempt to describe the correlation between thyroid function, dysfunction and CAD severity according to the SYNTAX Score in the Entire study population and euthyroid population.

Hypothyroidism affects between 4% and 10% of the population, and the prevalence of subclinical hypothyroidism is reported to be as high as 10% in various studies.Hypothyroidism is diagnosed when low levels of the thyroid hormones result in elevated levels of thyroid-stimulating hormone (TSH) (18).

Sub clinical hypothyroidism is diagnosed when there is a normal level of TSH associated with elevated thyroid hormones whereas in Overt hypothyroidism, the TSH lies within the normal range with a decrease in t4 levels.

The thyroid hormone is an important regulator of cardiac gene expression and, many of the cardiac manifestations of thyroid dysfunction are associated with alterations in T3-mediated gene expression (21). Thyroid hormones increase the Ca2+ ATPase and downregulate the expression of phospholamban. Overall, hyperthyroidism is characterized by an increase in resting heart rate, blood volume, stroke volume, myocardial contractility, and ejection fraction. high-output heart failure in hyperthyroidism is due to tachycardia-mediated cardiomyopathy. In contrast, hypothyroid conditions result in lower heart rate and weakening of myocardial contraction and relaxation, with prolonged systolic and early diastolic times (22). The T3-mediated effects include changes in various membrane ion channels for sodium, potassium, and calcium; effects on actin polymerization; and effects on the intracellular signalling pathways in the heart and vascular smooth muscle cells. Some abnormalities of cardiac function in patients with thyroid dysfunction directly reflect the effects of TH on calcium-activated ATPase and phospholamban, which are involved primarily in the regulation of systodiastolic calcium concentrations. The heart is a major target for TH action, and thyroid dysfunction has profound effects on the heart and cardiovascular system, i.e., changes in cardiac gene expression in the contractile apparatus, the sarcoplasmic reticulum, and the outer myocytic cell membrane (23).

Hypothyroidism is associated with decreased cardiac output due to and decreased availability of endothelial nitric oxide. This produces a cascade effect of increased arterial stiffness that leads to increased systemic vascular resistance (18)

Renin is expressed in the liver under the induced condition of T3. In a hypothyroid state, renin levels are suppressed and diastolic blood pressure increases. Assorted alterations in lipid parameters are noted in both overt and subclinical hypothyroidism, including elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B. A hypothyroid state results in decreased expression of hepatic LDL receptors and reduced activity of cholesterol-α-monooxygenase, which breaks down cholesterol, resulting in decreased LDL clearance.Also noted are elevations in both C-reactive protein and homocysteine(18).The hemodynamic effects of hypothyroidism are opposite to those of hyperthyroidism, although the clinical manifestations are less obvious with bradycardia being the most common sign accompanied by mild hypertension and a narrowed pulse pressure(20).

Amiodarone, the most commonly used class III anti-arrhythmic drug, is a Benz-furan compound and contains 37% of iodine which bears a significant structural resemblance to thyroid hormones.Although amiodarone is a well-well-established and effective drug, it is linked with several adverse effects including thyroid dysfunction (19).It can lead to hypothyroidism and less commonly hyperthyroidism. Amiodarone inhibits the activity of 5'deiodinase and thus blocks the conversion of t4 to t3 which results in a decrease in t3 levels and an increase in t4 levels, because of which TSH is accelerated due to a decrease in the inhibition of the Anterior pituitary. The majority of patients (>70%) on amiodarone will remain euthyroid. However, treatment may lead to either amiodarone-induced hypothyroidism (AIH) or amiodarone-induced thyrotoxicosis (AIT), with AIH more common in iodine-sufficient populations and AIT in iodine-deficient populations.(19).

There is a great deal of evidence that, in addition to stimulating fatty acid oxidation through an increased NEFA (non-esterified

fatty acids) availability, thyroid hormones induce lipogenesis in the liver.Hepatic synthesis and output of triglycerides are decreased by thyroid hormones(7). Thyroid hormones regulate the expression of lipogenesis by binding to their specific THR receptors.

thyroid hormones also indirectly regulate hepatic lipogenesis as a result of their effects on the expression and activities of other transcription factors, such as sterol regulatory element-binding protein 1C (SREBP1C), liver X receptors (LXRs) and carbohydrate-responsive element-binding protein (ChREBP), which all have crucial roles in hepatic lipogenesis(25).The synthesis and secretion of verylow-density lipoproteins (VLDL) are stimulated.Hyperlipidemia occurs in patients with overt hypothyroidism and might be responsible for an increased risk of coronary artery disease (CAD). Plasma levels of total cholesterol and LDL cholesterol are increased in patients with hypothyroidism (24).

II. Materials And Methods

Study Subjects

The present study is a randomly selected observational study, with a total of 300 patients,diagnosed with Coronary Artery Disease, and admitted to the Department of Cardiology, Meenakshi Medical College Hospital and Research Institute,Enathur, Kanchipuram Tamil Nadu, India. who are willing to undergo Coronary Angiography. The duration ofthe study was from August 2018 to August 2019. This study got Ethics committeeapproval from the institute.

Inclusion Criteria

- Age > 20 years (both male andfemale).
- Diagnosis of CAD and willing to under CoronaryAngiography
- Consenting to participate in the study

Exclusion Criteria

- Age <20 years ofage.
- Patients diagnosed with thyroid issues.
- Patients on Anti thyroid drugs
- Patients with Acute coronarysyndrome.
- Patients were not willing to participate in the study.
- Acute and systemicillnesses
- Malignancy.
- Congenital HeartDiseases.

Study Design

After the selection of cases, the purpose of this study was discussed with all study participants. Informed Written consent was taken from each of the participants before the recruitment. A detailed questionnaire which includes a detailed history to assess symptoms, risk factor profile, current medical therapy, physical examination and relevant investigations are done for each case. Patients were evaluated with ECG, 2D- Echocardiogram and TMT if required. Blood samples for investigations such as serum lipid profiles including serum cholesterol, LDL - cholesterol, HDL – cholesterol and Triglycerides were obtained. After confirming the diagnosis of CAD, patients were subjected to coronary angiography to see the extent of the disease and the SYNTAX Score was calculated.

Statistical Analysis

Data were analyzed using the SPSS software package, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed using range, mean, SD, and median, whereas qualitative data were expressed as frequency and percentage. P value

was assumed to be statistically significant at 0.05.

Ethicalconcern

Ethical clearance was obtained from the Ethical committee meeting conducted and approved by Institutional ethical committee at Meenakshi Medical College Hospital and Research Institute,Enathur, Kanchipuram Tamil Nadu, India.

III. Results

Age and Sex wise distribution

Table 1 showed that in the Present study, there were 300 patients enrolled. 198 (66%) patients were males and 102 (34%) patients were females. There were no patients encountered with subclinical hyperthyroidism or overt hyperthyroidism in this study. Therefore, the total study population was divided into 3 groups based on Serum TSH and Free T3 and T4 levels.

Table.1. Age and Sex wise distribution

Age Groups(years)	Male (%)	Female (%)
< 40	48 (16%)	21 (7%)
41-50	75 (25%0	36 (%)
51-60	27 (9)%	15(%)
>60	198 (66%)	102 (34%)

Distribution of patients based on thyroid categories

Figure. 1. Indicated that the distribution of patients was based on the thyroid profile. The First Group was the Euthyroid group which had 234(78%) patients with 177 (59%) male and 57 (19%) female patients. The euthyroid group (Reference range group) was again divided into 5 groups based on the values of Serum TSH - 1A, 1B, 1C, 1D, and 1E. Groups 1A, 1B, 1C, 1D, 1E had 30, 27, 30, 69 and 78 patients respectively. Among them, 33 patients had no CAD.

The second group was the Subclinical hypothyroidism group with 42 patients (14%) with 15 (5%) male and 27 (9%) female patients. 9 patients among them had no CAD. The third group was the Overt hypothyroidism group with 24 patients (8%) with 6(2%) and 18(6%) female patients.

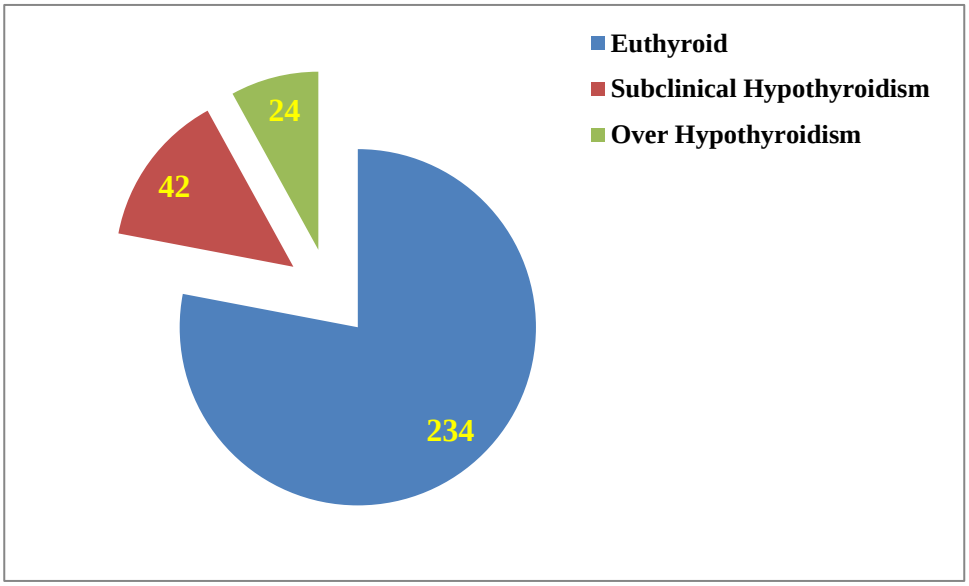

Figure1: distribution of patients based on the thyroid profile

Characteristics of the study population by CAD and Non- CAD

In the present study, Continuous variables were studied concerning CAD. It was observed that 258 patients had CAD and 42 patients had no CAD. There was no statistically significant difference in the mean age, height and FT3 between patients who

had CAD compared to Non -the CAD group p >0.05. Mean weight, BMI, total cholesterol, LDL, triglycerides, TSH and syntax score were significantly higher in patients with CAD compared to patients with no CAD p <0.05. Mean HDL and FT4 were significantly lower in the patients with CAD compared to patients with no CAD p <0.05.(Table.2)

Table.2. Characteristic study population by CAD and Non- CAD

Variables	CAD	No CAD	P Value
Age	49.63 ± 7.83	53.31 ± 6.69	0.149
Height	163.41± 8.52	162.37 + 8.22	0.702
Weight	63.85 + 8.68	58.83 + 6.63	0.006
BMI	26.67 + 2.63	23.38 + 2.94	<0.001
TCHOL	208.60 + 20.59	149. 66 + 14.8	<0.001
LDL	144.08 + 23.44	89.58 + 9.65	<0.001
HDL	36.38 + 4.91	39.93 + 4.45	0.013
TGL	199.65 + 29.04	136.00 + 20.93	<0.001
FT3	1.2 + 0.15	3.3 + 0.42	<0.001
FT4	0.97 + 0.32	1.10 + 0.20	0.001
TSH	6.31 + 0.82	3.08 + 0.45	0.001
Syntax	20.34 + 0.22	0.19 +).11	<0.001

Characteristics of categorical variables in the study population by thyroid function category

In the table.3. indicated that the thyroid function abnormality was observed to be more common in females compared to males (p <0.05). Patients with a history of smoking were significantly higher in the euthyroid group whereas patients with statin use were significantly higher in a subclinical hypothyroid group. There was no statistically significant difference observed in diabetes and hypertension concerning thyroid status p >0.05.

Table.3. Study population by thyroid function category

Variables	**Euthyroid**	**Subclinical hypothyroid**	**Overt hypothyroid**	**Chi-Square**	**P Value**
Gender				48.8	<0.001
Male	177 (75.6%)	15 (35.7%	6 (25%)		
Female	57 (24.4%)	27 (64.3%	18(75%)		
Diabetes	111(47.4%)	24(57.1%)	12(50%)	1.35	0.508
HTN	105(44.9%)	24(57.1%)	9(37.5%)	2.91	0.233
Smoking	123(52.6%)	9(21.4%)	6(25%)	18.52	<0.001
Statin use	21(9%)	9(21.4%)	0(0%)	9.03	0.011

Association of TSH concerning CAD in Euthyroid patients

In the present study, TSH was sub-classified in euthyroid patients and the level of TSH was studied with the severity of CAD it was observed that in patients with triple vessel disease 100 % had TSH values between 4.26 – 5.25, similarly in patients with DVD 45.8% patients had TSH levels between 4.26 – 5.25 and 45.8% had TSH levels between 3.26 – 4.25 when compared to patients with single-vessel disease 45.5% had TSH levels between 3.26 – 4.25, 18.2 % each had TSH levels between 4.26 – 5.25, 2.26 - 3.25 and 1.26 - 2.25 respectively. As the severity increased the level of TSH was observed to be more than p <0.05. (Table.4)

Table.4. Association of TSH in relation to CAD in Euthyroid patients

TSH	CAG				
	No CAD	Mild CAD	SVD	DVD	TVD
0.25-1.25	12(36.4%)	18(60.0%)	0(0.0%)	0(0.0%)	0(0.0%)
1.26-2.25	6(18.2%)	9(30.0%)	12(18.2%)	0(0.0%)	0(0.0%)
2.26-3.25	9(27.3%)	3(10.0%)	12(18.2%)	6(8.3%)	0(0.0%)
3.26-4.25	6(18.2%)	0(0.0%)	30(45.5%)	33(45.8%)	0(0.0%)
4.26-5.25	0(0.0%)	0(0.0%)	12(18.2%)	33(45.8%)	33(100.0%)
Total	33(100.0%)	30(100.0%)	66(100.0%)	72(100.0%)	33(100.0%)

Chi-Square =230.6, p<0.001.

Comparison between TSH levels and SYNTAX in Euthyroid patients

Table.5. showed that the presence of overt hypothyroidism was significantly more in high-risk syntax scoresof 28.1% compared to intermediate risk of 17 %. The presence of subclinical hypothyroidism was significantly more in the high-risk syntax score of 18.8% compared to the intermediate risk of 11.4 %. The presence of euthyroid was significantly higher in low risk at 85.6% compared to intermediate risk at 71.6% and high risk at 53.1 %

Table.5. Comparison between TSH and Syntax in Euthyroid patients

TSH levels	SYNTAX – RISK		
	Low Risk <22	Intermediate Risk 22-32	High Risk >32
Euthyroid	154(85.6%)	63(71.6%)	17(53.1%)
Subclinical	26(14.4%)	10(11.4%)	6(18.8%)
Overt Hypothyroid	0(0.0%)	15(17.0%)	9(28.1%)
Total	180(100.0%)	88(100.0%)	32(100.0%)

Chi square =44.89 p<0.001.

IV. Discussion

The thyroid hormone exerts its action on the heart and cardiovascular system through its intranuclear genomic effects and extranuclear nongenomic effects. The ability of thyroid hormone to alter vascular smooth muscle cells and endothelial function is very important. In hypothyroidism, arterial compliance is reduced, which leads to increased systemic vascular resistance and a rise in diastolic blood pressure. Thyroid hormone paucity is escorted by a reduced expression of Low-Density Lipoprotein (LDL) receptors in the liver and a decreased LDL receptor activity, which leads to impaired LDL clearance. As a result, overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in LDL-C. LDL-C is also increased in subclinical hypothyroidism as reported by DUNDAS et al.11

The lipid profile changes are reversible with thyroid hormone replacement.12,13 dyslipidemia and diastolic hypertension predispose hypothyroidism patients to accelerated atherosclerosis and CHD. Although direct evidence about the effect of levothyroxine on CHD is lacking, clinical studies have shown that levothyroxine treatment of subclinical hypothyroidism

may have beneficial effects on early markers of atherosclerosis like endothelial function and carotid artery intima-media thickness as reported by F MONZANI et al in 2016.14

In the present study, a total of 300 consecutive patients who were diagnosed with CAD and were willing to undergo a Coronary Angiography were enrolled and studied. 198 (66%) patients were males and 102 (34%) patients were females. The age group with the most common presentation was 41-50-year-old with 37% of the study population. There were no patients encountered with subclinical hyperthyroidism or overt hyperthyroidism in this study. Therefore, the total study population was divided into 3 groups based on Serum TSH Free T3 and T4 levels.

In this study, overt and subclinical hypothyroidism measured value was 8% and 14%. The prevalence of hypothyroidism in the developed world is about 4-5%. The prevalence of subclinical hypothyroidism in the developed world is about 4-15% as reported by National Health and Nutrition Examination Survey (NHANES III). In India, hypothyroidism is usually categorized under the cluster of iodine deficient disorders. The prevalence reported in the Indian trial by AMBIKA et al5 showed slightly lower than in the present study with Overt Hypothyroidism at 10.95% and Subclinical Hypothyroidism at 8.2%.

Categorical variables were compared using the chi-square test, it was observed that there was no statistically significant difference in gender, HTN, statin use and thyroid function state in patients who had CAD compared to patients with no CAD p >0.05. Diabetics and Smokers were significantly more in the CAD group compared to patients with no CAD p >0.05.

YAN LING et al15 reported similar findings. Patients with CAD were more likely to be male and current and ex-smokers. Patients with CAD were older and had a higher proportion of diabetes and hypertension and a higher level of fasting plasma

glucose, 2-hour postprandial plasma glucose, HbA1c, and systolic blood pressure. There were more statin users in the CAD group than non- the CAD group. The levels of total cholesterol, LDL-C, and triglyceride were similar between CAD and non-CAD groups, but the HDL-C level was lower in the CAD group.

In the present study, continuous variables were studied concerning thyroid function categories. It was observed that 234 patients were euthyroid, 42 patients had subclinical hypothyroidism and 24 patients had overt hypothyroidism. There was no statistically significant difference in the mean age, HDL and triglycerides in relation to thyroid function status $p > 0.05$. Mean height, weight, BMI, total cholesterol, LDL, FT3, FT4, TSH and syntax score showed a significant mean difference concerning thyroid function status $p < 0.05$.

In the present study, there was a significant and negative correlation observed between FT4 and presence of CAD when studied in entire population. $P < 0.05$. There was a significant and positive correlation observed between TSH and presence of CAD. $P < 0.05$ and negative correlation observed between TSH and FT4.

TSH was sub classified in euthyroid patients and the level of TSH was studied with severity of CAD it was observed that in patients with triple vessel disease 100 % had TSH values between

4.26 – 5.25miu/l, similarly in patients with DVD 45.8% patients had TSH levels between 4.26 – 5.25miu/l and 45.8% had TSH levels between 3.26 – 4.25 when compared to patients with single vessel disease 45.5% had TSH levels between 3.26 – 4.25miu/l, 18.2 % each had TSH levels

between 4.26 – 5.25miu/l, 2.26 - 3.25miu/l and 1.26 - 2.25miu/l respectively. Therefore, As the severity increased the level of TSH was observed to be more ($p < 0.05$.) even in euthyroid population.

YAN LING et al observed in the entire population, free T4 as a continuous variable was significantly associated with decreased odds of CAD in the multiple logistic regression model. The association of TSH with CAD was not significant Unlike in the present study. FT4 was still associated with CAD when FT4 and TSH entered the model together. To explore if free T4 and TSH in the reference range (Euthyroid) were associated with CAD, they did analysis in the euthyroid individuals and found Neither free T4 nor TSH was found to be associated with CAD Unlike in the present study where in it was studied that as the severity increased the level of TSH was observed to be more. MING

Weiss IA et al (2011)16 reported that the patients with Overt hypothyroidism and low T3 syndrome had a high prevalence of CHD, increased severity of coronary artery lesions and poor prognosis.

TIAN et al in 201017 demonstrated that TSH could upregulate 3-hydroxy-3- ethylglutaryl coenzyme A reductase in the liver, which indicated a direct role of TSH in the development of hypercholesterolemia.

V. Conclusion

We conclude that the importance of the study lies in the earliest detection of preclinical TSH of more than 4.15 mIU/L could predict CAD and the Severity of coronary atherosclerosis. TSH is as an early diagnostic marker for CAD patients.

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