Relationship between Coronary Artery Disease and Subclinical Hypothyroidism - A Descriptive Study in a Rural Tertiary Care Centre in South Kerala

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Background
Subclinical Hypothyroidism (mild thyroid failure) is diagnosed when Serum thyroid hormones are within normal range but S.T.S.H level is mildly elevated. It occurs in 3 – 12.5% of general population(1) It is more common in women than men, and its prevalence increases with age. After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10%(2)
Before diagnosis of SCH, other causes of an elevated TSH level, such as recovery from non thyroidal illness, assay variability, presence of heterophile antibodies interfering with the TSH assay, and certain cases of central hypothyroidism with biologically inactive TSH and thyroid hormone resistance, should be excluded(2). Once Diabetes is excluded Thyroid diseases constitute the main bulk of endocrine disease in common practice.

Adverse Consequences of Sub Clinical Hypothyroidism
1. Progression to Overt Hypothyroidism A TSH level greater than 10 mIU/L predicts a higher rate of progression, and a level of less than 6 mIU/L predicts a lower likelihood of progression.
2. Lipid Abnormalities and Other Cardiac Risk Factors. Increase in low-density lipoprotein cholesterol and TGL is noted in patients with Subclinical Hypothyroidism
3. Adverse Cardiac End Points. Increased chance of myocardial infarction and aortic calcification is seen in patients with Subclinical Hypothyroidism.
4. Cardiac Dysfunction. Studies have shown slowed left ventricular relaxation time, increased vascular tone at rest, and left ventricular systolic dysfunction with exercise and impaired endothelial function in patient with Subclinical Hypothyroidism(3).
5. Adverse Fetal Effects A 7-point reduction in intelligence quotient in children aged 7 to 9 years whose mothers had Subclinical Hypothyroidism at pregnancy compared with the children of euthyroid mothers.

6. Neuromuscular Dysfunction Neuromuscular symptoms and dysfunction are common in patients with SCH and can be reversed by levothyroxine treatment.

7. Psychiatric and Cognitive Dysfunction. Aggravation of depression, bipolar disorder, and effect on cognitive function is seen in patients with SCH(3).

Levothyroxine replacement therapy is recommended for all patients with a TSH greater than 10 mIU/L, even if the free thyroxine concentration is within normal range. Treatment of patients with a serum TSH level between 5 and 10 mIU/L remains controversial. The arguments for levothyroxine therapy are the high risk of progression to overt hypothyroidism, improvement of quality of life, and possibility that SCH is a cardiovascular risk factor. Increased cardiovascular risk is to persons younger than 70 years; 70 and 80 years have no additional risk, and more than 80 years have a protective benefit. So therapy should be individualized by considering presence of symptoms, age, and associated medical conditions

Subclinical hypothyroidism is an independent risk factor for myocardial infarction and radiologically visible aortic atherosclerosis. Subclinical hypothyroidism also increases the total cholesterol, L.D.L and Triglycerides which further increase the risk of coronary artery disease. The relevance of the study is early identification and treatment of Subclinical hypothyroidism, can prevent or delay the complication of Subclinical hypothyroidism. Studies showed that Subclinical hypothyroidism can lead to CAD It also give knowledge regarding proportion of patients with Subclinical Hypothyroidism among Coronary artery disease patients. This helped to improve outcome of the patients.

Aims and Objectives of this Study

Primary Objective
To assess the proportion of patients having Sub clinical hypothyroidism among those patients admitted with Coronary Artery disease.

Secondary objective
To describe the clinical and biochemical profile of patients with Subclinical Hypothyroidism and Coronary Artery disease.

Methodology

Study Design: Descriptive study (Hospital based)

Duration of Study: One year

Study Subjects: Coronary Artery Disease Patients above 35 years of age who are admitted for 1 year from March first 2017.

Inclusion Criteria: Patients of age 35 years and above who are admitted with Coronary Artery Disease in the medical ward, after getting their written consent.

Exclusion Criteria: Patients with diagnosed Diabetes Mellitus and diagnosed case of hypothyroidism are excluded from the study.

Sample Size
Sample size is calculated using the formula 4Pq/d 2 where P is proportion of patients with subclinical hypothyroidism, q is 100 - P and is allowable error. According to the study Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death by Rodondi. N, Newman A.B, Vittinghoff. E et al P=12%. Consider P as 12% and q as 88% with an absolute precision of 4 sample size is calculated to be 264. 38

Procedure in Detail
In our department about 10 patients get admitted per day following Coronary artery disease. After detailed physical examination investigations like Serial E.C.G's, Troponin I, Random Blood Sugar, Renal Function Tests, Liver Function tests, Serum Electrolytes, Fasting Lipid Profile, Serum T.S.H. were done as routine.

If Serum T.S.H. is abnormal then Serum T3 and Serum T4 are done. The state—an elevated TSH
level with a normal free T4 level—is referred to as subclinical hypothyroidism. That is

- A mildly high thyroid-stimulating hormone (TSH) level.
- A normal thyroxine (T4) level.
- A normal (T3) level.

Normal hormone levels in the body is

S.T3 - 1.2 – 2.1 nmol/L
S.T4 - 70 – 150 nmol/L
S.T.S.H- 0.34 – 4.25 mIU/L

**Study Variables**

Age, Sex, Clinical features, Routine Blood Investigations, Serum TSH, Serum T3, Serum T4, Total cholesterol, LDL, HDL, VLDL, Triglyceride levels, E.C.G., Trop-I.

**Study Tools**


**Data Collection**

All patients who satisfy the inclusion criteria were evaluated as per the proforma designed for the study. All patients were subjected to a detailed clinical examination with particular reference to Thyroid function test and Lipid profile.

**Analysis**

Data entered into excel sheet and analysis done by using SPSS version 16. Qualitative variables summarised using proportions. Quantitative variables were assessed using mean with standard deviation / median. Associations were checked using Chi-square test. Group Statistics, Descriptive Statistics, independent sample t test were also used.

**Observations**

There were total of 264 patients included in this study.

**Figure 1: Age Distribution**
Figure 2: Sex Distribution of Cases of Coronary Artery Disease

Figure 3: Sex Distribution of Sub Clinical Hypothyroidism

Table 1: TSH Levels among the Patients

<table>
<thead>
<tr>
<th>TSH</th>
<th>Percentage</th>
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<tr>
<td>0.34-4.25</td>
<td>88.6%</td>
</tr>
<tr>
<td>4.6-10</td>
<td>7.6%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>3.8%</td>
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</table>

Subclinical hypothyroidism was present in 11.4% of the patients.

Table 2: Sex and Subclinical Hypothyroidism

<table>
<thead>
<tr>
<th>SEX</th>
<th>SUB CLINICAL HYPOTHYROIDISM</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PRESENT</td>
</tr>
<tr>
<td>MALE</td>
<td>11</td>
</tr>
<tr>
<td>FEMALE</td>
<td>19</td>
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</table>

p value = 0.001

So there is statistically significant association between sex and sub clinical hypothyroidism.
Table 3: Hemoglobin, ESR and lipid profile among the patients with sub clinical hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>30</td>
<td>9.5</td>
<td>14</td>
<td>10.483</td>
<td>1.1024</td>
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<tr>
<td>ESR</td>
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<td>20</td>
<td>16.07</td>
<td>3.258</td>
</tr>
<tr>
<td>Total Cholesterol</td>
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<td>184</td>
<td>313</td>
<td>254.33</td>
<td>30.274</td>
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<tr>
<td>Triglycerides</td>
<td>30</td>
<td>90</td>
<td>355</td>
<td>177.3</td>
<td>62.638</td>
</tr>
<tr>
<td>HDL</td>
<td>30</td>
<td>26</td>
<td>60</td>
<td>47.33</td>
<td>7.783</td>
</tr>
<tr>
<td>VLDL</td>
<td>30</td>
<td>18</td>
<td>71</td>
<td>36.47</td>
<td>12.264</td>
</tr>
<tr>
<td>LDL</td>
<td>30</td>
<td>101</td>
<td>196</td>
<td>170.07</td>
<td>24.484</td>
</tr>
</tbody>
</table>

Table 4: Hemoglobin, ESR and lipid profile among patients without sub clinical hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>N</th>
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<th>Maximum</th>
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</tr>
</thead>
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<tr>
<td>Hb</td>
<td>234</td>
<td>10</td>
<td>16</td>
<td>13.575</td>
<td>1.1963</td>
</tr>
<tr>
<td>ESR</td>
<td>234</td>
<td>6</td>
<td>20</td>
<td>10.68</td>
<td>3.183</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>234</td>
<td>143</td>
<td>274</td>
<td>209.16</td>
<td>24.944</td>
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<tr>
<td>Triglycerides</td>
<td>234</td>
<td>56</td>
<td>198</td>
<td>115.29</td>
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<tr>
<td>HDL</td>
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<td>26</td>
<td>76</td>
<td>46.4</td>
<td>6.263</td>
</tr>
<tr>
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<td>11</td>
<td>40</td>
<td>23.08</td>
<td>5.936</td>
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<tr>
<td>LDL</td>
<td>234</td>
<td>65</td>
<td>196</td>
<td>140.25</td>
<td>25.639</td>
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</tbody>
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Table 5: Comparison of blood parameters in patients with and without sub clinical hypothyroidism

<table>
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<tr>
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<th>Sub Clinical Hypothyroidism</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
<th>P Value</th>
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In this study Sub clinical hypothyroid patients are found to have low Hb levels, increased ESR level, increased TC, increased TGL, increased VLDL, increased LDL level, all are statistically significant.

Discussion

Here the patients were grouped into four age groups 35-45 years, 46 – 55 years, 56 – 65 years, > 66 years. Incidence of coronary artery disease is 6.1%, 18.2% , 45.5% , 30.3 % respectively in these age group. The number of patients with sub clinical hypothyroidism are 0, 12, 12, 6 respectively in these age group.

There is an increase in incidence of coronary artery disease and sub clinical hypothyroidism as the age advances. Majority of patient with coronary artery disease is 56 – 65yrs., and sub clinical hypothyroidism is 46 – 55, 56 – 65yrs. As advances there is increased chance of coronary artery disease.

Sex distribution in coronary artery disease is male- 63.6 % and female – 36.4%. The number of patients with sub clinical hypothyroidism are male -11, female -19. Male sex is a risk factor coronary artery disease. As in many studies here the coronary artery disease is more in males. Gaurab Agarval in his study observed that women with age group 40- 60 yrs had higher incidence of
thyroid dysfunction. This study shows high prevalence of thyroid dysfunction in south Indian women.\(^{(4)}\)

The mean age group of the study is 52.68 ± 10.2 As in many studies sub clinical hypothyroidism is more common in females and the incidence increases as the age advances.

There is female preponderance of SCH among study group. This is similar to study of Sanjay. K Bhandopadyay et al study where there is female preponderance\(^{(5)}\). Study by Rhodonti et al shows increased incidence of cardiac mortality and morbidity with sub clinical hypothyroidism\(^{(6)}\). A study on Risk Factors for Cardiovascular Disease in Women with Sub clinical Hypothyroidism by Rafael Luboshitzky Ariel Aviv Paula Herer Lena Lavie says that subclinical hypothyroidism in middle-aged women is associated with hypertension, hypertriglyceridemia, and elevated TC/HDL-C ratio\(^{(7)}\).

88.6% of the studied population is having normal TSH. Value, ie. euthyroid. Rest (11.4%) is having high TSH value, ie, sub clinical hypothyroidism. Hypothyroid patients are excluded in this study. The mean TSH value of Sub clinical hypothyroidism in this study is 8.55 ± 2.41.

This is similar to the study by kul dip singh et al on Sub clinical hypothyroidism in north Indian population were the mean TSH value is 8.23 ± 2.48\(^{(8)}\). In the study by Revi shekhar et al in coastal areas of Andhra Pradesh the mean TSH was 7.5 ± 1.13\(^{(9)}\). Sub clinical hypothyroidism Present - 11.4% Absent - 88.6% This is the primary objective of our study, is to find the proportion of patients with sub clinical hypothyroidism among the patients coronary artery diseases. It is on upper limit of normal prevalence in the community. Misa Imaizumi et al in their studies observed that subclinical hypothyroidism was associated with ischemic heart disease independent of age, systolic blood pressure, body mass index, cholesterol, smoking, erythrocyte sedimentation rate, or presence of diabetes mellitus\(^{(10)}\).

In this study Subclinical hypothyroid patients are found to have low Hb levels, increased ESR level, increased TC, increased TGL, increased VLDL, increased LDL level. 60 The mean TGL observed in Subclinical Hypothyroid patient here is 177.30 ± 62.64. This is comparable to the study by Kuldip et al were the mean TGL was 174 ± 32.92 mmol/dl\(^{(8)}\). Another comparable study is by Ravi shekhar et al where the mean TGL level 170 ± 111.01 mmol/dl\(^{(9)}\). Euthyroid patient s are having TGL value of 115.29± 29.64 The mean T.C. value in Subclinical Hypothyroid patient in this study is 254 ± 30.27.Kuldip et al observed a TC of 181± 35.1mg /dl. Some studies shows significantly higher than 250mg/dl\(^{(8)}\). Revi shekhar etal observed a T.C value of 203.41± 29 mgm/dl\(^{(9)}\).

The observed mean values of LDL in Subclinical hypothyroidism here is LDL = 170.07±24.48. Vierhapper et al observed in his study LDL of 137± 40. Our study population is coronary artery diseases\(^{(11)}\). Most of these patients are elderly. This may leads to high values in LDL Cholesterol level.

Euthyroid patients are having LDL value of 140.25 ± 25.64 The observed mean values of HDL= 47.33 ±7.78. Revi shekhar et al observed a HDL value of 40± 8.22. Different studies not showed much difference in HDL value. Euthyroid patient s are having HDL value of 46.40± 6.26. The observed mean values of VLDL = 36.47± 12.26. Many studies shows increase in VLDL level in Subclinical hypothyroidism. Euthyroid patient s are having VLDL value of 23.08 ± 5.94 A study from a South Indian Population Study in the year 2018, shows worsening of lipid profiles in patients with Subclinical hypothyroidism\(^{(12)}\). They noted in the study, out of 986 study population, 110 were found to have subclinical hypothyroidism (8.9%), diabetes 19.5%, hypercholesterolemia 57.2% and systolic hypertension 24.6%.

Gupta et al assessed echocardiographic changes and lipid profile alteration in patients with subclinical and overt hypothyroidism. Mean serum cholesterol was significantly raised in both sub clinical and overt hypothyroidism as compared to controls. Western studies also shows
that about 10%-15% of older women have subclinical hypothyroidism (SCH) and thyroid autoimmunity. They concluded that subclinical hypothyroidism in middle-aged women is associated with hypertension, hypertriglyceridermia, and elevated TC/HDL-C.

Conclusion
1) Coronary artery diseases more in the male population.
2) Coronary artery diseases increases as the age advances.
3) Hypertension is the predominant co morbidity in the study group.
4) The risk factors for Coronary artery diseases in the study group are Smoking, Hypertension Dyslipidemia, Male sex, Advanced age and Subclinical hypothyroidism.
5) High proportion of Subclinical hypothyroidism among the patients with coronary artery diseases in the study group.
6) Subclinical hypothyroidism is more common in female population.
7) Subclinical hypothyroidism increases as the age advances.
8) Subclinical hypothyroidism causes dyslipidemia.
9) Elevated Triglycerides, Low density lipoprotein, Total Cholesterol and Very low density lipoprotein are the characteristic lipid profile abnormality seen in the study group.
10) Early identification and treatment of Subclinical hypothyroidism can prevent or delay the complication of Subclinical hypothyroidism.

Limitations
1) As the study has a small sample size and included only Coronary artery diseases patients the observations cannot be generalized to the general population.
2) Larger sample studies should be done to confirm the findings of the study.

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