ABSTRACT

Introduction and Aim: Raised cardiovascular morbidity is common among patients with primary hypothyroidism. Study of electrocardiogram (ECG) and echocardiography (ECHO) and correlation with lipid profile may help in early detection of cardiovascular diseases in hypothyroidism. By this study, we aimed at studying the cardiovascular profile in patients with primary hypothyroidism and correlating ECHO and ECG changes in primary hypothyroidism with the LDL cholesterol.

Materials and Methods: This was a single centre cross-sectional observational study. All patients diagnosed with primary hypothyroidism were included. The laboratory parameters pertaining to primary hypothyroidism were recorded. ECG and ECHO were noted and correlated with lipid profile.

Results: Total 240 subjects were selected according to inclusion and exclusion criteria, of which males were 25% and females 75%. Mean ± SD of LDL-C among subjects having ST-T changes was 160.98 ±14.86. Mean ± SD of LDL-C among subjects having no ST-T changes was 128±10.15. Unpaired student t test was used to compare mean of lipid profile in patient having ST-T changes with patients having no ST-T changes. A strong correlation was observed between LDL cholesterol and ST-T changes in ECG (P value =0.001)

Conclusion: Diastolic dysfunction is more common than systolic dysfunction in primary hypothyroidism. LDL levels were high in patients with primary hypothyroidism who had ST-T changes in electrocardiogram. Levothyroxine replacement causes decrease in Total as well as LDL cholesterol in primary hypothyroidism. ECG changes correlated with abnormal lipid profile in patients with primary hypothyroidism.

Keywords: Electrocardiogram; diastolic dysfunction; hypertension; LDL cholesterol; lipid profile; primary hypothyroidism; systolic dysfunction.

INTRODUCTION

Hypothyroidism has been proven to be one of the risk factors for cardiovascular disease in several studies (1). The 20 years follow up survey of Whickham study did not show any significant improvement in cardiovascular mortality rate in patients having subclinical hypothyroidism (2).

Recognized ECG changes in hypothyroidism include bradycardia, low voltage complexes, prolonged QT interval and T-wave changes that are non-specific. ST segment changes are not well documented (3). Hypothyroidism can also cause variations in blood pressure and cardiac functions in ECHO. Treatment of overt and subclinical hypothyroidism in certain circumstances are important. Those patients with TSH >10mIU/L should be treated. Pregnant women and women who are planning a pregnancy are advised to take treatment for subclinical hypothyroidism, to decrease the incidence of impaired cognitive development of offspring. We undertook this topic to study cardiovascular manifestations in hypothyroidism and to see if the ST-T changes in ECG is associated with elevated LDL cholesterol, which is a common laboratory derangement in hypothyroidism.

MATERIALS AND METHODS

A cross sectional observational study was conducted among patients aged ≥ 18 years admitted to medical wards and out patients from November 2017 to August 2019 with primary hypothyroidism. Ethical approval (IEC 635:2017) was obtained from Kasturba Hospital Ethics Committee before commencing the study.

Cases with concomitant essential hypertension, ischemic heart disease, valvular and congenital heart diseases, diabetes mellitus and those with dyslipidaemia on statins were excluded from the study. Informed consent from the patients and Institutional ethical clearance was obtained before commencement of data collection. Demographic data, clinical characteristics, laboratory parameters like serum complete blood tests, thyroid function test, lipid profile, ECG, ECHO, and treatment details were noted. Sample size was calculated using the formula for estimation of proportion.
N+\left(1-\frac{\alpha}{2}\right) \geq 2 \text{ at level of significance } \alpha = 5\%

Frequencies and percentages were used to summarize categorical variables. Mean and median were used as applicable for continuous variables with normal or skewed distribution. Wilcoxon test was used for comparing the change in lipid profile before and after thyroxin replacement. Student unpaired t test was used to find out correlation between lipid profile and ST-T changes in ECG. P value < 0.05 considered significant. Statistical analysis was done using the Statistical Package for Social Sciences version 16.0.

**Case definitions used**

**Primary hypothyroidism:** thyroid hormone deficiency due to thyroid gland dysfunction  
**Central hypothyroidism:** hypothyroidism despite normal functional gland due to decreased TSH secretion from pituitary (secondary) or tertiary hypothyroidism due to deceased TRH (thyroid releasing hormone) from hypothalamus.  
**Overt hypothyroidism:** decreased serum free thyroxine (T4) and triiodothyronine (T3) concentrations with elevated TSH concentration.  
**Subclinical hypothyroidism:** Supernormal TSH concentration in the presence of normal levels of serum free thyroxine (T4) and triiodothyronine (T3)  
**ST-T changes:** ST segment elevation >1 mm and T inversion.  
**Total hypercholesterolemia:** total cholesterol > 200mg/dl  
**Hypertriglyceridemia:** Triglyceride levels >150mg/dl  
**Hyper LDL cholesterolemia:** LDL cholesterol > 130mg/dl  
**Bradycardia:** heart rate less than 60  
**Systolic hypertension:** prehypertensive:120-129mmHg  
Stage 1: 130-139 mmHg; Stage 2: >140mmHg  
**Diastolic hypertension:** prehypertensive:80-89 mmHg  
Stage 1: 90- 99 mmHg; Stage 2: >100 mmHg

**RESULTS**

The most common symptoms seen were tiredness (88%), followed by hair loss and dry skin. Most important cardiovascular symptom angina was reported only by 3.75%. Dyspnoea was reported by 54% of the patients; however its cardiac origin could not be established clinically.

**Table 1:** Distribution of demographic variables

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>46.8±14.86</td>
</tr>
<tr>
<td>Weight (Kgs)</td>
<td>63.0±8.74</td>
</tr>
<tr>
<td>Height (metres)</td>
<td>1.63±0.13</td>
</tr>
<tr>
<td>BMI</td>
<td>25.89±4.02</td>
</tr>
</tbody>
</table>

In the present study, 240 subjects were selected according to inclusion and exclusion criteria, of which males were 25% and females 75%. The mean age of the study population in this study was 46.8±14.86. Average BMI was 25.89 (Table 1).

**Table 2:** Distribution of (mean) laboratory values

<table>
<thead>
<tr>
<th>Lab parameters</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>11.45±1.76</td>
</tr>
<tr>
<td>T4</td>
<td>2.9 ± 1.2</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>192 ± 13.5</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>149 ± 18.59</td>
</tr>
<tr>
<td>HDL</td>
<td>36 ± 9.7</td>
</tr>
<tr>
<td>LDL</td>
<td>138 ± 19.10</td>
</tr>
</tbody>
</table>

Average T4 was found to be 2.9, and total cholesterol was 192. Average LDL among the study group was 138 (Table2).

As seen in Fig.2, significant ST-T changes were seen in ECG in 27.9% of patients. With the above finding, we tried to find the association between patients having significant ST-T changes in ECG and lipid profile.
ECHO changes were also observed. Predominantly diastolic dysfunction was present, 16.66% had mild and diastolic dysfunction, whereas 3.33% had moderate diastolic dysfunction (Fig. 3).

**Table 3:** Comparison of lipid profile among 2 groups—before and after thyroxine replacement

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Before thyroxine replacement</th>
<th>After thyroxine replacement</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>192±13.50</td>
<td>172±17.80</td>
<td>0.001*</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>149±18.59</td>
<td>141±20.70</td>
<td>0.001*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>36±9.70</td>
<td>34±10.03</td>
<td>0.001*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>138±19.10</td>
<td>118±20.77</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*unpaired t test

Unpaired t test to compare LDL cholesterol between patients with and without ST-T changes in ECG showed that there is a strong correlation between elevated LDL cholesterol levels and ST-T changes in ECG with a p value of 0.001. Analysis using Wilcoxon rank test showed statistically significant reduction in lipid profile after levo-thyroxine replacement therapy (Table 3).

The most common symptoms seen were tiredness (88%), followed by hair loss and dry skin. Most important cardiovascular symptom angina was reported only by 3.75%. Dyspnoea was reported by 54% of the patients; however its cardiac origin could not be established clinically.

**DISCUSSION**

The present study was undertaken in a tertiary care hospital in southern India with an aim to study cardiovascular manifestations in primary hypothyroidism.

In the present study population, majority were 41-50 years of age, which is slightly higher compared to few other Indian studies but similar to a study conducted specifically to determine correlation between lipid profile and hypothyroidism by Alamdari et al., (3).

Hypothyroidism is the most common condition affecting one in every eight women, women being 5 to 8 times more susceptible to the disease as shown by Ohal et al., (4). Gender distribution is similar to other studies- being 3 times more common in females as compared to males in the present study.

The symptoms that are most common in hypothyroid adults are fatigue, cold intolerance, constipation, lethargy, weight gain, hoarseness of voice, and dry skin, but clinical presentation vary depending on age and gender, among other factors (5). Most common cardiovascular symptom observed in current study was dyspnoea (50%) followed by angina in 3.5 % patients. However, cardiac origin of dyspnoea could not be established.

Verdugo et al.,(6) and Leonidas et al.,(7) in 2 different studies found that the lipid profile in hypothyroidism is characterized by raised total and LDL cholesterol with increased or normal HDL cholesterol levels involving HDL2 sub fraction. However, in present study HDL was low in 72.92% of patients, normal in 23.75% patients and marginally elevated in 3.33% of patients.

In the present study TG levels are either unchanged or are slightly elevated, consistent with a study done by O’Brien et al., (8). The most frequent form of dyslipidaemia, reported by O’Brien et al.,(8) in their study with 295 hypothyroidism patients was total hypercholesterolemia (56%), hypertriglyceridermia and combined hypercholesterolemia (34%) and isolated hypertriglyceridermia (1.5%), and patient having no lipid abnormalities as only 8.5%. In present study 31.25% had total hypercholesterolemia, 40.83% had hypertriglyceridermia, 16% had isolated hyper-LDL cholesterolemia, 9.16% patients had no lipid abnormality. This difference may be due to small sample size.

Comparison of lipid profile in different studies (Table 5) was expressed as Mean ± SD, except in the study of O’Brien et al.,(8) where it was expressed as median with interquartile range. As seen in Table 5, lipid profile in the present study was similar to lipid profile of study by Satpathy et al., (9) conducted in India. However, it was different as compared to Monzani et al., Italy (10). Lipid profile in hypothyroidism as observed in present study was similar to Indian study, but was different from study done in Italy and USA. This difference is probably because of difference in dietary habits and ethnicity.

A significant improvement was seen in lipid profile following thyroxine replacement- from 16% hyper-LDL cholesterolemia before thyroxin replacement to 5.4% after thyroxin replacement in present study.

**Table 5:** Comparison of laboratory parameters

<table>
<thead>
<tr>
<th>Lab parameters</th>
<th>Satpathy et al., (India)</th>
<th>Present study</th>
<th>Monzani et al., (Italy)</th>
<th>O’Brien et al., (USA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>240.38 ±48.61</td>
<td>192 ± 13.5</td>
<td>184.9 ± 22.9</td>
<td>257 (106-541)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>174.40 ±20.80</td>
<td>149 ±18.59</td>
<td>80.5 ± 33.1</td>
<td>125 (26-1,107)</td>
</tr>
<tr>
<td>HDL</td>
<td>32.00 ± 5.83</td>
<td>36 ± 9.7</td>
<td>55.0 ± 14.3</td>
<td>50 (23-102)</td>
</tr>
<tr>
<td>LDL</td>
<td>144 ± 17.81</td>
<td>138 ± 9.10</td>
<td>113.8 ± 21.1</td>
<td>180 (89-403)</td>
</tr>
</tbody>
</table>

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This was consistent with that reported by de Bruin et al. (11), Martínez-Triguero et al. (12), Crowley et al. (13) and Prakash and Lal (14).

We did not study the changes in cardiovascular function in hypothyroidism that respond to thyroxin supplementation since we had no provision to repeat ECHO after treatment. Thyroid hormone deficiency can significantly affect human heart and circulatory system. The most common clinical signs are a narrowed pulse pressure, increased diastolic blood pressure, diastolic dysfunction, systolic dysfunction and bradycardia (9). Also, hypothyroidism is associated with accelerated atherosclerosis and Coronary artery disease due to hypercholesterolemia and diastolic hypertension (15). However, in the present study we found that 57% of the patients had higher diastolic blood pressure, 45.83% systolic hypertension and 3.33% of patients had combined systolic and diastolic hypertension. Among systolic hypertension 26.6% patients had stage 1 hypertension, 19.6% had stage 2 hypertension. Among diastolic hypertension 50% had blood pressure in prehypertensive range and 7% had grade 1 diastolic hypertension but stage 2 diastolic hypertension was not seen in any patient.

Gumieniak et al., proved that subnormal levels of serum freeT4 and supernormal serum TSH are associated with hypertension in hypothyroid individuals and that serum fT4 is strongly related to hypertension than TSH (16). A lower fT4 level was found to be associated with higher absolute values of baseline DBP (independent of TSH values) which proves that hypothyroidism predominantly affects DBP (17). In the present study, 45.83% of patients had systolic blood pressure in hypertensive range with a total of 64.58% having elevated systolic blood pressure (of which 18.75 had pre-hypertension) and 57% of the patients had elevated diastolic blood pressure.

Sinus bradycardia was seen in 31% of patients of hypothyroidism in the study done by Roos et al., (18). Similarly, Prasanna et al., reported sinus bradycardia (27.27%) as the second most common ECG abnormality only after ST-T (34%) segment changes in hypothyroid patients. In the present study 12% of subjects had bradycardia.

Patients who had significant ST-T ECG changes were shown to have angina and CAD on subsequent investigation in the study of Satpaty et al. (9). In the present study, 27.9% of hypothyroid patients showed significant ST-T ECG changes and only 3.33% had angina as symptom. However, we did not have follow up ECG after thyroxin replacement and no coronary angiography was available to establish the relation between ST-T changes and CAD.

ECG changes in hypothyroidism are due to increased water imbibition, prolonged ventricular action potential due to abnormal vagal tone, and associated pericardial effusion (4). It has been found that only a minor shift in the intracellular and extracellular water exchange of the cardiac muscle was required to produce ECG changes.

Electrocardiographic findings in hypothyroidism are sinus bradycardia, QT prolongation, decreased amplitude of P waves, low-voltage complexes, atrioventricular and interventricular block, incomplete or complete right bundle branch block, and atrial fibrillation. A study done by Ramesh et al (19) showed diastolic dysfunction mostly mild dysfunction in 27.5% of subjects and systolic dysfunction in 7.5% of the subjects. In a study by Verma et al.,(20) it was observed that 27% of patients had diastolic dysfunction and low indices of systolic dysfunction. Most common 2D ECHO abnormality observed in present study was diastolic dysfunction- which was seen in 20% of the patients, majority of them being mild dysfunction (16.66%) and moderate in 3.33% patients but none of the patients had severe diastolic dysfunction. Systolic dysfunction was not observed in present study as patients with ischemic heart disease and any structural heart disease were excluded. Frofar et al., (21), Yamada et al.,(22) and Rawat and Satyal (23) are a few other studies which did not find any evidence of systolic dysfunction in hypothyroid patients. These observations are consistent with observation in present study in which we did not find any systolic dysfunction in hypothyroid subjects. However, Smallridge, et al., (24) strongly stated that this could be related to relatively elderly patients included in the above studies and they also found no such impairment in systolic function in their younger group of subjects (aged 20-48 years) included in the study.

CONCLUSION

Hypothyroidism causes elevated systolic and diastolic blood pressure as well as elevated LDL cholesterol. ST-T changes in ECG which is more in those with elevated LDL-cholesterol. Levothyroxine replacement causes decrease in total as well as LDL cholesterol levels. Diastolic dysfunction is more common than systolic dysfunction in hypothyroidism. Hence prompt treatment with thyroxine could improve cardiovascular morbidity and mortality in subjects with primary hypothyroidism.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES