ORIGINAL ARTICLE

Left Ventricular Function in Patients of Subclinical Hypothyroidism and Effect of L- Thyroxine Therapy

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Abstract

Subclinical hypothyroidism (SCH) has been recognized in several studies to be associated with markers of cardiovascular risk and cardiovascular impairment. Even minor deviations from serum TSH normal range might have adverse effects on cardiovascular performance in the general population. Cardiac function was evaluated in 30 patients of SCH using 2-D Doppler echocardiography before & after replacement of L-thyroxine.. On comparative evaluation of echocardiography diastolic indices before and after LT4 replacement, DT decreased from 208.96 ± 21.34 msec to 194.13 ± 20.57 msec ($p < 0.05$), IVRT decreased from 86.9 ± 9.06 msec to 84.77 ± 8.26 msec ($p <0.05$), E wave increased from 0.65 ± 0.19 m/s to 0.69 ± 0.19 m/s ($p <0.05$), A wave decreased from 0.74 ± 0.10 m/s to 0.71 ± 0.08 m/s ($p <0.05$), E/A increased from 0.88 ± 0.29 to 0.97 ± 0.28 ($p <0.05$). On statistical evaluation, all echocardiographic diastolic indices before and after LT4 replacement were significant ($p <0.05$).The present study reveals abnormalities of the Left Ventricular diastolic function in patients of Subclinical Hypothyroidism which can be reversed by short-term Levo-thyroxine replacement therapy.

Key Words

Subclinical Hypothyroidism, L-thyroxine, Echocardiography, Myocardial Contractility

Introduction

Subclinical hypothyroidism (SCH) is defined as a serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine (1) . Despite this definition, not all adult subjects with SCH are really asymptomatic, sometimes presenting symptoms or signs of hypothyroidism, such as dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramps, cold intolerance, puffy eyes, constipation, and hoarseness (2). Up to 80% of patients with SCH may have vague non-specific symptoms of hypothyroidism, but attempts to identify the patients on the basis of clinical findings have not been successful, so the diagnosis can only be made with laboratory findings (3) SCH has been recognized in several studies to be associated with markers of cardiovascular risk and cardiovascular impairment. Even minor deviations from serum TSH normal range might accelerate the development of atherosclerosis and have adverse effects on cardiovascular performance in the general population (4,5). Furthermore, the abnormalities in myocardial contractility and the changes of the lipoprotein profile that are frequently documented in hypothyroid patients have been reported. Diastolic function, however, rather than systolic cardiac function, seems to be mostly impaired by thyroid hormone deprivation (6). One large, cross-sectional epidemiologic study concluded that subclinical hypothyroidism was a risk factor for aortic atherosclerosis and myocardial infarction with a risk comparable to that associated with diabetes mellitus, hypercholesterolemia, and smoking(7). Therefore, SCH may be considered a true risk factor for the development of coronary heart disease. Indeed, a progression of coronary angiographic lesions in untreated SCH patients in comparison with L-T4 treated SCH patients has been reported. Recently, it has been reported by an ultrasonic tissue characterization technique (videodensitometry) that SCH is associated with early abnormalities in both myocardial function and structure, which are reversible

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with replacement therapy (8).

Material and Methods

A prospective, open label trial was conducted in Post Graduate Department of Internal Medicine and Endocrinology Unit in collaboration with the Department of Cardiology at Government Medical College, Jammu over a period of one year starting from Nov 2010 to Nov 2011.The study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from all the subjects after explaining them the nature & purpose of study.

The patients reporting to the Medical OPD were screened for the selection criteria followed by enrollment in the study. A total of 40 patients attending Medicine OPD were enrolled for the study. Out of these 40 patients, 35 patients fulfilled the eligibility criteria and were subsequently included in the study. Out of these only 30 patients completed the study. 20 age and sex matched control were taken.

Following criteria for the selection of patients was used:

Inclusion Criteria

Established cases of SCH of either sex in the age group of 18-55 years. Patients giving written informed consent.

Exclusion Criteria

Known cases of cardiovascular disease (Hypertension, Ischaemic heart disease, congestive heart disease, coronary heart disease, congenital heart disease, valvular heart disease. Associated co-morbid conditions (Diabetes, COPD, Chronic kidney disease. Drugs affecting thyroid function (Beta blockers, corticosteroids, rifampicin, amiodarone. Smoker,Pregnancy and lactation, Pituitary/ hypothalamic disorders, any functional thyroid disorders in the past, H/O drug abuse/dependence

After screening for the above mentioned selection criteria, all the patients were screened on the basis of a detailed history, physical examination, baseline investigations, followed by enrollment in the study. T3, T4, TSH levels were performed in the endocrine laboratory of Govt. Medical College, Jammu by radioimmunoassay.

The enrolled patients were screened for the left ventricular function on Toshiba, Nemio trans-thoracic 2-D conventional and color Doppler echocardiography with subjects in partial left decubitus for LV systolic and diastolic functions. M-mode quantitative analysis was performed as per the guidelines laid down by the American Society for Echocardiography (9).

The subclinical hypothyroid patients with established LVD were put on Levo-thyroxine substitutive therapy with a starting dose of 25microgms daily, titrated if required on an individual basis aiming to normalize TSH. None of the subjects received any medication during the study period, other than L-thyroxine for the subgroup of patients randomly selected. 20 age and sex matched controls were taken. L-thyroxine therapy was continued until the patient became euthyroid or until 6 months of institution of therapy.SCH patients with established LVD on L-thyroxine therapy were evaluated as per the following protocol:T3, T4 and TSH estimated by radioimmuno assay method repeated every 6 weekly. 2-D echocardiography at the start of therapy and re-evaluated once the patient became euthyroid. The echocardiographer was blinded as to whether the person he is examining is hypothyroid or a control subject.

Quantification of Left Ventricle:

Linear measurements of inter ventricular septal wall thickness, posterior wall thickness, left ventricle internal dimension recording was made from the parasternal long-axis acoustic window. Left ventricle internal diameter, LVID (d) & LVID (s) respectively, & wall thickness was measured at the level of the left ventricle minor axis, approximately at the mitral valve leaflet tips. Left ventricle internal diameter, left ventricle posterior wall thickness (LVPWT), interventricular septal thickness (IVST) were measured at end-diatole & end-systole from 2D-& M-mode recordings on several cardiac cycles.End-diastole measurements were made at the frame after mitral valve closure & end-systole at the frame proceeding mitral valve opening.Mid wall fraction & shortening was computed from linear measures of diastolic & systolic cavity sizes & wall thickness.

Statistical Analysis

Comparisons among subclinical hypothyroid patients with established LVD before and after thyroxine treatment are performed using Student's t test for paired data whereas comparisons among controls and subclinical hypothyroid patients are performed using the Student's t-test for unpaired data. A p value of less than <0.05 was considered statistically significant. characteristics are presented as percentages for quantitative variables.

Results

A total of 40 patients attending Medicine OPD were enrolled for the study. Out of these 40 patients, 35 patients fulfilled the eligibility criteria and were subsequently included in the study. Out of these only 30 patients completed the study. 20 age and sex matched controls were taken. Out of a total of 20 subjects in the control group, 16 (80%) were females & 4 (20%) were males (*Table 1*) whereas out of a total of 30 subjects in the test group, 27 (90%) were females & 3 (10%) were males (*Table 2*).

Table 1. Sex Distribution of the Subjects in Control Group (N=20)

Sex	Number	Percentage
Male	4	20
Female	16	80
Total	**20**	**100**

Table 2. Sex distribution of the subjects in test group (n=30)

Sex	Number	Percentage
Male	3	10
Female	27	90
Total	**30**	**100**

Baseline values of T3 in the control group ranged from 0.88-1.27ng/dl (Mean 1.05 ± 0.13), T4 ranged from 72-103ng/dl (Mean 81.5 ± 8.69), TSH ranged from 1.9-4.4 uIU/ml (Mean 3.63 ± 0.63). Similarly, baseline values of T3 in the test group ranged from 0.81-1.25 ng/dl (Mean 0.99 ± 0.13), T4 ranged from 64-101 ng/dl (Mean 77.73 ± 8.73), TSH ranged from 8.99-21 uIU/ml (Mean 13.57 ± 2.87). As expected, TSH levels were significantly higher in patients than in controls (*Table 3*).

On comparative evaluation of echocardiographic systolic indices among the test group and controls it was found that IVST (s), IVST (d), LVID (s), LVID (d), LVPWT (s), LVPWT (d) values were higher in the test group as compared with controls & FS, SV & CO values were lower in the test group as compared with controls. However, on statistical evaluation the differences were non-significant (p >0.05) (*Table 3*).

In the control group mean DT was 191.35 ± 21.98 msec, IVRT was 78.55 ± 10.65 msec, E wave was 0.76

Table 3.Baseline Thyroid Profile in the Test (n=30) and Control Group (n=20) (mean sd)

Group	T3 (ng/dl)	T4 (ng/dl)	TSH (μIU/ml)
Control	1.05 ± 0.13	81.5 ± 8.69	3.63 ± 0.63
Test	0.99 ± 0.13	77.73 ± 8.73	13.57 ± 2.87

Table 3. Comprison of Echocardiographic systolic Parameters in the Control (n=20) and test group (n=30) Group (mean sd)

Index		Control	Test Group
IVST (mm)	S	9.62 ± 1.44	9.69 ± 1.4
	D	8.4 ± 1.06	8.42 ± 0.79^
LVID (mm)	S	33.25 ± 0.92	33.29± 0.82^
	D	49.34 ± 1.06	49.38 ± 0.95^
LVPWT (mm)	S	8.17 ± 1.93	8.23 ± 2.22^
	D	6.89 ± 1.52	6.97 ± 1.36^
FS (%)		36.20 ± 2.82	35.83 ± 3.46^
SV (ml)		70.50 ± 8.43	70.16 ± 8.39^
CO (lts/min)		5.50 ± 8.43	5.75 ± 0.61^
EF (%)		61.15 ± 3.84	60.33 ± 3.15^

Table 4. Comparison of Echocardiography Diastolic Parameters in the Control (n=20) and Test (n=30) Group (mean ± sd)

Index	Controls	Test group
DT (msec)	191.35 ± 21.98	208.96 ±21.34*
IVRT (msec)	78.55 ± 10.65	86.9 ±9.06*
E wave (m/s)	0.76 ± 0.19	0.65 ±0.19*
A wave (m/s)	0.67 ± 0.09	0.74 ±0.10*
E/A	1.13 ±0.29 *	0.88 ± 0.29*

*n= number of subjects *= p<0.05 (Significant) =p>0.05 (Non-significant)*

Table 5. Echocardiography Systolic (sv) Indices in the Test Group Before and After lt4 Replacement (mean sd)

Index		Control	Test Group
IVST (mm)	**S**	9.69 ±1.4	9.56 ±1.08^
	D	8.42 ± 0.79	8.37 ±0.69^
LVID (mm)	**S**	33.29 ±0.82	33.23± 0.83^
	D	49.38 ±0.95	49.36 ± 0.92^
LVPWT (mm)	**S**	8.23 ± 2.22	8.10 ±1.74^
	D	6.97 ± 1.36	6.93 ±1.25^
FS (%)		35.83 ±3.46	36.27 ± 3.48^
SV (ml)		70.16 ±8.39	70.2 ±8.25^
CO (lts/min)		5.75 ± 0.61	5.78 ±0.70^
EF (%)		60.33 ±3.15	60.37 ± 2.68^

*n= number of subjects *= p<0.05 (Significant) =p>0.05 (Non-significant)*

Table 6. Echocardiographic diastolic indices in the test group (n=30) before and after lt4 Replacement (mean ± sd)

Index	Before	After
DT (msec)	208.96 ±21.34	194.13 ±20.57*
IVRT (msec)	86.9 ±9.06	84.77 ±8.26*
E wave (m/s)	0.65 ±0.19	0.69 ±0.19*
A wave (m/s)	0.74 ±0.10	0.71 ±0.08*
E/A	0.88 ±0.29	0.97 ±0.28*

±0.19 m/s, A wave was 0.67 ± 0.09 m/s, E/A ratio was 1.13 ± 0.29.In the test group mean DT was 208.96 ± 21.34 msec, IVRT was 86.9 ± 9.06 msec, E wave was 0.65 ± 0.19 m/s, A wave was 0.74 ± 0.10 m/s, E/A ratio was 0.88 ± 0.29. On statistical evaluation the differences were highly significant ($p < 0.05$). Doppler-derived indices of left ventricular (LV) diastolic filling showed clear abnormalities of myocardial relaxation, as indicated by significant prolongation of the isovolumic relaxation time and significant reduction of the early diastolic mitral flow velocity/late diastolic mitral flow velocity (E/A) ratio. There was no significant change in left atrial diameter in both the groups (*Table 4*).

On comparative evaluation of echocardiography diastolic indices before and after LT4 replacement, DT decreased from 208.96 ± 21.34 msec to 194.13 ± 20.57 msec ($p < 0.05$), IVRT decreased from 86.9 ± 9.06 msec to 84.77 ± 8.26 msec ($p < 0.05$), E wave increased from 0.65 ± 0.19 m/s to 0.69 ± 0.19 m/s ($p < 0.05$), A wave decreased from 0.74 ± 0.10 m/s to 0.71 ± 0.08 m/s ($p < 0.05$), E/A increased from 0.88 ± 0.29 to 0.97 ± 0.28 ($p < 0.05$). On statistical evaluation, all echocardiographic diastolic indices before and after LT4 replacement were significant ($p < 0.05$). There was no change in left atrial diameter after L-T4 replacement therapy (*Table 6*).

Discussion

As cardiovascular system is one of the principal targets of thyroid hormone so, cardiac function was evaluated in 30 patients of SCH using 2-D Doppler echocardiography before & after replacement of L-thyroxine.

Analysis of the results reveals that out of a total of 30 subjects in the test group, majority of the patients (90%) were females. Cardiac function has been previously evaluated in patients with SCH, by systolic time intervals, with conflicting results (10,11). Evaluation of the data generated from the current study reveals that in comparison to controls, the test group showed numerically impaired left ventricular systolic function but on statistical evaluation, the impairment was non-significant ($p > 0.05$). The results are in accordance with the study which found that the isovolumic contraction time, the preejection period, and the ratio of preejection period to LV ejection time

were normal in patients with SCH, as assessed by simultaneous recording of aortic and mitral flow velocities . . . . . *et al* also showed no abnormalities of the left ventricular morphology but a slight, but not significant, reduction in the systolic function in the patient group (13) . Mishra TK *et al* confirmed similar findings that systolic function was normal in patients with SCH. EF, an index of LV systolic function was comparable between controls & the patients.(14)

On evaluation of left ventricular diastolic parameters (DT, IVRT, E wave, A wave, E/A ratio) in the control and test group, it was found that there was a statistically significant ($p < 0.05$) impairment of the left ventricular diastolic functions in the test group on 2-D and M-mode echocardiography. Our results are in comparable with the results of Vitale G et al, who demonstrated significant abnormalities in LV diastolic function (15). Brenta G *et al*, 2003 also reported that time to peak filling rate (TPFR), a parameter of left ventricular (LV) diastolic function is impaired in subclinical hypothyroid patients both at rest and during exercise (6). Kosar F *et al*, 2005 found significantly lower early diastolic mitral and tricuspid annular velocity (Ea), early / late (Ea / Aa) diastolic mitral and tricuspid annular velocity ratio, and significantly longer isovolumetric relaxation time (IRT) of left and right ventricles and concluded that SCH is associated with impaired RV diastolic function in addition to impaired LV diastolic function (16).

In the present study, on comparative evaluation of echocardiographic systolic indices before and after LT4 replacement there was a numerical improvement of the systolic parameters in the test group but on statistical evaluation, the indices were found to be non-significant ($p >0.05$). Results of our study are comparable with the study conducted by Mishra TK et al (14).

On comparative evaluation of echocardiographic diastolic indices (DT, IVRT, E wave, A wave, E/A ratio in the present study, before and after LT4 replacement, there was a statistically significant ($p <0.05$) improvement of the diastolic parameters in the test group. Our results are comparable with the study of Biondi B *et al* who showed significant shortening of IVRT, reduction of A wave and increase in E/A ratio which were reversible on LT4 therapy(13). Brenta G *et al* concluded in his study that time to peak filling rate (TPFR), a parameter of LV diastolic function is impaired in SCH both at rest and during exercise and returns to normal values after LT4 therapy(6) . Franzoni F *et al* also confirmed that subclinical hypothyroid patients exhibited a lower E, a higher A and, subsequently, a reduced E/A ratio of both lateral wall and interventricular septum ($P < 0.001$ or both) (17). The IVRT was distinctly longer in subclinical hypothyroid patients, as compared to controls ($P <0.001$). At 6 months, L-thyroxine treated patients showed a significant increase of E and a subsequent increase of E/A ratio where as IVRT significantly reduced ($P <0.05$). Similar results were also reported by Yazicia M *et al* (18). Possible mechanism for diastolic dysfunction can be attributed to the fact that thyroid hormones modulate the expression and function of several enzymes and proteins involved in the cardiac performance, such as sarcoplasmic reticulum CaATPase (SERCA II), Na/K ATPase, and alpha/beta-myosin heavy chains (19). Thyroid hormones effects on the heart are exerted both by direct influence at cellular level, involving nuclear and extranuclear mechanisms, and by indirect interactions with the renin-angiotensin-aldosterone system, sympathetic nervous system, natriuretic peptides and erythropoietin secretion (20). There is experimental evidence showing a regulatory involvement of thyroid hormones on interstitial protein gene expression, modulating production of collagen type I, a main component of the heart matrix, which plays an important role in maintaining the integrity of myocardial function (21).

The discrepant results reported in previous studies of cardiac involvement in SCH might be, in part, related to the different patient selection. Inability to demonstrate significant systolic dysfunction in our present study could be explained on the basis of fact that an an impairment of diastolic function is a common finding in many cardiac diseases, and it often precedes & causes systolic dysfunction. It has been documented that 30-40% of heart failure syndromes are secondary to impaired diastolic function (22).

Therefore, the doppler-derived indices of left ventricular (LV) diastolic function of the current study showed clear abnormalities of myocardial relaxation, as indicated by significant prolongation of the isovolumic

relaxation time, DT and significant reduction of the early diastolic mitral flow velocity/late diastolic mitral flow velocity (E/A) ratio. These changes were reversible with short term LT4 replacement therapy.

There was no significant difference in systolic functions as evaluated by 2-D echocardiography between patients of Subclinical Hypothyroidism and controls. Diastolic dysfunction was demonstrated by significant prolongation of the isovolumic relaxation time and significant reduction of the early diastolic mitral flow velocity/late diastolic mitral flow velocity ratio echocardiographically in Subclinical Hypothyroid patients as compared to controls. Systolic function as demonstrated by 2-D echocardiography showed no significant change in patients of Subclinical Hypothyroidism after Levo-thyroxine replacement therapy. Diastolic dysfunction as demonstrated by 2-D echocardiography in patients with Subclinical Hypothyroidism improved significantly after Levo-thyroxine replacement therapy.

In conclusion, the present study reveals abnormalities of the Left Ventricular diastolic function in patients of Subclinical Hypothyroidism which can be reversed by short-term Levo-thyroxine replacement therapy. Therefore, the patients of Subclinical Hypothyroidism need to be evaluated and followed for Left Ventricular function. Studies of longer duration with a large sample size are further recommended to evaluate the efficacy of Levo-thyroxine replacement therapy in patients with Subclinical Hypothyroidism.

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