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Left Ventricular Diastolic Dysfunction in Primary Hypothyroid Patients before and After L-Thyroxine Therapy

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Abstract

Introduction: *Hypothyroidism is the most common form of thyroid disorder throughout the world. It is a clinical state which results from deficient production of thyroid hormonedue to structural and/functional abnormalities. Diastolic dysfunction is defined as left ventricular diastolic dysfunction indicating a functional abnormality of diastolic relaxation, elasticity or distensibility of the left ventricle, regardless of whether the left ventricle ejection fraction is normal or abnormal and whether the patient is symptomatic or not.*

Aims and Objectives: *The objective of the study will be to examine the effect of thyroid hormone replacement (L-thyroxine) on left ventricular diastolic dysfunction in patients with overt hypothyroidism[19].*

(a) What percentage of hypothyroid patients have left ventricle diastolic dysfunction.
(b) Whether this diastolic dysfunction could be reversed by thyroxine treatment.
(c) To see if any correlation exists between serum TSH and Doppler echocardiography findings regarding diastolic dysfunction of left ventricle.

Materials: *Among 120 Hypothyroidism patients 50 patients were found to have Echo-doppler criteria of left ventricular diastolic dysfunction. These 50 patients were finally selected for the study.*

Patient with clinical features suggestive of hypothyroidism will be selected from OPD & IPD of katihar medical college &hospital. Patient will be assessed clinically & will be subjected to Thyroid Function Test, Blood Sugar, Lipid Profile, Chest X-Ray, and Echocardiography i.e 2D M Mode and Doppler technique will be used.

50 Patients with raised TSH (>5ml/L10)[64]and Echocardiographic finding of left ventricular diastolic dysfunction will be selected for the study.

One hundred and twenty patients were selected from our Medicine and Endocrinology outdoor and indoor medical wards of Katihae Medical College And Hospital. After selection they were evaluated by Doppler echocardiography study. Among 120 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)[65].

Diastolic Inter Ventricular septal thickness (d-IVST) , Diastolic left ventricular posterior wall thickness (d-LVPET),

Left ventricular end diastolic diameter (LVEDD) will be evaluated.
50 patient with age sex matched controls will be taken for comparative study to see wheather Left Ventricular Diastolic dysfunction is more common in hypothyroidism.
These 50 patients will be treated with Levothyroxine. After 3 month, Thyroid profile and Echocardiography will be repeated to see if Left ventricular diastolic dysfunction improves with it.
Inclusion Criteria: *Aged between 15 to 70 years; With positive clinical history of increased TSH Level.*
Exclusion Criteria: *valvular abnormalities, Congenital heart disease, Arrhythmias, Hypertrophic cardiomyopathy, Pericardial disease, Ischemic heart disease, LVH, Systemic illness like DM, hypertension.*
Duration of study: *Dec2016 – May2018.*
Results: *In this study among 120 hypothyroidism patients 50 patients having diastolic dysfunction. Improvement in the left ventricular diastolic function following L-thyroxine replacement therapy was observed in all the patients during follow-up. After 3 months of treatment along with an increase in E_{max}(increased from 60.14 ± 8.12 cm/sec to 76.43±5.26 cm/sec) there was a significant decrease in A_{max} i.e. late diastolic filling velocity of mitral valve (from 79.40 ± 11.21 cm/sec to 63.76±10.12 cm/sec), leading to an increase in E/A $_{max}$ ratio from 0.7498 ± 0.084 to 1.21±0.10. This signified a reversal of the diastolic dysfunction of the left ventricle. There was also a decrease in isovolumic relaxation time from 95.50±5.92 to 83.09 ±6.04msec (IVRT) and deceleration time of mitral E wave (DT) from 237.26±14.33msec to 213.8 ± 10.68msec – indicating an overall improvement in the diastolic function of the left ventricle. We also found a significant decrease in left ventricular end diastolic diameter (LVEDD), inter ventricular septal thickness (IVST) & left ventricular .posterior wall thickness (LVPWT) and IVST/LVPWT ratio after 3 months of therapy- suggesting structural changes of left ventricle. But there is slight change in only EF%. seen.*
Conclusion: *The subsequent improvement in overall diastolic function of left ventricle in patients with L-Thyroxine therapy was possibily related to continued to biochemical and structural changes in myocardium. However a long term follow up using 2D Echocardiography required.*

Introduction

The Thyroid gland produces two related hormone, thyroxine (T4) and triidiothyronine (T3). Autoimmune disorder of the thyroid gland can stimulate over production of thyroid hormones (thyrotoxicosis) or causes glandular destruction and hormone deficiency (hypothyroidism)[1] Hypothyroidism is the most common form of thyroid disorder throughout the world. It is a clinical state which results from deficient production of thyroid hormonedue to structural and/functional abnormalities.

Symptoms–weight gain, cold intolerance, fatigue, dry skin, hair loss , menorrhagia, dyspnoea and hoarseness of voice[2] .

Sign– weight gain, puffy face, bradycardia, hypertention, carpel tunnel syndrome, diffuse alopecia.

Doppler Echocardiography and Hypothyroidism

Gupta A et al[7] studied 44 hypothyroid patients and found that inter ventricular septal dimensions were significantly raised ($p<0.005$) and mean left ventricular posterior wall thickness was also increased significantly. This showed concentric hypertrophy. Zia Q Farooki et al[10] studied 11 children with hypothyroidism and found asymmetric septal hypertrophy (ASH), e.g. (Inter ventricular septal thickness: Left ventricular posterior wall diastolic thickness >1.3) present in two children without left ventricular outflow tract obstruction. After thyroxine substitution it reversed to normal.

TK Mishra et al[11] studied 32 patients and the systolic function of LV was normal in patients with SH. There was significant diastolic dysfunction in the SH patients as compared with controls. There was prolongation of deceleration above time (169+6.1 msec. vs. 148.1+5.4 msec in controls, $p < 0.05$), isovolumic relaxation time (89.1+7.3 msec vs. 79.4+5.9 msec., $p<0.05$), increased A wave (0.63+0.6 m/sec. vs. 0.54+0.05 m/sec) and reduced E/A ratio (0.7+0.09 vs. 1.4+0.3, $p < 0.05$). Echocardiography at the end of one year of hormone therapy revealed considerable improvement in diastolic function of the LV[11].

Aims and Objectives

The objective of the study will be to examine the effect of thyroid hormone replacement (L-

thyroxine) on left ventricular diastolic dysfunction in patients with overt hypothyroidism[13].

a) What percentage of hypothyroid patients have left ventricle diastolic dysfunction.
b) Whether this diastolic dysfunction could be reversed by thyroxine treatment.
c) To see if any correlation exists between serum TSH and Doppler echocardiography findings regarding diastolic dysfunction of left ventricle.

Material and Methods

Patient with clinical features suggestive of hypothyroidism will be selected from OPD & IPD of katihar medical college & hospital. Patient will be assessed clinically & will be subjected to Thyroid Function Test, Blood Sugar, Lipid Profile, Chest X-Ray, and Echocardiography i.e 2D M Mode and Doppler technique will be used.

50 Patients with raised TSH (>5ml/L10)[64]and Echocardiographic finding of left ventricular diastolic dysfunction will be selected for the study.

One hundred and twenty patients were selected from our Medicine and Endocrinology outdoor and indoor medical wards of Katihar Medical College And Hospital. After selection they were evaluated by Doppler echocardiography study. Among 120 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).

⇒ Diastolic Inter Ventricular septal thickness (d-IVST), Diastolic left ventricular posterior wall thickness (d-LVPET), Left ventricular end diastolic diameter (LVEDD) will be evaluated.

50 patients with age sex matched controls will be taken for comparative study to see wheather Left Ventricular Diastolic dysfunction is more common in hypothyroidism.

These 50 patients will be treated with Levothyroxine. After 3 month, Thyroid profile and Echocardiography will be repeated to see if Left ventricular diastolic dysfunction improves with it.

The inclusion criteria were as follows:

⇒ Aged between 15 to 70 years.
⇒ With positive clinical history of increased TSH LEVEL.

The exclusion criteria were as follows :

⇒ Significant valvular abnormalities
⇒ Congenital heart disease
⇒ Arrhythmias eg, chronic atrial fibrillation or flutter
⇒ Hypertrophic cardiomyopathy
⇒ Pericardial disease
⇒ Ischemic heart disease
⇒ Left ventricular hypertrophy
⇒ Systemic illness like diabetes mellitus, hypertension
⇒ Patient not giving consent

Duration of study- Dec2016 – May2018.

Out of 120 hypothyroid patients, 50 patients were found to have Echodoppler evidence of left ventricular diastolic dysfunction. 33% percentage of hypothyroid patients had echo Doppler evidence of left ventricular diastolic dysfunction as against not a single case of left ventricular diastolic dysfunction in the control group. The age and sex distribution of these 50 hypothyroid patients are shown in Table 1. The age varied from 30 years to 48 years (mean age 38.52+/-5.076 years).

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.

Table 1 Change in Serum Thyroid hormone levels before and after treatment of hypothyroid patients with L-thyroxine

Serum Thyroid Hormone level	Before treatment (n=50) (Mean± SD)	After 3 months of treatment (n=42) (Mean± SD)	P value of change
T_3 (nmol/L)	0.85 ± 0.48	2.14± 0.62	P<0.01 (S)
T_4 (nmol/L)	43.64 ± 16.37	92.13± 18.35	P<0.01 (S)
TSH (miu/L)	51.33 ± 30.00	4.41± 1.70	P<0.01 (S)
S = Significant, NS = Not significant			

Table 1 compares change in serum thyroid hormone levels in hypothyroid patients before and after treatment. Significant rise was observed in serum T3 level after 3 months of treatment, from 0.85 ± 0.48 to 2.14± 0.62 respectively. Serum T4 level also showed significant rise after 3 months of treatment with L-thyroxine from 43.64 ± 16.37 to 92.13± 18.35 respectively. Serum TSH level show a significant decrease after 3 months of treatment with L-thyroxine from 51.33 ± 30.00 to 4.41± 1.70.

Table 2A Comparison of Echo Doppler findings in hypothyroid patients before and after treatment with L-thyroxine

Left ventricular diastolic function parameters	Before treatment (n=50) (Mean± SD)	After 3 months of treatment (n=42) (Mean± SD)	P value of change
E_{max} (cm/sec)	60.14 ± 8.12	76.43 ± 5.26	P<0.01 (S)
A_{max} (cm/sec)	79.40 ± 11.21	63.76 ± 10.12	P<0.05 (S)
E/A_{max} ratio	0.75 ± 0.08	1.21 ± 0.10	P<0.001 (S)
IVRT (msec)	95.50 ± 5.92	83.09 ± 6.04	P<0.01 (S)
DT(msec)	237.26 ± 14.33	213.8 ± 10.68	P<0.01 (S)
S = Significant, NS = Not significant			

Table 2A, compares left ventricular diastolic function parameters in hypothyroid patients before and after treatment with L-thyroxine therapy.

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 2B Comparison of left ventricular dimensions in hypothyroid patients before and after L-thyroxine therapy

Left ventricular dimensions	Before treatment (n=50) (Mean± SD)	After 3 months of treatment (n=42) (Mean± SD)	P value of change
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)
S = Significant, NS = Not significant			

Table no. 2B reveals that after 3 month of treatment of hypothyroid patients, there was significant decrease in LVEDD, IVST, LVPWT or in IVST/LVPWT ratio. 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 that is from 66.90±4.97 to 67.99± 4.94 only.

Table 3A Change in serum triglyceride level in hypothyroid patients (females) before and after treatment with L-thyroxine

Triglyceride level before treatment (n=38) (Mean± SD) mg/dl	**Triglyceride level after 3 months of treatment (n=31) (Mean± SD) mg/dl**	**P value of change**
141.82 ± 71.68	130.61± 55.65	P>0.05(NS)

Table 3B Change in serum triglyceride level in hypothyroid patients (males) before and after treatment with L-thyroxine

Triglyceride level before treatment (n=12) (Mean± SD) mg/dl	**Triglyceride level after 3 months of treatment (n=11) (Mean± SD) mg/dl**	**P value of change**
113.92 ± 37.46	96.82± 19	P>0.05(NS)

Table 3A and 3B depicts the change in serum triglyceride level in male and female hypothyroid patients before and after 3 months of treatment. Mean serum triglyceride level in female patients were higher than normal (141.82 ± 71.68) before treatment and decreased to 130.61± 55.65 mg/dl after 3 months of treatment, though the change was statistically not significant, may be a longer follow-up was needed. Similarly, the decrease in mean serum triglyceride in male hypothyroid patients after 3 months of treatment was not significant. However the pretreatment value of mean serum triglyceride in the male patients were within normal limit. A longer follow-up and larger study is needed in this aspect.

Table 3 Change in serum total cholesterol level in hypothyroid patients before and after treatment with L-thyroxine

Serum total cholesterol level before treatment (n=50) (Mean± SD) mg/dl	**Serum total cholesterol level after 3 months of treatment (n=42) (Mean± SD) mg/dl**	**P value of change**
192.16 ± 52.43	177.76± 35.76	P>0.05(NS)

Table 3 shows the change in serum total cholesterol level in hypothyroid patients before and after 3 months of treatment. Though the pretreatment mean serum total value (192.16 ± 52.43) was within normal limit, 28% of the hypothyroid patients (Table 12B) showed a serum total cholesterol value above 200mg/dl. No significant change was observed after 3 months of treatment, may be due to a short follow –up.

Table 4A Percentage of Hypertriglyceridemia in hypothyroid patients before treatment with L-thyroxine

Serum Triglyceride Level	
	Males
>160mg/dl	1/ 12 (8.33%)
	Females
>135mg/dl	14/ 38 (36%)

Table 4A, reveals that hypertriglyceridemia was found in 8.33% of males and 36% of females before treatment with L-thyroxine.

Discussion

One hundred and twenty 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 & sex matched normal persons served as a control group.

Change in Serum Thyroid hormone level: 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 & 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.

In our study we found hypertriglyceridemia in 8.33% of males & in 36% of females, hypercholesterolemia was found in 28% of cases compared to the reports published from Mayo Clinic 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 triglyceride or mean serum cholesterol level in our study, although Arem & Patsch 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.

In our study diastolic dysfunction of left ventricle was observed in 38% of hypothyroid patients. This finding is consistent with that of R. Verma et al[6], who found diastolic dysfunction in 27.27% of overt hypothyroid patients.

Diastolic dysfunction of left ventricle in the pre-treatment hypothyroid patients was evident by significantly decreased early diastolic filling velocity of mitral valve (E_{max}) (60.14± 8.12 m/sec) compared to significant increase in late diastolic filling velocity of mitral valve- Amax (79.40 ± 11.21 cm/sec) and E/A_{max} ratio of less than one compared to control group. Also isovolumic relaxation time- IVRT (95.50 ± 5.92 msec) and mitral E wave deceleration time- DT (237. 26 ± 14.33) were found to be significantly increased in our patients, compared to control group, signifying diastolic dysfunction. Our findings were consistent with that of V. K. Virtamen et al[12], who found decreased E_{max}, increased Amax, E/A_{max} ratio of less than one, increased IVRT and DT in hypothyroid patients before treatment.

Regarding left ventricular dimensions, interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), IVST /LWPWT ratio & left ventricular end diastolic diameter (LVEDD) were found increased in the hypothyroid patients before treatment, when compared to control group.

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. Virtanen et al[12] found that E_{max} had a tendency to increase during thyroxine therapy

Regarding left ventricular dimensions a significant decrease was observed in LVEDD, IVST, LVPWT & IVST/LVPWT ratio from 44 ± 4.58 mm to 40.36 ± 4.96 mm, 12.38 ± 3.43 mm to 8.62 ± 1.65 mm, 10.64 ± 1.77 mm to 9.52 ± 1.71 mm and 1.15 ± 0.16 to 0.89 ± 0.052 mm respectively

after 3 months of therapy. There was normalizaton of asymmetric septal hypertrophy and concentric hypertrophy as well after 3 months of treatment. These changes in left ventricular dimensions were probably due to structural changes of myocardium, after L-thyroxine substitution therapy.

We found a significant correlation between serum TSH & IVST/LVPWT ratio and serum TSH & 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.

Preload &E_{max} are directly proportional to each other. In our study there was a significant change in left ventricular dimensions (i. e. LVEDD, IVST & LVPWT) after 3 months of therapy, which led to an improvement in diastolic filling and left ventricular relaxation.

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 & anatomical changes in the myocardium.

Summary

Out of one hundred and twenty 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.

Improvement in the left ventricular diastolic function following L-thyroxine replacement therapy was observed in all the patients during follow-up. After 3 months of treatment along with an increase in E_{max}(increased from 60.14 $\pm$ 8.12 cm/sec to 76.43$\pm$5.26 cm/sec) there was a significant decrease in A_{max} i.e. late diastolic filling velocity of mitral valve (from 79.40 $\pm$ 11.21 cm/sec to 63.76 $\pm$ 10.12 cm/sec), leading to an increase in E/A_{max} ratio from 0.7498 $\pm$ 0.084 to 1.21 $\pm$ 0.10. This signified a reversal of the diastolic dysfunction of the left ventricle. There was also a decrease in isovolumic relaxation time from 95.50 $\pm$ 5.92 to 83.09 $\pm$ 6.04 msec (IVRT) and deceleration time of mitral E wave (DT) from 237.26 $\pm$ 14.33 msec to 213.8 + 10.68 msec – indicating an overall improvement in the diastolic function of the left ventricle. We also found a significant decrease in left ventricular end diastolic diameter (LVEDD), inter ventricular septal thickness (IVST) & left ventricular posterior wall thickness (LVPWT) and IVST/LVPWT ratio after 3 months of therapy- suggesting structural changes of left ventricle.

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 & associated structural changes in the myocardium. So we conclude that diastolic dysfunction of LV is abnormal in patient in hypothyroidism , which can be reversed by L-thyroxine therapy. Doppler echocardiography is reliable, simple and inexpensive method for assessment of diastolic dysfunction. However a long term follow-up is required in this aspect.

Conclusion

The subsequent improvement in overall diastolic function of left ventricle in patients with L-Thyroxine therapy was possibily related to continued to biochemical and structural changes in myocardium .However a long term follow up using 2D Echocardiography required.

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