Original Research Article

Correlation exists between serum TSH and doppler echocardiography findings regarding diastolic dysfunction of left ventricle

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Abstract

Background: Thyroid hormonal abnormalities and cardiovascular disease goes well beyond the risk of atherosclerosis in association with hypothyroidism and the risk of atrial fibrillation in persons with hyperthyroidism. Early identification of patients with sub-clinical hypothyroidism may lead to early treatment and thereby favourable effect on cardiovascular morbidity and mortality. **Methods:** Patients admitted in the department of Medicine, Darbhanga Medical College and Hospital with heart failure and diabetes mellitus who were willing to be enrolled in the study. Study Period: March 2017 to April 2018. Patients were initially selected on the basis of clinical suspicion. They were then subjected to thyroid function test (serum T3, T4, TSH estimation). Elevated TSH was the prime criterion in the diagnosis of hypothyroidism (serum TSH>6 mIU/L). **Results**: Out of the 50 hypothyroid patients with left ventricular diastolic dysfunction, we lost follow-up of 8 patients during our study before the first assessment. compares change in serum thyroid hormone levels in hypothyroid patients before and after treatment. Significant rise was observed in serum T3 level after 3 weeks and 3 months of treatment, from 0.85 ± 0.48 to 1.10± 0.41 and 2.14± 0.62 respectively. Serum T4 level also showed significant rise after 3 weeks and 3 months of treatment with L-thyroxine from 43.64 ± 16.37 to 52.12± 14.73 and 92.13± 18.35 respectively. Serum TSH level did not show a significant decrease after 3 weeks of treatment (44.90± 25.19, P>0.05), but a significant decrease was seen after 3 months of treatment with L-thyroxine from 51.33 ± 30.00 to 4.41± 1.70. compares left ventricular diastolic function parameters in hypothyroid patients before and after treatment with l-thyroxine. After 3 weeks of treatment a significant increase was observed in E_{max} from 60.14 ± 8.12 to 62.02± 6.08, but there was no significant decrease in A_{max} value. However due to an increase in E_{max}, the E/Amax ratio was significantly increased from 0.75 ± 0.08 to 0.81± 0.09 after 3 weeks of treatment. No significant decrease was observed in IVRT and DT after 3 weeks. **Conclusion:** The probable mechanism of improvement of left ventricular diastolic dysfunction in the early part of thyroxine replacement therapy was due to biochemical changes i.e. induction of calcium ATPase b L-thyroxine in sarcoplasmic reticulum of myocardial cells.

Key Words: Cardiovascular disease, atrial fibrillation, hyperthyroidism, diabetes mellitus, L-thyroxine, left ventricular diastolic function.

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INTRODUCTION

The heart is affected by thyroid hormone, and it is could to have adverse cardiac effects in thyroid disorder.[1] Thyroid dysfunction itself exists in a wide range – from hyperthyroid state to hypothyroid with subclinical hyperthyroidism and subclinical hypothyroidism in between. Clinically, apparent illness in the extreme two disorders can easily seek medical attention. The problem exists in dealing with the subclinical dysfunctions. A number of studies have demonstrated cardiac problems in both subclinical hyperthyroidism and subclinical hypothyroidism. There is

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an increased resting heart rate; supravenrticular arrhythmias, diastolic dysfunction, and increased left ventricular mass are some of the established cardiological manifestations of subclinical hyperthyroidism.[2,3] Subclinical hypothyroidism is defined as variable increase in serum thyroid stimulating hormone (TSH) concentration with apparently normal serum free T4 and free T3 levels.[4] Prevalence of subclinical hypothyroidism is about 10% among individuals over age 60 years, with a higher prevalence in women.[4] According to some literature, it is associated with left ventricular diastolic dysfunction and may also lead to exercise intolerance and diastolic heart failure or atherosclerosis.[5] Doppler echocardiography has been used extensively to evaluate left ventricular systolic and diastolic function in patients with subclinical hypothyroidism. Alterations of left ventricular diastolic function, indications by a prolonged isovolumetric relaxation time (IVRT), and abnormal time-to-peak filling rate are the most common association reported.[5] On the other hand, some authors clearly deny any association of cardiac dysfunction in subclinical hypothyroidism.[15-16] That is why, there is no established guideline regarding treatment plan of these patients. Some favour treatment with levothyroxine whereas others disagree. Diastolic failure appears when the ventricle cannot be filled properly because it cannot relax or because its wall is thick or rigid. This situation presents usually a concentric hypertrophy. In contrast, systolic heart failure has usually an eccentric hypertrophy.[6] Diastolic failure is characterized by an elevated diastolic pressure in the left ventricle, despite an essentially normal/physiologic end diastolic volume (EDV). Histological evidence supporting diastolic dysfunction demonstrates ventricular hypertrophy, increased interstitial collagendeposition and infiltration of the myocardium. These influences collectively lead to a decrease in distensibility and elasticity (ability to stretch) of the myocardium. As a consequence, cardiac output becomes diminished. When the left ventricular diastolic pressure is elevated, venous pressure in lungs must also become elevated too: left ventricular stiffness makes it more difficult for blood to enter it from the left atrium. As a result, pressure rises in the atrium and is transmitted back to the pulmonary venous system, thereby increasing its hydrostatic pressure and promoting pulmonary edema.[7] It may be misguided to classify the volume-overloaded heart as having diastolic dysfunction if it is behaving in a stiff and non-compliant manner. The term diastolic dysfunction should not be applied to the dilated heart. Dilated ("remodeled") hearts have increased volume relative to the amount of diastolic pressure, and therefore have increased (*not* decreased) distensibility. The term diastolic dysfunction is sometimes erroneously applied in this circumstance, when increased fluid volume retention causes the heart to be over-filled (High output cardiac failure).[6] An echocardiographic examination was performed before enrollment and three months after euthyroid state was achieved. The cardiologists (A.F.E. and M.C.) who performed and interpreted the echocardiograms were blind to the clinical and treatment status of the patients. A Vingmed System V echocardiography unit was used (General Electric, Norway). Frequence of the probe was 1.7 MHz and it was capable of harmonic imaging. B-mode, M-mode, continous wave Doppler, and colour Doppler examinations were performed utilising parasternal long axis, parasternal short axis, and apical two- and four-chamber views with the patient in the left lateral decubitus position. Left ventricular end-diastolic and end-systolic diameters, systolic and diastolic thicknesses of the interventricular septum, and the posterior wall were measured during M-mode examination. Left ventricular mass index (LVMI) was calculated according to Devereux’s formula[8]. Left ventricular ejection fraction was calculated according to Teicholtz method. Transmitral flow velocities were measured using pulsed-wave Doppler in the apical four-chamber view. A sample volume of 2 mm was placed between the mitral leaflet tips, E and A velocities were measured, and E/A ratio was calculated. E wave deceleration time was measured in milliseconds. Using continous-wave Doppler tracings obtained at the apical five-chamber view, isovolumetric contraction time (ICT), isovolumetric relaxation time (IVRT), and aortic ejection time (ET) were measured. Myocardial performance index (MPI) was calculated by dividing the sum of ICT and IVRT by ET. Tissue Doppler was employed to measure systolic and diastolic mitral annular velocities. Tissue Doppler sample volume was placed on septal and lateral localizations of the mitral annulus in the apical four-chamber view and the anterior and inferior localizations in the apical two-chamber view. Systolic (S) and diastolic (E′ and A′) velocities of the annulus were measured Pulsed wave Doppler-derived E wave velocity/tissue Doppler-derived E′ velocity ratio (E/E′). An echocardiographic examination was performed before enrollment and three months after euthyroid state was achieved. The cardiologists (A.F.E. and M.C.) who performed and interpreted the echocardiograms were blind to the clinical and treatment status of the patients. A Vingmed System V echocardiography unit was used (General Electric, Norway). Frequence of the probe was 1.7 MHz and it was capable of harmonic imaging. B-mode, M-mode, continous wave Doppler, and colour Doppler examinations were performed utilising parasternal long axis, parasternal short axis, and apical two- and four-chamber views with the patient in the left lateral decubitus position. Left ventricular end-diastolic and end-systolic diameters, systolic and diastolic thicknesses of the interventricular septum, and the posterior wall were measured during M-mode examination. Left ventricular mass index (LVMI) was calculated according to Devereux's formula [8]. Left ventricular ejection fraction was calculated according to Teicholtz method. Transmitral flow velocities were measured using pulsed-wave Doppler in the apical four-chamber view. A sample volume of 2 mm was placed between the mitral leaflet tips, E and A velocities were measured, and E/A ratio was calculated. E wave deceleration time was measured in milliseconds. Using continous-wave Doppler tracings obtained at the apical five-chamber view, isovolumetric contraction time (ICT), isovolumetric relaxation time (IVRT), and aortic ejection time (ET) were measured. Myocardial performance index (MPI) was calculated by dividing the sum of ICT and IVRT by ET. Tissue Doppler was employed to measure systolic and diastolic mitral annular velocities. Tissue Doppler sample volume was placed on septal and lateral localizations of the mitral annulus in the apical four-chamber view and the anterior and inferior localizations in the apical two-chamber view. Systolic (S) and diastolic (E′ and A′) velocities of the annulus were measured Pulsed wave Doppler-derived E wave velocity/tissue Doppler-derived E′ velocity ratio (E/E′).

MATERIALS AND METHODS

Study Population: Patients admitted in the department of Medicine, Darbhanga Medical College and Hospital, with heart failure and diabetes mellitus who were willing to be enrolled in the study.

Study Period: March 2017 to April 2018.

Selection of hypothyroid patients: Patients were initially selected on the basis of clinical suspicion. They were then subjected to thyroid function test (serum T3, T4, TSH estimation). Elevated TSH was the prime criterion in the diagnosis of hypothyroidism (serum TSH>6 mIU/L). One hundred and fifteen patients were selected from our Medicine outdoor and indoor medical wards of Darbhanga Medical College and Hospital, Bihar. After selection they were evaluated by Doppler echocardiography study. Among 115 patients, 50 patients were found to have Echo-doppler criteria of left ventricular diastolic dysfunction. These 50 patients were finally selected for the study.

Left ventricular diastolic dysfunction was considered when; (Echodoppler criteria)

- E_{max} (early diastolic filling velocity of mitral valve) was decreased compared to A_{max} (Late diastolic filling velocity of mitral valve) i.e, $E_{max}<A_{max}$ and their ratio E/Amax is less[63] than one (E/A =1.7+/-0.6,normal range)
- Mitral E wave decleration time (peak of E wave to end of E wave, i.e, DT) and Isovolumic relaxation time(IVRT) with higher than normal values also reflected diastolic dysfunction.(DT=184+/-24msec, IVRT=74+/-26msec,normal range).

Echocardiographic assessment: One hundred and fifteen patients with overt hypothyroidism underwent echodoppler study. Amongst these 115 patients, fifty patients of overt hypothyroidism with echodoppler evidence of left ventricular diastolic dysfunction were selected for our study. Echocardiographic study was repeated after 3 weeks and 3 months, after thyroxine supplement therapy. 8 patients lost follow-up during our study before the first assessment at 3 weeks of treatment. 50 sex and age matched normal subjects served as control.

Position of windows: Patients were examined in left lateral position after 30 minutes of recumbency, from parasternal and apical windows.

2D Scanning: 2D sector scanning was used from parasternal and apical windows to screen valvular abnormalities, systolic anterior motion of mitral valve and pericardial disease.

M mode measurement: IVST in end diastole, LVPWT in end diastole, Left ventricular internal diameter in diastole and (LVEDD) were noted.

Diastolic dysfunction: Pulsed wave doppler was used to measure mitral flow velocities with the sample volume placed between leaflet tips. The following diastolic filling parameters were obtained: E_{max} = mitral E peak velocity (Early diastolic filling velocity of mitral valve) A_{max} = mitral A peak velocity (Late diastolic filling velocity of mitral valve) E/A_{max} ratio was calculated DT = mitral E wave deceleration time IVRT = Isovolumic relaxation time

Biochemical evaluation of Thyroid function: Serum T3,T4 and TSH were measured with CLIA Methods (Monobind)

Normal range of [62]

T3 → 1.54-3.08 nmol/L
T4 → 4.5-11.8 nmol/L
TSH → 0.3-6 mIU/L

TSH above the normal range was the prime criterion in the diagnosis of hypothyroidism.

RESULTS

Table 1: Age and Sex wise distribution in case group

Age	Male		Female	
	No of Cases	Percentage (%)	No of Cases	Percentage (%)
20-30yrs	1	2	1	2
31-40yrs	5	10	28	56
41-50yrs	6	12	9	18
Total 50	**12**	**24**	**38**	**76**

Table 2: Age and sex distribution in control group

Age	Male		Female	
	No	Percentage (%)	No	Percentage (%)
20-30yrs	1	2	2	4
31-40yrs	8	16	22	44
41-50yrs	5	10	12	24
Total 50	**14**	**28**	**36**	**72**

Out of the 50 hypothyroid patients with left ventricular diastolic dysfunction, we lost follow-up of 8 patients during our study before the first assessment.

Table 3: Symptoms of hypothyroid patients before and after 3 months of treatment with L-thyroxine

Sl. No.	Symptoms	Before treatment (n=50)		After 3months of treatment (n=42)	
		No of Patients	Percentage (%)	No of Patients	Percentage (%)
1	Hoarseness of voice	25	50	7	16.66
2	Fatigue	37	74	0	0
3	Cold intolerance	41	82	0	0
4	Depression	10	20	0	0
5	Weight gain	35	70	0	0
6	Joint pain	20	40	0	0
7	Constipation	13	26	0	0
8	Dry skin	44	88	36	85.71
9	Hair Loss	20	40	7	16.66
10	Menorrhagia	11	22	0	0
11	Dyspnea	0	0	0	0

Compares the symptoms of hypothyroid patients before and after treatment with L-thyroxine. It shows that dry skin was the commonest symptom (88%), followed by cold intolerance (82%), fatigue in 74%, weight gain (70%), hoarseness of voice (50%), joint pain in 40%, hair loss (40%), according to descending order of frequency. Constipation, menorrhagia and depression were found in 26%, 22% and 20% of patients respectively. All the symptoms resolved after treatment except dry skin, hoarseness of voice and alopecia persisted in 85.71%, 16.66%, and 16.66% of patients respectively. Dyspnea was found in none of the patients.

Table 4: Change in body weight after 3 months of treatment of hypothyroid patients with L-thyroxine

Before treatment (n=50)		After 3 months of treatment (n=42)		p value of change
Mean	±SD Kg	Mean	±SD Kg	
67.12	± 7.008	59.67	± 8.42	<0.01(S)

Table 5 compares the mean body weight of hypothyroid patients before and after treatment. There was a significant reduction in body weight ($p<0.01$) after 3 months of treatment, no significant reduction in body weight was seen after 3 weeks of treatment.

Table 5: Change in pulse rate after 3 months of treatment of hypothyroid patients with L-thyroxine

Before treatment (n=50) (Mean+ SD)		After 3 months of treatment (n=42)		p value of change
Mean	±SD beats / min	Mean	±SD beats / min	
76.2	+ 14.32	78.38	+ 10.17	> 0.05 (NS)

Table 6, compares the pulse rate of hypothyroid patients before and after treatment. No significant reduction in pulse rate was observed after 3 months of treatment.

Table 6: A Change in Serum Thyroid hormone levels before and after treatment of hypothyroid patients with L-thyroxine

Serum Thyroid Hormone level	Before treatment (n=50)		After 3 weeks of treatment (n=42)		p value of change
	Mean	±SD	Mean	±SD	
T_3 (nmol/L)	0.85	+ 0.48	1.10	+ 0.41	p< 0.01 (S)
T_4 (nmol/L)	43.64	+ 16.37	52.12	+ 14.73	p< 0.01 (S)
TSH (miu/L)	51.33	+ 30.00	44.90	+ 25.19	p> 0.05 (NS)

Table 6: B Change in Serum Thyroid hormone levels before and after treatment of hypothyroid patients with L-thyroxine

Serum Thyroid Hormone level	Before treatment (n=50)		After 3 months of treatment (n=42)		p value of change
	Mean	±SD	Mean	±SD	
T_3 (nmol/L)	0.85	+ 0.48	2.14	±0.62	p< 0.01 (S)
T_4 (nmol/L)	43.64	+ 16.37	92.31	±18.35	p< 0.01 (S)
TSH (miu/L)	51.33	+ 30.00	4.41	±30.00	p< 0.01 (S)

Table 6a and 6b compares change in serum thyroid hormone levels in hypothyroid patients before and after treatment. Significant rise was observed in serum T3 level after 3 weeks and 3 months of treatment, from 0.85 + 0.48 to 1.10+ 0.41 and 2.14+ 0.62 respectively. Serum T4 level also showed significant rise after 3 weeks and 3 months of treatment with L-thyroxine from 43.64 + 16.37 to 52.12+ 14.73 and 92.13+ 18.35 respectively. Serum TSH level did not show a significant decrease after 3 weeks of treatment (44.90+ 25.19, P>0.05), but a significant decrease was seen after 3 months of treatment with L-thyroxine from 51.33 + 30.00 to 4.41+ 1.70.

Table 7: a(i) Comparison of Echo Doppler findings in hypothyroid patients before and after treatment with L-thyroxine

Left ventricular diastolic function parameters	Before treatment (n=50)		After 3 weeks of treatment (n=42)		p value of change
	Mean	+ SD	Mean	+ SD	
E_{max} (cm/sec)	60.14	+ 8.12	62.02	+ 6.08	p< 0.05 (S)
A_{max} (cm/sec)	79.40	+ 11.21	75.50	+ 12.12	p> 0.05 (NS)
E/Amax ratio	0.75	+ 0.08	0.81	+ 0.09	p< 0. 05 (S)
IVRT (msec)	95.50	+ 5.92	92.69	+ 5.79	p> 0.05 (NS)
DT(msec)	237.26	+ 14.33	233.14	+ 13.31	p> 0.05 (NS)

Table 7: Comparison of EchoDoppler findings in hypothyroid patients before and after treatment with L-thyroxine

Left ventricular diastolic function parameters	Before treatment (n=50)		After 3 months of treatment (n=42)		p value of change
	Mean	+ SD	Mean	+ SD	
E_{max} (cm/sec)	60.14	+ 8.12	76.43	+ 5.26	p< 0.05 (S)
A_{max} (cm/sec)	79.40	+ 11.21	63.76	+ 10.12	p< 0.05 (S)
E/Amax ratio	0.75	+ 0.08	1.21	+ 0.10	p<0. 05 (S)
IVRT (msec)	95.50	+ 5.92	83.09	+ 6.04	p< 0.05 (S)
DT(msec)	237.26	+ 14.33	213.8	+ 10.68	p< 0.05 (S)

Table 7a (i) and (ii), compares left ventricular diastolic function parameters in hypothyroid patients before and after treatment with l-thyroxine. After 3 weeks of treatment a significant increase was observed in E_{max} from 60.14 + 8.12 to 62.02+ 6.08, but there was no significant decrease in A_{max} value. However due to an increase in E_{max}, the E/Amax ratio was significantly increased from 0.75 + 0.08 to 0.81+ 0.09 after 3 weeks of treatment. No significant decrease was observed in IVRT and DT after 3 weeks. After 3 months of treatment, significant increase was observed in E_{max} from 60.14 + 8.12 to 76.43 + 5.26, along with a significant decrease in A_{max} value from 79.40 + 11.21 to 63.76 + 10.12. This led to a significant increase in E/Amax ratio from 0.75 + 0.08 to 1.21 + 0.10. A significant decrease in IVRT and DT was also observed at the end of 3 months study from 95.50 ± 5.92 to 83.09 ± 6.04 and 237.26 ± 14.33 to 213.8 ± 10.68 respectively. So, after 3 months of study there was improvement in all parameters of diastolic function of left ventricle.

Table 8: Comparison of left ventricular dimensions in hypothyroid patients before and after L-thyroxine therapy

Left ventricular dimensions	Before treatment (n=50)		After 3 weeks of treatment (n=42)		p value of change
	Mean	± SD	Mean	± SD	
LVEDD(mm)	44	± 4.58	43.05	± 4.94	p> 0.05 (NS)
IVST(mm)	12.38	± 3.43	11.87	± 3.05	p> 0.05 (NS)
LVPWT (mm)	10.64	± 1.77	10.55	± 1.83	p> 0.05 (NS)
IVST/LVPWT ratio	1.15	± 0.16	1.12	± 0.13	p> 0.05 (NS)
Ejection fraction	66.90	± 4.97	67.09	± 5.09	p> 0.1 (NS)

Table 8: Comparison of left ventricular dimensions in hypothyroid patients before and after L-thyroxine therapy

Left ventricular dimensions	Before treatment (n=50)		After 3 months of treatment (n=42)		P value of change
	Mean	± SD	Mean	± SD	
LVEDD(mm)	44	± 4.58	40.36	± 4.96	P<0.01 (S)
IVST(mm)	12.38	± 3.43	8.62	± 1.65	p< 0.01 (S)
LVPWT (mm)	10.64	± 1.77	9.52	± 1.71	p< 0.01 (S)
IVST/LVPWT ratio	1.15	± 0.16	0.89	± 0.052	p< 0.01 (S)
Ejection fraction (%) (EF)	66.90	± 4.97	67.98	± 4.94	p> 0.05 (NS)

Table no. 8a,b (i) and (ii) reveals that after 3 weeks of treatment of hypothyroid patients, there was no significant decrease in LVEDD, IVST, LVPWT or in IVST/LVPWT ratio. But after 3 months of treatment a significant decrease was found in all the aforesaid parameters; LVEDD decreased from 44 ± 4.58 to 40.36 ± 4.96, IVST decreased from 12.38 ± 3.43 to 8.62 ± 1.65, simultaneously LVPWT showed a decrease from 10.64 ± 1.77 to 9.52 ± 1.71. A significant decrease was also observed in the IVST/LVPWT ratio from 1.15 ± 0.16 to 0.89 ±0.052. On the other hand, ejection fraction percentage did not show any significant increase after 3 months of treatment.

Table 9: Comparison of echocardiographic findings cases versus control

Left ventricular diastolic function parameters and dimensions	Cases before treatment (n=50)		Control (n=50)		p value of difference
	Mean	± SD	Mean	± SD	
E_{max} (cm/sec)	60.14	± 8.12	73.48	± 6.53	p< 0.01
A_{max} (cm/sec)	79.40	± 11.21	49.17	± 5.28	P< 0.01
E/A_{max} ratio	0.75	± 0.08	1.63	± 0.31	p< 0.01
DT(msec)	237.26	± 14.33	186.18	± 14.44	p< 0.01
IVRT (msec)	95.50	± 5.92	79.74	± 7.61	p< 0.01
LVEDD(mm)	44	± 4.58	41.6	± 1.59	p< 0.05
IVST(mm)	12.38	± 3.43	8.08	± 0.48	p< 0.01
LVPWT (mm)	10.64	± 1.77	8.25	± 0.49	p< 0.01
IVST/LVPWT ratio	1.15	± 0.16	0.98	± 0.06	p< 0.01
Ejection Fraction (%)	66.90	± 4.97	67.72	± 5.31	p> 0.05

Table 8 shows a comparison of echocardiographic findings between cases (before treatment) and control. It shows that E max (Mitral E peak velocity) was significantly lower in pre-treatment hypothyroid patients (60.14 ± 8.12cm/sec) compared to control group (73.48 ± 6.53cm/sec). Amax (Mitral A peak velocity) was significantly higher in pre-treatment patients (79.40 ± 11.21cm/sec) compared to control group (49.17 ± 5.28 cm/sec). E/Amax ratio was significantly lower in the cases (<1) signifying diastolic dysfunction of left ventricle, when compared to control group (1.63±0.31), which showed no evidence of diastolic dysfunction. Deceleration time of E wave (DT) and isovolumic relaxation time (IVRT) both were significantly higher in the pre-treatment hypothyroid patients, pointing towards diastolic dysfunction of left ventricle, as compared to control group. Inter ventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT) and IVST/LVPWT ratio- all the three parameters were significantly raised in the pre-treatment hypothyroid patients when compared to the control group. Asymmetric septal hypertrophy (IVST/LVPWT ratio>1.3) was observed in 26% (13/50) patients, while concentric hypertrophy (IVST/LVPWT>1) was found in 34% (17/50) of patients.

DISCUSSION

One hundred and fifteen patients with overt hypothyroidism were studied by echo doppler, among which fifty patients with Echo Doppler criteria of left ventricular diastolic dysfunction were finally selected for our study. We lost follow- up of 8 patients during our study before the first assessment. Fifty age and sex matched normal persons served as a control group. Mean age of our study group was 38.52 ± 5.08 years.

Change in Serum Thyroid hormone levels: Serum TSH level showed a significant decrease in our patients from 51.33 ± 30(m Iu/L) to 4.41 ± 1.7 (mIu/L) after 3 months of L- thyroxine therapy. Serum T_3 and T_4 showed a significant rise in our patients from 0.85 ± 0.84 (Nmol/L) to 2.14 ± 0.61 (nmol/L) and 43.64 ± 16.37 (Nmol/L) to 92.13 ± 18.35 (Nmol/L) respectively after 3 months of treatment. This is comparable to the findings of V. K. Virtanen *et al*[9]. Regarding pulse rate, no significant change was observed in our study before and after treatment with L-thyroxine in the mean pulse rate value. This is in contrast to the findings of Virtamen *et al*[9] who found an increase in pulse rate from 61 ± 8 to 68 ± 10(P =0.05) during therapy. Mean pulse rate in the hypothyroid patients before treatment, was comparable to the control group. Similarly systolic and diastolic blood pressure in the pretreatment hypothyroid patients were comparable to the control group. This is in contrast to the findings of Streeten[10] who found it increased in 15% of patients. No significant change in blood pressure was observed after 3 months if therapy in our study. This is consistent with the findings of Virtanen *et al*[9]. In our study we found hypertriglyceridemia in 8.33% of males and in 36% of females, hypercholesterolemia was found in 28% of cases compared to the reports published from Mayo Clinic[11] which found hypertriglyceridemia in 1.5% and hypercholesterolemia in 56% of hypothyroid patients. After 3 months of treatment no significant change was observed in mean serum triglycride or mean serum cholesterol level in our study, although Arem and Patsch[82] noted a significant change in LDL cholesterol concentration after 4 months of thyroxine therapy in hypothyroid patients. May be a longer follow-up was needed in our patients.

ECG abnormalities: Low Voltage complexes were found in 34% of patients in our study group compared to E. J. Wayne[12] who found it in 62% of cases. Non specific ST- T change were observed in 6% compared to A. A. Khaleeli[13] who found it in 18% while sinus bradycardia was observed in 12% of patients. Sinus bradycardia with low voltage complexes were found in 8% of patients as compared to 20% of cases in A. A. Khaleeli's[13] study. All the ECG abnormalities reverted to normal after 3 months of treatment, similar result was observed by A. A. Khaleeli[13]. After 3 weeks of therapy with L-thyroxine, a significant increase was observed in E max from 60.14 ± 8.12 (cm/sec) to 62.02 ± 6.08 cm/sec, but no significant change was observed in Amax, IVRT, DT, IVST, LVPWT or LVEDD. Due to an increase in E_{max} i. e. early diastolic filling of mitral valve, E/A_{max} ratio was also significantly increased from 0.7498 ± 0.1282 to 0.8126 ± 0.1036 after 3 weeks of therapy. This short term improvement in E_{max} and E/A_{max} ratio signifying an improvement in diastolic function of left ventricle, was probably due to underlying biochemical mechanisms. Virtanen *et al*[9] found that E_{max} had a tendency to increase during thyroxine therapy, but not significantly. Their follow-up period was 1-2 months. After 3 months of therapy with L-thyroxine, we found a significant increase in E_{max} value from 60.14 ± 8.12 cm/sec to 76.43 ± 5.26 cm/sec, along with a significant decrease in A_{max} value from 79.40 ± 11.21 cm/sec to 63.76 ± 10.12 cm/sec. This led to a significant increase in E/A_{max} ratio from 0.7498 ± 0.084 to 1.21 ± 0.10, signifying that diastolic dysfunction of left ventricle was normalized in the hypothyroid patients after 3 months of L-thyroxine therapy. Simultaneously there was a significant decrease in IVRT and DT after 3 months of therapy from 95.50 ± 12.02 msec to 83.10 ±7.49 msec and 237.10 ± 16.18 to 213.8 ±10.67 msec respectively, implying an overall improvement in left ventricular diastolic function in the study group. Systolic dysfunction of left ventricle (ejection fraction) was not observed in the hypothyroid patients during our study, ejection fraction (%) in the study group (66.90 ± 4.97%) was comparable with the control group (67.72 ± 5.31%). No significant change was observed in the ejection fraction percentage during follow-up of the study group. Our finding was consistent with that of Arem *et al*[14] who did not find any systolic dysfunction in subclinical hypothyroid patients. However B. P. O Malley *et al*[15] found systolic dysfunction in 62% of cases. We found a significant correlation between serum TSH and IVST/LVPWT ratio and serum TSH and DT. No significant correlation was observed between serum TSH and E_{max}, A_{max}, E/A_{max} and IVRT. No significant correlation was observed between E/A_{max} ratio and pulse rate neither between E/A_{max} ratio and age. We did not find any significant correlation between the other indices of diastolic dysfunction (i.e., E_{max}, A_{max}, IVRT, and DT) and age or pulse rate. Age is one of the major determinants of Doppler indices both in normal subjects and patients[16]. In our study we did not find any significant correlation between age and E_{max}, A_{max}, E/A_{max} ratio, IVRT or DT. A_{max} is directly related to heart rate[17,18], although in our study there was a significant decrease in A_{max} value no significant change was observed in the heart rate of our patients. Heart rate did not correlate with E/A_{max} ratio, E_{max}, A_{max}, IVRT or DT. Preload and E_{max} are directly proportional to each other[19]. In our study there was a significant change in left ventricular dimensions (i. e. LVEDD, IVST and LVPWT) after 3 months of therapy, which led to an improvement in diastolic filling and left ventricular relaxation. Left ventricular diastole is not a mere passive phenomenon. It depends on enzymes which regulates the calcium fluxes in the heart eg; calcium dependent ATPase, phospholamban[20]. Several of these enzymes are regulated by thyroid hormone. Hypothyroidism decreases the expression and activity of these enzymes leading to an impaired diastolic function of left ventricle. Thyroxine substitution causes induction of sarcoplasmic reticulum Calcium ATPase[21] leading to reversal of diastolic dysfunction. So, in the early stages of thyroxine substitution therapy an increase in the early diastolic filling velocity of mitral valve (E_{max}) may be explained by biochemical alterations in the sarcoplasmic reticulum. In the later half of treatment, the overall improvement in the diastolic dysfunction of left ventricle can be contributed both to biochemical and anatomical changes in the myocardium.

CONCLUSION

Out of one hundred and fifteen hypothyroid patients, fifty patients were selected for our study who had echo Doppler evidence of left ventricular diastolic dysfunction. Apart from hypothyroidism there were no other cause to account for their diastolic dysfunction. The probable mechanism of improvement of left ventricular diastolic dysfunction in the early part of thyroxine replacement therapy was due to biochemical changes i.e. induction of calcium ATPase by L-thyroxine in sarcoplasmic reticulum of myocardial cells. The subsequent improvement in the overall diastolic function of left ventricle was possibly related to continued biochemical and associated structural changes in the myocardium. However a long term follow-up is required in this aspect.

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