Original Research Article

Evaluation of cardiac functions in hypothyroidism and subclinical hypothyroidism before and after treatment

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Abstract

Introduction: Hypothyroidism has been found to be associated with increased cardiovascular morbidity and mortality. Cardiac manifestations in hypothyroidism could be due to pericardial effusion (usually accumulates slowly), increased atherosclerosis risk , reduced heart rate and the contractile states of myocardium. It affects cardiac structures, function as well as cardiovascular hemodynamic.**Aim:** To evaluate cardiac functions in hypothyroidism and subclinical hypothyroidism before and after treatment.**Materials and Methods:** A prospective observational study including untreated 36 overt hypothyroid and 42 primary subclinical hypothyroid patients, age ranged 15-60 years. Included patients underwent clinical assessment, thyroid profile , 12 lead EGG, standard M-mode 2D echo and Doppler echocardiography before and 6 months after LT4 replacement therapy. Chi-square test was used to find statistical significance of change in mean values of various parameters obtained before and after treatment.**Results:** Majority of the study population (44.8%) were in the age group of 31-40 years with mean age being 38.5 ± 5.5 years, females accounted for 73.1% and males accounted for 26.9%.Among the overt hypothyroid group pretreatment heart rate was significantly lower ($p<0.01$) compared to post treatment, low voltage QRS complex was the common ECG finding and became normal post treatment,IVS and LVPW thickness decreased after treatment but it was not statistically, significant ($p>0.05$),diastolic dysfunction was noted in all patients and showed marked improvement after treatment ($p<0.01$).Among subclinical hypothyroidism patients abnormal LV diastolic filling (suggestive of impaired LV relaxation) was a common finding, EF an index of LV systolic function was comparable between pre and post treatment patients,diastolic functions were impaired in patients with stable subclinical hypothyroidism but reversible after 6 months of substitutive thyroxine therapy.**Conclusion:** Early detection and treatment of cardiac abnormalities in hypothyroidism prevents permanent structural abnormality of the heart.Doppler echocardiography technique is simple, reliable and reproducible method for assessment of cardiac functions in hypothyroidism

Keywords: Overt hypothyroidism, subclinical hypothyroidism, M-Mode Echocardiography, Doppler Echocardiography

Introduction

Many of the clinical manifestations of hypo and subclinical hypo-thyroidism are due to ability of thyroid hormone to alter cardiovascular structural and hemodynamic characters[1]. The characteristic dilated cardiac silhouette, pericardial effusion, low electrocardiographic voltage and slow indolent heart action are well recognized in overt hypothyroidism[1].Subclinical hypothyroidism is characterized by variably increased serum TSH and normal serum free T4 and T3 levels ,occurs in 10-15% of the general population[2] Though the clinical presentation of subclinical hypothyroidism is nonspecific, and the symptoms are usually subtle as compared with those of overt hypothyroidism, it is well proved to alter several metabolic and organ function indices which become clinically relevant over a period of time. .With the advent of newer echocardiographic techniques mechanism of altered myocardial contractile function in both clinical and subclinical thyroid dysfunction has been well delineated[3].

Aims and Objectives

To evaluate cardiac functions in hypothyroid and subclinical hypothyroid patients before and after treatment by clinical assessment, electrocardiography and echocardiography.

Materials and Methods

This was a prospective observational study including untreated 36 overt hypothyroid and 42 subclinical hypothyroid patients, age ranged 15-60 years attending the General Medicine out patient department, Government Medical College/ Government General Hospital Nizamabad,Telangana State, from July 2019 to December 2020

Inclusion Criteria

Untreated newly diagnosed overt hypothyroid and subclinical hypothyroid patients age ranged from 15-60 years.

Exclusion Criteria:Patients with known cardiac disorder, hyper-tension, diabetes mellitus, renal failure, pregnancy and patients with

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non-reproducible TSH, T3 and T4 values were excluded from the study

Methodology

After taking informed written consent from the patients,institutional scientific and ethical committee clearance, all included patients were subjected to clinical assessment, thyroid profile,12 lead EGG , standard M-mode 2 D echo and Doppler echocardiography before and 6 months after LT4 replacement therapy with biochemical euthyroidism.For assessment of thyroid status blood samples were collected in the morning time after overnight fast.

Normal levels of thyroid profile was taken as

TSH (0.3-4.5mIU/L), FT4 (1.0-3.0ng/ml), FT3 (0.25-0.65ng/ml).

T4 (52-127ng/ml), T3 (0.7-2.15ng/ml).

Diagnosis of hypothyroidism was confirmed by

1.FT3< 0.25ng/ml,

2.T4< 52ng/ml,

3.TSH>15mIU/ml

Diagnosis of subclinical hypothyroidism was confirmed by

1.TSH> 5mIU/ml and

2.Normal T3, T4 levels.

2DEchocardigraphic techniques and measurements:

M-Mode Echocardiography:

Following parameters were assessed using standard M- mode echo-cardiography:

LVEDD (mm):The distance between left side of IVS and posterior left ventricular endocardium at the level of chorda tendinae at end diastole.LVESD (mm):Above distance at end systole.Diastolic. IVST (mm):Measured as distance between anterior edge of right and left ventricular septalendocardial surface at diastole.Diastolic LVPWT (mm): Measured as vertical distance from anterior edge of endocardial surface to anterior edge of epicardial surface of left ventricular posterobasal wall at end diastole and at end systole.

Doppler Echocardiography:

Systolic Function:

Fractional shortening (FS %):Calculated by the formula

$$FS\% = \frac{LVIDd - LVIDs}{LVIDd}$$

Ejection fraction (EF %):

Diastolic Function:

Peak E (cm/sec):Earlytransmitral flow velocity

Peak A (cm/sec):Latetransmitral flow velocity

IRT (msec):Isovolumic relaxation time.

Statistical Method: The data obtained before and after were compared. Chi-square test was used to find statistical significance of change in mean values of various parameters obtained before and after treatment

Observations and Results

Table 1: Distribution of Study Population according to Age and Gender

Age (in years)	Number	Percentage
≤20	02	2.5%
21-30	15	19.3%
31-40	35	44.8%
41-50	21	26.9%
>50	05	6.5%
Total	78	100%
Gender		
Male	21	26.9%
Female	57	73.1%
Total	78	100%

Majority of the study population (44.8%) were in the age group of 31-40 years with mean age being 38.5 ± 5.5 year. Majority of the study population were females who accounted for 73.1% and males accounted for 26.9%.

Overt Hypothyroidism:At the time of diagnosis all the patients were biochemically hypothyroid with varying clinical features like general weakness, fatigue, weight gain, dry skin .Almost all symptoms disappeared after thyroxine supplementation.

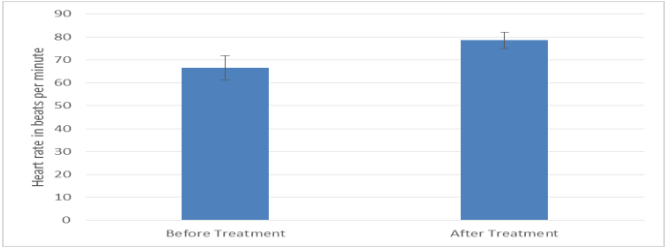

Fig 1: Heart Rate Changes Before and After Treatment

The mean heart rate was 66.5 ± 5.4 before treatment and 78.5 ± 3.5 after treatment (p value <0.01).New onset hypertension was noticed in 12 out of 36 cases. 8 patients had reduction in blood pressure and hypertension persisted in remaining 4 patients. Hypertensives were significantly older (mean age 47.5 ± 10.2 years) than normotensives (31.7 + 5.7 years). They were not on antihypertensive therapy.

Table 2: Electrocardiographic Changes in Overt Hypothyroidism

WNL	10
Low voltage complexes	13
Generalized T wave inversions	05
Nonspecific T wave changes	04
LAHB	04
AV blocks	NIL

Above Table 2 reveals low voltage complexes in 13 patients which became normalized after treatment in all of them.Generalized T-wave inversion was seen in 5 patients which became upright.Nonspecific T-wave changes, left anterior hemi block were seen in 4 cases each which persisted after treatment.QT prolongation was seen in 1 case which became normal after treatment.

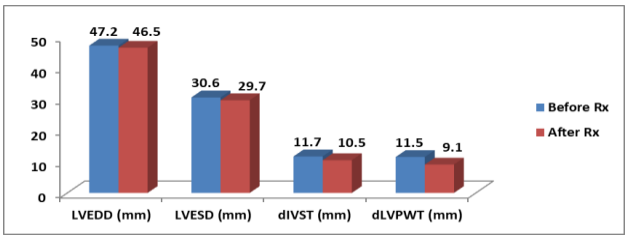

Fig 2:M-Mode Echocardiographic parameters of left ventricular function in overt hypothyroid patients before and after thyroxine replacement therapy

Reduction in interventricular septal thickness(dIVST)was statistically significant (from 11.7 ± 0.8 mm to 10.5 ± 0.5 mm* p<.001). Left ventricular posterior wall thickness (dLVPWT) was significantly more in pretreatment patients (11.5 ± 0.7mm) and after treatment there was significant reduction in thickness (9.1 ± 0.5mm), p <0.01.Though there was change in left ventricular end diastolic (LVEDD) and end systolic (LVESD) diameters after treatment,it was not statistically significant(p>0.05).Mild to moderate pericardial effusion was seen in 22 patients. Severe pericardial effusion was seen in 4 patients of whom 2 had evidence of tamponade and required pericardiocentesis.After treatment pericardial effusion disappeared in 22 patients and mild pericardial effusion was persisting in remaining 4 patients who had very high TSH levels at onset of therapy.

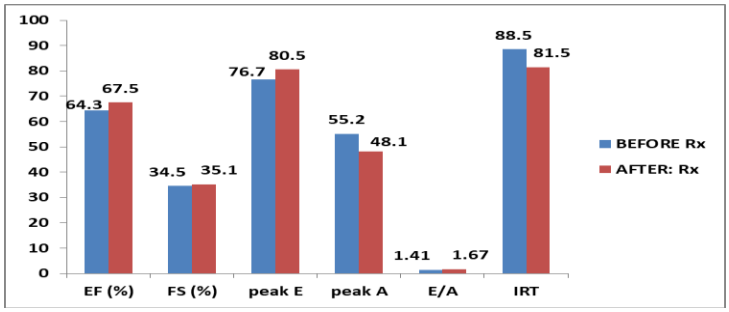

Fig 3:Doppler-Echocardiographic parameters of left Ventricular function in overt hypothyroid patients before and after thyroxine replacement

E/A was significantly reduced in pretreatment patients (1.41 + 0.2), post treatment E/A increased to 1.67 ± 0.1 (p<0.01).Isovolumetric relaxation (IRT) time was "significantly prolonged in pretreatment patient. There was statistically significant reduction of IRT after treatment from 88.5 ± 5.8 to 81.5 ± 4.1 (p<0.01).Above two parameters directly reflect impaired diastolic functions in overt hypothyroidism.

Subclinical Hypothyroidism:Easy fatigue, weight gain and inability to lose weight were common clinical features in patients with subclinical hypothyroidism. Most of the patients had reduction in symptoms after treatment. Mean heart rate was 75.1 ± 5.3 before and 77.8 ± 3.1 after treatment which was statistically not significant. Similar observations were made for blood pressure. 8 patients had blood pressure on upper range which persisted after treatment and all these patients were on higher age side.

Table 3: Thyroid Profile Before and After Treatment

	Before Treatment	After Treatment	p Value
TSH	10.6 ± 2.1	1.7 + 0.6	P< 0.01
T4	101.1 ± 6.5	144.3 ± 1.5	P< 0.01
T3	6.4 ± 1.1	8.6 ± 0.5	P< 0.01

Mean TSH in pretreatment group was 10.6 ± 2.1. TSH normalized after treatment to 1.7 + 0.6. (statistically significant reduction p<0.01). T3, T4 levels though in normal range were on lower side. After treatment increase in T3, T4 levels were significant, (from 101.1 ± 6.5 ng/dl and 6.4 ± 1.1µg/dl) to 144.3 ± 1.5 ng/dl and 8.6 ± 0.5µg/dl. (p<0.01).

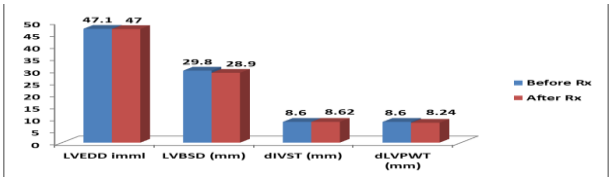

Fig 4:M-Mode Echocardiographic parameters of left ventricular function in subclinical hypothyroid patients before and after thyroxine replacement therapy

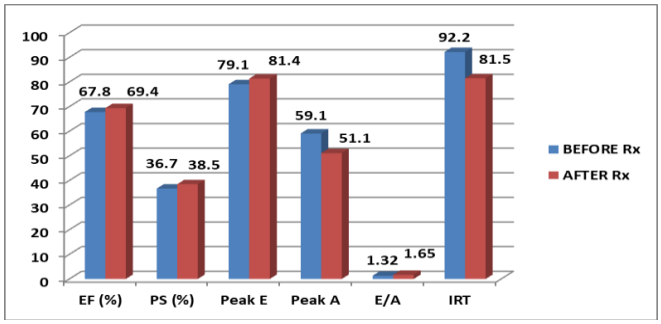

Fig 5:Doppler-Echocardiographic parameters of left ventricular function in subclinical hypothyroid patients before and after thyroxine replacement therapy

Mean E/A was 1.32 ± 0.1 in pretreatment group which increased to 1.65 + 0.5 after hormone therapy (significant "p" value 0.001). Isovolumetric relaxation time was significantly prolonged in subclinical hypothyroidism patients which shortened after treatment (92.2 ± 2.1 vs. 81.5 ± 3.5) (p=0.001).

Discussion

Hypothyroidism has been found to be associated with increased cardiovascular morbidity and mortality , It affects cardiac structures, function, as well as cardiovascular haemodynamics.Cardiac manifestations in hypothyroidism could be due to pericardial effusion (usually accumulates slowly), increased atherosclerosis risk and reduced heart rate and the contractile states of myocardium.

Overt Hypothyroidism

Present study included thirty six subjects of overt hypothyroidism and were evaluated by clinical assessment ,electrocardiography and echocardiographcally, then prospectively compared after 6 months of thyroxine replacement therapy. The study population was dominated by female patients. On thyroxine replacement therapy, the thyroid functions showed an expected improvement to normal. In these patients bradycardia,pericardial effusion and abnormal ECG findings were frequently observed.Verma et.al[4] reported significant bradycardia in overt hypothyroid patients before treatment which improved significantly after treatment. In the present study pretreatment heart rate was significantly lower ($p<0.01$) compared to post treatment. Both bradycardia and decreased stroke volume accounts for decreased cardiac output in patients of hypothyroidism. Kral et al[5] and Rawat et al[6]demonstrated that thyroid hormone replacement increased the cardiac output as both heart rate and stroke volume increased.In the present study of the abnormal ECG changes, low voltage QRS complex was the common finding caused by multiple factors which include severity and duration of hypothyroidism, large pericardial effusion and aging. Of the 13 patients exhibiting low voltage complexes which were severely hypothyroid, 12 had associated pericardial effusion but only three patients were over 50 years age. All the patients had normal voltage complexes post treatment. Saritha et.al[7] reported similar findings in study of 33 patients with hypothyroidism,10 patients who were overtly hypothyroid had low voltage complexes, one patient in whom low voltage complexes persisted despite normalization of thyroid function and disappearance of pericardial effusion. In present study pericardial effusion was found in 26 of 36 patients. It persisted in 4 patients after 6 months of treatment all were severely hypothyroid. Following hormone replacement pericardial effusion was found to typically resolve over 2-12 months without sequelae. A longer period of treatment may possibly lead to complete disappearance of the effusion. Hypothyroidism has long been known to produce abnormalities of cardiac structure and performance. Systolic and diastolic myocardial functions are a sensitive index of myocardial abnormality. In terms of structural changes, various studies have shown alteration in myocardial wall thickness in patients of hypothyroidism. Rawat et al[6] also showed a relatively increased thickness of IVS and LVPW. Increased interventricular septal thickness and diastolic dysfunction, may be the earliest features of progressive thyroid failure[9]. Verma et al[8] and Rawat et al[6] did not find significant differences in LV size between hypothyroid patients. In the present study IVS and LVPW thickness decreased after treatment from 11.7 ± 0.8 to 10.5 ± 0.5 and 11.5 ± 0.7 to 9.1 ± 0.5 respectively, a significant ($p<0.01$) improvement in overtly hypothyroid patients compared to euthyroid patients as observed by Varma et.al, Santos AD, miller et.al,[10] however in present study LVEDD and LVESD did not defer between pre and post treatment patients ($p>0.05$) similar to the study conducted by Sarith Bajaj, PC saxena et.al[7] In the present study, although FS increased from 34.5 ± 1.5 to 35.1 ± 2.1 and EF showed an improvement from 64.3 ± 2.1 to 67.5 ± 3.5 but these value were statistically not significant. Rawat et al[6] demonstrated no significant change in parameters of systolic function while Monzani et al[9] observed that fractional shortening and thus systolic function of LV significantly improved after treatment similar to Fazio, Biondi et.al[11] who reported decreased fractional shortening in overtly hypothyroid patients which improved after treatment while Sarith Bajaj, PC Saxena et.al[7] found no change in FS%.In the present study diastolic dysfunction as suggested by reduced E/A and increased IRT was noted in all patients and showed marked improvement after treatment ($p<0.01$).Saritha Bajaj et.al[7] who studied hypothyroid patients just three months after hormone replacement reported that improvement in diastolic dysfunction though incomplete but was significant. Rajan et al[12] also found significant differences in IVRT in the hypothyroid. Both 'E' wave and 'A' wave velocities increased significantly but there were no significant changes in E/A ratio after treatment. Tielen et al[13]observed an increase in 'E' wave velocity, whereas Virtanen et al[14] found a significant increase in E/A ratio. Rapid improvement in cardiac functions following thyroxine replacement has been previously documented by Santos Ad, Miller et.al[10]Cardiovascular effects of the thyroid hormones are quite dramatic and the cardiac abnormalities associated with thyroid dysfunction have attracted a great deal of investigative effort. Alteration in thyroid status can lead to changes in both systolic and diastolic function of the left ventricle. Such changes may have clinical relevance when they affect target organs over a period of several years. Our study has also substantiated the effects of thyroid hormones on cardiac structure and function. Thus hypothyroid state,which has significant impact on cardiac structure / functions, associated with increased CVS morbidity and mortality is reversible with treatment. The changes in cardiovascular system are directly proportional to the returning euthyroid state.

Subclinical Hypothyroidism: Subclinical hypothyroidism does not produce structural abnormalities but it does manifest functional disturbances. More specifically, these patients have resting LV diastolic dysfunction, evidenced by delayed relaxation, and impaired

systolic dysfunction on effort that results in poor exercise capacity. These changes are reversible when euthyroidism is restored. Cardiac function has been previously investigated by noninvasive, techniques in patients with subclinical hypothyroidism. Earlier, systolic time intervals were measured to give an insight into the myocardial function[14,15].In present study also we did not found any abnormality in LV systolic function. The EF, an index of LV systolic function was comparable between pre and post treatment patients.. Some authors reported prolonged systolic time intervals in subclinical hypothyroidism, which improved after thyroxine therapy. In contrast, Tseng et al[16]found that the isovolumic contraction time, the pre ejection period, and the ratio of pre ejection period to LV ejection time were normal in patients with subclinical hypothyroidism.Arem et al[17], using Doppler echocardiography at rest and during exercise in eight patients with subclinical hypothyroidism, found normal cardiac structure and function, and mild prolongation of the pre ejection period during exercise and slightly reduced LV diastolic dimensions at rest. Bell et al[18], by radionuclide ventriculography showed that patients with subclinical hypothyroidism have normal ejection fraction at rest, with a small (but significant) increase in LV ejection fraction during maximal exercise after thyroxine therapy. Forfar et al[19]. also reported a blunted increase in ejection fraction during exercise, with a clear improvement in this parameter after thyroxine replacement therapy.Foldes et al[20]found a lower ejection fraction, both at rest and during physical exercise, in patients with subclinical hypothyroidism. The discrepant results reported in previous studies of cardiac involvement in subclinical hypothyroidism might be in part related to the different patient selection (age, inclusion of patients with previous hyperthyroidism, evaluation of patients with acute or unstable subclinical hypothyroidism) and to the different diagnostic criteria (too-large range of TSH levels).Ridgway et al[21]reported prolongation of LV pre ejection period (PEP) and an increase in ratio between PEP and LV ejection time (LVET). Bell et al[18]reported decrease in LV ejection fraction (EF) during exercise. This abnormality in EF was reversed after thyroxine therapy. However, Arem et al[17]found normal cardiac function in patients with SH both at rest and during exercise.In the present study, we performed a strict selection of patients with stable subclinical hypothyroidism, excluding patients with confounding factors particularly affecting the cardiovascular system. The impaired diastolic function in this group of patients suggests that subclinical hypothyroidism is a condition of minimal tissue hypothyroidism rather than a compensated state. If this is the case, the patients with subclinical hypothyroidism should all be considered as potential candidates for therapy with thyroxine. Among the indices of systolic function, only mean aortic acceleration was significantly reduced in the group of patients with subclinical hypothyroidism. Therefore, this index seems to be the most susceptible to variations in thyroid hormone levels. Furthermore, in the groups of patients with subclinical hypothyroidism treated with replacement thyroxine therapy, SVR was significantly reduced, which confirms a directvasodilatory effect of thyroid hormone. Estimation of mean aortic acceleration was not done in our study.Subclinical hypothyroidism may impair directly diastolic function by reducing sarcoplasmatic calcium ATPase activity, with consequent impairment of ventricular diastolic function[20,21].Present study demonstrated a wide range of LV relaxation abnormality with prolonged DT, IVRT and reduced E/A ratio.Similar findings have been reported by Biondi et al[11]. Vitale et al[22] studied LV diastolic function both by conventional Doppler and tissue Doppler echocardiography and they demonstrated significant abnormalities in LV diastolic function though tissue Doppler echocardiography was more valuable in finding subtle abnormalities, they concluded that regional E/ A ratio was a reliable parameter to detect diastolic properties of LV walls.We found the diastolic function abnormalities to be reversible 6 months after thyroxine therapy , Biondi et al[11] reported similar findings. The diastolic parameters depend upon cytosolic calcium concentration modulated by sarcoplasmic reticulum, ATP dependent calcium. Calcium transport is controlled by thyroid hormones. Hence, diastolic dysfunction can occur in patients with subclinical hypothyroidism. This diastolic impairment may be a prelude to systolic dysfunction. Therefore, the diastolic dysfunction observed in the current study could be the prelude to more serious limitations of cardiac function and physical performance and our finding may be causally related to the blunted increase of LV ejection fraction during exercise observed in patients with Subclinical hypothyroidism

Limitations of Study: Controls with cardiac manifestations without hypothyroidism were not included in the study and follow up period was of 6 months only.

Conclusion

Mild to moderate pericardial effusion is a common finding in our study. Pericardial effusion disappeared significantly after 6 months of thyroxine therapy. Majority did not require pericardiocentesis. Interventricularseptal thickness and left ventricular posterior wall thickness are significant markers of structural abnormalities of myocardium and their regression to normal is significant after thyroxine therapy. With thyroxine therapy the improvement in diastolic dysfunction is much more when compared to systolic dysfunction of heart. Structural abnormalities of heart are less commonly seen in subclinical hypothyroidism cases. Doppler-echocardiography represents a simple and reliable method for the evaluation of morphology and function in patients with hypothyroidism with its additional advantage of repeatability it can be used to serially evaluate the adequacy and efficacy of thyroxine dose.

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