# CARDIAC EVALUATION AMONG NEWLY-DETECTED PATIENTS OF CLINICAL AND SUBCLINICAL HYPOTHYROIDISM

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**ABSTRACT**

**BACKGROUND**

Hypothyroidism is characterised by a low cardiac output due to the decreased heart rate and stroke volume. Systolic and diastolic functions are reduced at rest and during exercise, thus impairing quality of life. In particular, an increased risk of coronary heart disease events and mortality has been reported in young patients affected by subclinical hypothyroidism with TSH >10 mU/L.

The aim of the study is to evaluate the cardiovascular system using electrocardiogram and echocardiogram among patients with clinical and subclinical hypothyroidism.

**MATERIALS AND METHODS**

A cross-sectional comparative study was conducted for a period of one year on 50 patients attending the Outpatient Medicine Department in our hospital. The 50 patients were made into 2 groups of 25 each, group I are patients with clinical hypothyroidism and group II are patients with subclinical hypothyroidism. The cardiac status of all the patients was assessed by doing ECG and a 2D echo was done to assess their systolic and diastolic function.

**RESULTS**

The systolic function was normal in both the groups except for a slight increase in the septal wall and posterior wall thickness of LV among the clinical hypothyroidism patients. There is no statistical significant difference in the diastolic parameters among the two groups ($p > 0.05$), but it proves that there is a diastolic dysfunction, which would be in the starting stage in both the groups. Among the hypothyroid patients, 20% of them had mild pericardial effusion, which was detected through 2D echo, whereas none of the patients with subclinical hypothyroidism had pericardial effusion and this difference was found to be statistically significant ($p < 0.05$).

**CONCLUSION**

Doppler echocardiography technique being a simple, reliable and reproducible method for assessment of heart functions has to be routinely done in patients with clinical and subclinical hypothyroidism to detect diastolic dysfunction at an early stage and manage them appropriately in such a way preventing morbidity and mortality due to cardiovascular system.

**KEYWORDS**

Clinical Hypothyroidism, Subclinical Hypothyroidism, Systolic and Diastolic Function.

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## BACKGROUND

Heart Failure (HF) is a major cause of morbidity and mortality globally today and it is responsible for a high rate of hospitalisation.[1] Despite lot of newer modalities in treating HF over the last 10 years, the prognosis of this dysfunction still remains poor.[2] In recent years, untreated overt hyperthyroidism and hypothyroidism have been reported to be common causes of heart failure.[3] Moreover, persistent subclinical thyroid dysfunction has recently been associated with the development of HF in patients with and without underlying heart disease.[4] Thyroid dysfunction is a modifiable risk factor in patients who are at risk of HF.[5]

Besides its metabolic and thermoregulatory tissue effects, thyroid hormone regulates cardiac performance by acting on the heart and vascular system.[6] The relationship between thyroid hormone and the cardiovascular system has been extensively demonstrated in numerous experimental and clinical studies. This association has been recently confirmed by significant changes in cardiac structure and function in patients with persistent subclinical thyroid dysfunction.[7]

Subclinical thyroid dysfunction is present in patients who have an abnormal thyrotropin (Thyroid-Stimulating Hormone (TSH)) level and a normal Free Thyroxine (FT4) level.[8] Subclinical thyroid dysfunction is common, particularly in older individuals with a prevalence of subclinical hypothyroidism of 10% and subclinical

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hyperthyroidism of 1.5%.[9] Whereas, it is generally accepted to treat the abnormal free thyroxine levels of overt thyroid dysfunction, the indications and threshold TSH for treatment of subclinical hypothyroidism and subclinical hyperthyroidism are areas of clinical controversy because current evidence about the risks is limited.[10,11]

Hypothyroidism is characterised by a low cardiac output due to the decreased heart rate and stroke volume.[7] Systolic and diastolic functions are reduced at rest and during exercise, thus impairing quality of life.[12] Cardiac preload is decreased due to the impaired diastolic function and the decreased blood volume. Vascular function may also be deranged in overt and mild thyroid hormone deficiency.[13] Renal perfusion is decreased with a consequent reduction in glomerular filtration, impaired free water clearance and hyponatraemia. The cardiac energetic efficiency of the hypothyroid human heart is impaired despite its reduced cardiac oxygen consumption.[6] Moreover, important metabolic effects may develop in long-term untreated hypothyroidism. An increased cardiovascular risk has been reported in patients with various degrees of hypothyroidism.[14,15] This may be linked to the increased risk of coronary artery disease and HF associated with hypothyroidism. In particular, an increased risk of coronary heart disease events and mortality has been reported in young patients affected by subclinical hypothyroidism with TSH >10 mU/L.[16]

On the basis of the known effects of thyroid hormone on the heart, it is reasonable to expect adverse cardiac effects in subclinical thyroid dysfunction. Subclinical thyroid disease has been associated with systolic and diastolic cardiac dysfunction and small studies have shown that thyroxine replacement improved measurements of cardiac function in subjects with subclinical hypothyroidism.[17] However, the clinical importance of these effects is unclear. Data on cardiovascular risks are conflicting and no Randomised Clinical Trials (RCTs) have assessed the impact of thyroxine replacement on clinical cardiac endpoints.[18] Only one study has examined the relationship between subclinical thyroid dysfunction and Heart Failure (HF) events. In a population-based study of adults, ages 70 to 79 years, participants with TSH ≥7.0 mU/L had a more than 2-fold greater risk of HF events compared with euthyroid subjects, but echocardiography was not performed.[19] As of today, very few Indian studies were conducted to assess the cardiac function in hypothyroid patients and no such studies had done echocardiography in assessing the cardiac status. So, the present study was undertaken in assessing the systolic and diastolic function by means of echocardiography among the clinical and subclinical hypothyroid patients.

**Aim**- To evaluate the cardiovascular system using electrocardiogram and echocardiogram among patients with clinical and subclinical hypothyroidism.

## MATERIALS AND METHODS

A cross-sectional comparative study was conducted for a period of one year on 50 patients attending the Outpatient Medicine Department in our hospital. The 50 patients were made into 2 groups of 25 each, group I are patients with clinical hypothyroidism and group II are patients with subclinical hypothyroidism.

All patients in the age of 15-60 years who were newly diagnosed and untreated primary clinical and subclinical hypothyroid patients were included in the study. Patients with a known history of diabetes, hypertension, renal disease and pregnancy were excluded from the study. The study was carried out after getting the clearance from the institutional ethical committee and the informed consent from individual patients. A complete clinical assessment was done on all patients. Early morning blood sample was collected for thyroid profile after an overnight fast. The diagnosis of hypothyroidism was made when the FT3<70 pg/dL, FT4 <3 mcg/dL and TSH >15 mcIU/mL and subclinical hypothyroidism was made with TSH >5 mcIU/mL and normal FT3 and FT4 levels.

The cardiac status of all the patients was assessed by doing ECG and a 2D echo was done to assess their systolic and diastolic function. The following measurements were determined by echocardiography- Left and right ventricle cavity dimensions in systole and diastole (SLVD and DLVD); Left Atrium (LA); aortic root diameter (AO); Left Ventricle Mass (LVM) and parameters of systolic and diastolic function. Left ventricular hypertrophy was defined as left ventricular mass index ≥110 g/m2.[20]

Parameters of systolic function were- Left Ventricle Volume (SLVV) in millilitres (mL); Left Ventricular Systolic Diameter (LVSD) in millimetres (mm); ejection volume in mL; Ejection Fraction in % (EF); fractional shortening (%); Ejection Time in milliseconds (ET); Isovolumetric Contraction Time in milliseconds (ICT); and cardiac output (CO) in L/m. Ventricular volume was determined by Teichholz formula and cardiac output was calculated according to the formula- ejection volume x heart rate. Specific diastolic function parameters were- Left Ventricle Diastolic Volume (LVDV) in mL; Left Ventricle Diastolic Diameter (LVDD) in mm; Isovolumetric Relaxation Time (IRT) in ms, E Wave Velocity (EW) in m/s, A Wave Velocity (AW) in m/s, E wave to A wave ratio (E/A) and E wave deceleration time in ms (DT). Diastolic dysfunction was defined by the presence of at least one of the following parameters- E/A ≤1.0, IRT ≥100 ms or DT ≥220 ms.[20]

All the data were entered and analysed by using SPSS version 21. Mean and standard deviation was calculated for all the parametric variables and Student's t-test was used on the echocardiographic parameters to assess the statistical significance between the clinical and subclinical hypothyroidism. Chi-square test was used to assess the statistical significance on the ECG readings between the two groups.

## RESULTS

The age and sex wise distribution of the study subjects was shown in Table 1. It is seen from the table that majority of the study subjects were in the age group between 20-40 years with a mean age of 31-32 years in both the groups.

The minimum age was 18 and the maximum age was 50 years. Females were found to be more in number than the males. The age and sex distribution was almost found to be similar in both clinical and subclinical hypothyroidism group and there is no statistical significant difference between the two groups (p >0.05). The ECG findings of majority (68%) of the patients with clinical hypothyroidism were found to have low voltage complexes and two patients had LBBB and the remaining 4 patients had T wave inversion, whereas among the subclinical hypothyroidism group 92% of them had a normal ECG and only one patient had a feature of right bundle branch block and the difference in the ECG features between the two groups was found to be statistically significant (p <0.05) (Table 2).

The systolic Echo parameters of the study subjects were shown in Table 3. Left ventricular dimensions both in systole and diastole among the two groups was almost similar and there is no statistical significant difference between them, whereas the interventricular septal thickness and the posterior wall thickness of the left ventricle was high among the patients with clinical hypothyroidism in comparison with subclinical hypothyroidism and the difference was found to be statistically significant. Similarly, the ejection fraction and fractional shortening of LV was significantly higher among the patients with subclinical hypothyroidism (p<0.05). The table also infers that the systolic function was normal in both the groups except for a slight increase in the septal wall and posterior wall of LV among the clinical hypothyroidism patients.

Among the diastolic function, the peak E indicates the peak velocity flow in early diastole and peak A indicates the peak velocity flow in late diastole. The E/A ratio is the ratio of the early (E) to late (A) ventricular filling velocities. In a healthy heart, the E velocity is greater than the A velocity, whereas in our study, E/A ratio is <1 in both the groups. Isovolumetric relaxation time is closure of the aortic valve to onset of filling by opening of the mitral valve. The normal level is 60-90 ms, and in our study, it is slightly higher in both the groups. The Deceleration Time (DT) is the time taken from the maximum E point to baseline. Normally, in adults, it is less than 220 milliseconds. In the present study, the mean DT was marginally increased in both the groups. There is no statistical significant difference in the diastolic parameters among the two groups (p >0.05), but it proves that there is a diastolic dysfunction, which would be in the starting stage in both the groups (Table 4). Among the hypothyroid patients, 20% of them had mild pericardial effusion, which was detected through 2D echo, whereas none of the patients with subclinical hypothyroidism had pericardial effusion and this difference was found to be statistically significant (p<0.05) (Table 4).

| Age Group | Gender | Hypothyroidism (n=25) | Subclinical Hypothyroidism (n=25) | P value |
|---|---|---|---|---|
| <20 | Male | 0 | 0 | 0.582 |
| | Female | 2 (8%) | 2 (8%) | |
| 20-30 | Male | 2 (8%) | 1 (4%) | |
| | Female | 13 (52%) | 10 (40%) | |
| 31-40 | Male | 0 | 2 (8%) | |
| | Female | 5 (20%) | 8 (32%) | |
| 41-50 | Male | 3 (12%) | 2 (8%) | |
| | Female | 0 | 0 | |
| Mean ± SD | | 31.5 ± 8.7 | 32.8 ± 6.7 | |

***Table 1. Age and Sex Wise Distribution of the Study Population***

P value derived by applying Chi-square test.

| ECG Findings | Hypothyroidism (n=25) | Subclinical Hypothyroidism (n=25) | P value |
|---|---|---|---|
| Within normal limits | 2 (8%) | 23 (92%) | <0.0001 |
| Low voltage complexes | 17 (68%) | 1 (4%) | |
| LBBB/RBBB | 2 (8%) | 1 (4%) | |
| Nonspecific T-wave inversion | 3 (12%) | 0 | |
| Generalised T-wave inversion | 1 (4%) | 0 | |

***Table 2. Comparison of ECG Findings between the Two Groups***

P value derived by applying Chi-square test.

| Systolic Function Parameters | Hypothyroidism (Mean ± SD) | Subclinical Hypothyroidism (Mean ± SD) | P value |
|---|---|---|---|
| LV in diastole (mm) | 47.7 ± 1.8 | 47.7 ± 1.7 | 1.000 |
| LV in systole (mm) | 30.2 ± 1.6 | 29.6 ± 1.4 | 0.819 |
| Interventricular septum thickness (mm) | 12.0 ± 1 | 8.7 ± 0.5 | 0.0271 |
| Posterior wall of LV thickness (mm) | 11.9 ± 1 | 8.5 ± 0.7 | 0.0310 |
| Ejection fraction (%) | 64 ± 4 | 67 ± 2 | 0.041 |
| Fractional shortening (%) | 35 ± 3 | 37 ± 2 | 0.0481 |

***Table 3. Comparison of Systolic Function Parameters among the Study Subjects Using 2D Echo***

P value derived by applying Student's t-test.

| Diastolic Function Parameters | Hypothyroidism (Mean ± SD) | Subclinical Hypothyroidism (Mean ± SD) | P value |
|---|---|---|---|
| Isovolumetric relaxation time (ms) | 96 ± 3.5 | 94.5 ± 3.2 | 0.871 |
| Peak E (ms) | 84 ± 5.5 | 83 ± 6.2 | 0.719 |
| Peak A (ms) | 87 ± 4.6 | 86 ± 5.3 | 0.819 |
| E/A ratio | 0.96 ± 5.1 | 0.96 ± 5.4 | 0.915 |
| Deceleration time (ms) | 234 ± 8.5 | 236 ± 7.8 | 0.901 |
| Pericardial effusion | 5 (20%) | 0 | <0.0001* |

***Table 4. Comparison of Diastolic Function Parameters among the Study Subjects Using 2D Echo***

P value derived by applying Student's t-test.
*p value derived by Chi-square test (Yate's correction).

## DISCUSSION

The prevalence of subclinical hypothyroidism ranges between 4% and 8.5%, although this figure increases with age and may reach up to 20% in women above 60 years of age. The progression to overt hypothyroidism is approximately 5% per year. The rate of progression is proportional to baseline TSH concentration and higher in individuals with antithyroid antibodies.[20] Subtle echocardiographic changes have been demonstrated in numerous small studies, however, all these studies had significant limitations.[21] Resting diastolic dysfunction is usually an early sign of the subclinical hypothyroidism and it has been clearly shown that it may cause impaired exercise capacity via disturbing the systolic function.[22]

In the present study, it was proven that there is a mild degree of diastolic dysfunction in both the groups (clinical and subclinical hypothyroidism), as there was increase in IVRT (Isovolumetric Relaxation Time) and a reduction in early (E) to late (A) ventricular filling velocity ratio, which clearly indicates that there is a resting diastolic dysfunction as the early sign of hypothyroidism. In a study done by Biondi et al[23] using Doppler echocardiography, they reported no change in the left ventricular structure and systolic function, but they found an increase in Em/Am rate and markedly prolonged IVRT disclosing diastolic parameters. In these subjects, they found significant improvement in the diastolic dysfunctional parameters following the 6 months of T-4 replacement. In another study on subclinical hypothyroidism and its cardiac impacts, diastolic cardiac dysfunction in the resting period and systolic dysfunction in the exercise period and a reduced exercise capacity were reported.[24] The studies on subclinical hypothyroidism and cardiovascular system are also controversial.

According to the certain studies, subclinical hypothyroidism is harmful to cardiovascular system, but there has not been enough controlled study to reveal this issue.[17]

Earlier studies done by R. Verma et al who had done echocardiography study on both subclinical and overt hypothyroidism and found both are associated with cardiovascular alteration both structural and functional. IVS and LVPW thickness are markedly affected, as well as there is impairment of left ventricular function more in diastole.[25] A. Gupta et al found that the diastolic dysfunction is present in both subclinical and overt hypothyroidism, while pericardial effusion is seen only in overt hypothyroidism.[26] In our study also, we found higher incidence of pericardial effusion among clinical hypothyroidism patients when compared to subclinical hypothyroidism and the difference was found to be statistically significant.

For most echocardiographic measurements, we found no significant differences for subclinical hypothyroidism or hyperthyroidism compared with euthyroidism results that are in contrast to several non-population-based studies,[18,23] but are consistent with other population-based studies.[27,28] Despite extensive research, there still exists clinical uncertainty on various aspects surrounding thyroid-related cardiovascular disease. The most recent ACC/AHA guidelines for the diagnosis and management of heart failure recommend measuring thyroid function in all patients with newly-diagnosed heart failure, since it represents a potential reversible cause of cardiovascular disease. Nonetheless, no specific recommendations have been made with regard to the management of subclinical hypothyroidism in patients with heart failure.[29]

Some randomised and placebo-controlled studies had demonstrated improvement of cardiovascular function in patients with mild and subclinical hypothyroidism after replacement doses of L-$T_4$.[30,31] Diastolic dysfunction due to slowed myocardial relaxation and impaired ventricular filling is reversible after replacement therapy. In the present study, as we had not followed-up the patients, we were not able to substantiate the above findings, which is a limitation in our study.

## CONCLUSION

Hypothyroidism is associated with intrinsic myocardial changes, which are reflected by alteration in contractility and relaxation. Clinical hypothyroidism in addition to common findings like bradycardia and ECG abnormalities, it also produces structural and functional abnormalities (systolic and diastolic) in cardiovascular system. Subclinical hypothyroidism though asymptomatic, can cause diastolic dysfunction of heart almost similar to that of clinical hypothyroidism. So, Doppler echocardiography technique being a simple, reliable and reproducible method for assessment of heart functions, it has to be routinely done in patients with clinical and subclinical hypothyroidism to detect diastolic dysfunction at an early stage and manage them appropriately in such a way preventing morbidity and mortality due to cardiovascular system.

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