ORIGINAL RESEARCH

An Observational Study on the Reversibility of Left Ventricular Diastolic Dysfunction, Impaired Left Ventricular Ejection Fraction and Abnormal Left Ventricular Mass with Levothyroxine Replacement in Primary Hypothyroid Patients of Indian Origin

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Abstract

Background: Cardiovascular performance is well-known to be compromised due to low level of thyroid hormone levels in terms of reduced cardiac performance, reduced chronotropy, and increased systemic vascular resistance. Persistent subclinical hypothyroidism (SCH) is also a known risk factor for cardiomyopathy and heart failure. Yet, the direct effect of hypothyroidism on the heart, independent of its effect on loading function remains to be elucidated. In this study, we wanted to see the effect of hypothyroidism correction within 6 months on cardiac performance as measured by pre-defined echocardiographic parameters.

Objectives: To find out the change in left ventricular systolic and diastolic function as well as left ventricular mass index (LVMI) with treatment of primary hypothyroidism with levothyroxine replacement in 6 months time frame and to detect reversibility, if present at all, of E/E´(E—early transmitral diastolic velocity, E´– tissue Doppler early diastolic velocity), left ventricular ejection fraction (LVEF) and LVMI after patient become biochemically euthyroid.

Results: A total of 51 cases of primary hypothyroidism were selected after excluding other comorbidities ranging from age 12–67 years, to undergo assessment of E/E´, LVEF, and LVMI echocardiographically at first OPD visit ($t = 0$) and at 6 months. Age- and sex-matched healthy controls were taken for comparison. Meanwhile, they were being treated with levothyroxine supplementation at an appropriate dosage to establish a euthyroid status during this period. They were monitored at regular intervals. At 6 months all of them became euthyroid biochemically and their echo parameters were compared. The mean age of the study group was 44.57 ± 10.53 years among cases. In case arm, 23 out of 51 (45.1%) patients were female and 28 (54.9%) patients were male. Male–female ratio was ~ 1.2:1. The mean thyroid stimulating hormone (TSH) at $t = 0$ (mean ± SD) was 19.90 ± 23.90 mIU/L. The mean FT4 at $t = 0$ (mean ± SD) of patients was 1.12 ± 0.15 ng/dL. The association of E/E´ at $t = 0$ in case vs control group was statistically significant ($p < 0.0001$). The association of EF at $t = 0$ in case vs control group was statistically significant ($p = 0.0068$). The association of LVMI at $t = 6$ months vs at $t = 0$ group was statistically significant ($p = 0.0339$). There was significant improvement in E/E´ ($p = 0.0010$), EF ($p < 0.0001$), in LVMI ($p < 0.0001$) after 6 months. The positive correlation between E/E´ at $t = 6$ months vs TSH at $t = 6$ months was not statistically significant ($p = 0.48$). Negative correlation between EF at $t = 6$ months vs TSH at $t = 6$ months was not statistically significant ($p = 0.57$). The positive correlation between LVMI at $t = 6$ months vs TSH at $t = 6$ months was not statistically significant ($p = 0.89$). Negative correlation between TSH at $t = 6$ months vs FT4 at $t = 6$ months was not statistically significant ($p = 0.348$).

Conclusion: Primary hypothyroidism is associated with diastolic dysfunction, left ventricular systolic dysfunction, and abnormal left ventricular mass. The most affected age group is the 5th decade or above. Diastolic dysfunction is more severe than systolic dysfunction. Levothyroxine supplementation can potentially revert these dysfunctions. It takes at least 6 months for cardiac function to reverse. Early diagnosis of hypothyroidism and levothyroxine supplementation can prevent potentially dangerous complications of cardiovascular system including heart failure

Keywords: E/E,' Hypothyroidism, Left ventricular ejection fraction, Left ventricular mass index.

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Introduction

Primary hypothyroidism is a medical condition associated with low level of thyroid hormone that results in loss of negative feedback on pituitary gland causing elevation in thyroid stimulating hormone (TSH). In subclinical hypothyroidism (SCH), TSH level remains elevated (but < 10 µIU/mL) above normal level in the presence of a normal level of free T4 hormonal level in blood.

Cardiovascular performance is well-known to be compromised due to low level of thyroid hormone levels in terms of reduced

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cardiac performance, reduced chronotropic, and increased systemic vascular resistance. Persistent SCH is also a known risk factor for cardiomyopathy and heart failure. Yet, the direct effect of hypothyroidism on the heart, independent of its effect on loading function remains to be elucidated.

To the best of our knowledge, the treatment of hypothyroidism with levothyroxine supplementation is known to improve cardiac performance, especially diastolic dysfunction, albeit it remains controversial whether this is as beneficial in preventing or reversing cardiac remodeling. The statement becomes even more inconspicuous when we put SCH patients under consideration. The exact duration taken by cardiac function to revert is also not definitively known. Data are lacking regarding the performance of the right ventricle also. Rapid correction of hypothyroidism may not have the same impact on cardiac performance as slow correction over several months to years. In this study, we want to see the effect of hypothyroidism correction within 6 months on cardiac performance as measured by pre-defined echocardiographic parameters.

Materials and Methods

For the study, 51 cases of primary hypothyroidism attending our hospital OPD (General medicine and Endocrine OPD) were included. The diagnosis of primary hypothyroidism is made by estimation of serum level of TSH and free thyroxine.

It was an observational and prospective study. The Clinical Research Ethics Committee of the Institution approved the study. Primary hypothyroidism was diagnosed in patients with TSH levels equal to or more than 10 µIU/mL and FT4 levels in normal or below-normal range. Exclusion criteria were, hypertension, atherosclerotic cardiovascular disease, diabetes mellitus, cardiomyopathy, history of alcoholism and tobacco intake. All 51 patients underwent echocardiographic evaluation at the time of diagnosis or at the first OPD visit, which is referred to as $t = 0$. Echocardiography was done using a GE Vivid E9 machine and three parameters were estimated in all of them viz., Left ventricular ejection fraction (LVEF), E/E´ (E—early transmitral diastolic velocity, E´—tissue Doppler early diastolic velocity) and left ventricular mass index (LVMI). LVEF was estimated using the modified Simpson method in all the subjects. E/E´ was calculated using the tissue Doppler method. Left ventricular mass was estimated using LV-M mode in the echo machine and LV mass index was calculated as the ratio of LV mass to body surface area (BSA) and expressed as gram/m^2. Patients were put on supplemental doses of levothyroxine at appropriate doses such as 12.5, 25, 37.5, 50, 62.5, 75, 87.5, 100, 112.5, 125, 137.5, and 150 µg. The highest dose of levothyroxine used in this study was 150 µg.

Patients were followed up for 6 months at an interval of 6–8 weeks with monitoring of serum level of TSH. The dose of levothyroxine was adjusted accordingly with a target to achieve a euthyroid state as early as possible. At 6 months, after the first OPD visit, all of them were reviewed echocardiographically, in terms of all three parameters as at $t = 0$. The same methods were used for the estimation of the parameters as in $t = 0$.

For E/E´, a cut-off value of less than 15 was considered normal. E/E´ equal to or above 15 was considered abnormal. For LVEF, a value equal to or greater than 55% was considered normal. LV systolic function was considered to be mildly impaired if the value of LVEF was between 45–54% and 30–44% was considered moderately impaired and less than 30% was considered severely impaired.

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Left ventricular mass index was categorized as follows: (all values in gm/m^2 of BSA)

- Normal category---------- Male—49–115, female—43–95.
- Mildly increased category-------- Male—116–131, female—96–108.
- Moderately increased category----- Male—132–148, female—109–121
- Severely increased category ------- Male---- ≥149, female— ≥122.

Statistical Analysis

For statistical analysis, the Microsoft Excel 2007 spreadsheet was used and then analyzed by SPSS 24.0. and GraphPad Prism version 5. Mean and standard deviation for numerical variables and count and percentages for categorical variables have been used for summarization of data. One-way ANOVA, that is, analysis of variance (one-way) was a technique used to compare means of three or more samples for numerical data (using the F distribution). Correlation was calculated using Pearson correlation analysis.

Results

In our current study, the study population was matched with respect to age and sex with the healthy control subjects. In the study group, the mean age was 44.5686 ± 10.5342 years among cases. Among the control group, the mean age was 45.0392 ± 10.4383 years. In the case group, 4 (7.8%) patients had ≤30 years of age, 16 (31.4%) patients aged between 31 and 40 years of age, 19 (37.3%) patients, between 41 and 50 years of age, 8(15.7%) patients between 51 and 60 years of age and 4 (7.8%) patients between 61 and 70 years of age. The difference of mean age vs group was not statistically significant ($p = 0.8212$)

In the case group, 23 (45.1%) patients were female and 28 (54.9%) patients were male. In control group, 28 (54.9%) patients were male and 23 (45.1%) patients were female. The association of sex vs group was not statistically significant ($p = 1.0000$).

In the case group, the mean TSH at $t = 0$ (mean ± SD) of patients was 19.9000 ± 23.9059 mIU/L. In the control group, the mean TSH at $t = 0$ (mean ± SD) of patients was 2.1294 ± 0.6780 mIU/L. Difference of mean TSH at $t = 0$ vs group was statistically significant ($p < 0.0001$). In the case group, the mean FT4 at $t = 0$ (mean ± SD) of patients was 1.1204 ± 0.1551 ng/dL. In the control group, the mean FT4 at $t = 0$ (mean ± SD) of patients was 1.4216 ± 0.1301 ng/dL. Difference of mean FT4 at $t = 0$ vs group was statistically significant ($p < 0.0001$).

In echocardiographical analysis, in the case group, the mean E/E´ at $t = 0$ (mean ± SD) of patients was 12.6588 ± 4.1943. In the control group, the mean E/E´ at $t = 0$ (mean ± SD) of patients was

Table 1: Distribution of age vs E/E´ at $t = 0$

Age	*Abnormal*	*Normal*	*Total*
≤ 30 years	1	3	4
Row%	25.0	75.0	100.0
Col%	4.2	11.1	7.8
30–40 years	10	6	16
Row%	62.5	37.5	100.0
Col%	41.7	22.2	31.4
41–50 years	5	14	19
Row%	26.3	73.7	100.0
Col%	20.8	51.9	37.3
51–60 years	4	4	8
Row%	50.0	50.0	100.0
Col%	16.7	14.8	15.7
61–70 years	4	0	4
Row%	100.0	0.0	100.0
Col%	16.7	0.0	7.8
Total	24	27	51
Row%	47.1	52.9	100.0
Col%	100.0	100.0	100.0

E/E´ at $t = 0$

Table 2: Distribution of EF at $t = 0$

Age	*Mildly reduced*	*Moderately reduced*	*Normal*	*Total*
≤30 years	0	1	3	4
Row%	0.0	25.0	75.0	100.0
Col%	0.0	20.0	7.9	7.8
30–40 years	3	4	9	16
Row%	18.8	25.0	56.3	100.0
Col%	37.5	80.0	23.7	31.4
41–50 years	1	0	18	19
Row%	5.3	0.0	94.7	100.0
Col%	12.5	0.0	47.4	37.3
51–60 years	3	0	5	8
Row%	37.5	0.0	62.5	100.0
Col%	37.5	0.0	13.2	15.7
61–70 years	1	0	3	4
Row%	25.0	0.0	75.0	100.0
Col%	12.5	0.0	7.9	7.8
Total	8	5	38	51
Row%	15.7	9.8	74.5	100.0
Col%	100.0	100.0	100.0	100.0

EF at $t = 0$

7.5294 ± 1.9935. The difference of mean E/E´ at $t = 0$ was statistically significant ($p < 0.0001$). Regarding E/E´ at $t = 0$ in case group, 24 (47.1%) patients had abnormal, 27 (52.9%) patients had normal and in the control group, all patients had normal. The association of E/E´ at $t = 0$ in the case vs control group was statistically significant ($p < 0.0001$). Distribution of age vs E/E´ at $t = 0$ was given in Table 1. It was seen that the association of age vs E/E´ at $t = 0$ was statistically significant ($p = 0.0384$).

In case group, the mean EF at $t = 0$ (mean ± SD) of patients was 61.9412 ± 5.1319. In the control group, the mean EF at $t = 0$ (mean ± SD) of patients was 65.7647 ± 3.3262. the difference of mean EF at $t = 0$ vs group was statistically significant ($p < 0.0001$). Regarding EF at $t = 0$ in case group, 8 (15.7%) patients had mildly reduced, 5 (9.8%) patients had moderately reduced, 38 (74.5%) patients had normal and in control group, 2(3.9%) patients had mildly reduced and 49 (96.1%) patients had normal. The association of EF at $t = 0$ in the case vs control group was statistically significant ($p = 0.0068$). The distribution of age vs EF at $t = 0$ was given in Table 2. It was seen that the association of age vs EF at $t = 0$ was not statistically significant ($p = 0.0731$).

In the case group, the mean LVMI at $t = 0$ (mean ± SD) of patients was 92.0549 ± 19.0841. In the control group, the mean LVMI at $t = 0$ (mean ± SD) of patients was 76.1137 ± 8.4386. The difference of mean LVMI at $t = 0$ vs group was statistically significant ($p < 0.0001$). Regarding LVMI at $t = 0$ in case group, 4 (7.8%) patients had mildly increased, 3 (5.9%) patients had moderately increased, 1 (2.0%) patient had severely increased and 43 (84.3%) patients had normal. LVMI at t = 0 in the control group, all patients had normal. The association of LVMI at t = 0 vs group was statistically significant ($p = 0.0339$). The distribution of age vs LVMI at t = 0 was given in Table 3. It was seen that the association of age vs LVMI at $t = 0$ was not statistically significant ($p = 0.5776$).

When compared with the values of E/E´ at $t = 0$ in the case group, 24 (47.1%) patients had abnormal (at $t = 6$, 16, i.e., 37.2% remained abnormal), 27 (52.9%) patients had normal and in the control group, all patients had normal E/E´. All patients E/E´ at $t = 0$ in normal, remained in the normal group at $t = 6$ months suggesting no change in E/E´ after treatment. The association of E/E´ at $t = 0$ vs E/E´ at $t = 6$ months was statistically significant ($p < 0.0010$).

Table 3: Distribution of age vs LVMI at $t = 1$

Age	*Mildly increased*	*Moderately increased*	*Severely increased*	*Normal*	*Total*
≤ 30 years	1	0	0	3	4
Row%	25.0	0.0	0.0	75.0	100.0
Col%	25.0	0.0	0.0	7.0	7.8
30–40 years	1	2	1	12	16
Row%	6.3	12.5	6.3	75.0	100.0
Col%	25.0	66.5	100.0	27.9	31.4
41–50 years	1	0	0	18	19
Row%	5.3	0.0	0.0	94.7	100.0
Col%	25.0	0.0	0.0	41.9	37.3
51–60 years	1	0	0	7	8
Row%	12.5	0.0	0.0	87.5	100.0
Col%	25.0	0.0	0.0	16.3	15.7
61–70 years	0	1	0	3	4
Row%	0.0	25.0	0.0	75.0	100.0
Col%	0.0	33.3	0.0	7.0	7.8
Total	4	3	1	43	51
Row%	7.8	5.9	2.0	84.3	100.0
Col%	100.0	100.0	100.0	100.0	100.0

LVMI at $t = 1$

When compared with the values of EF at $t = 0$ and $t = 6$ months, EF at $t = 0$ in the case group, 8 (15.7%) patients had mildly reduced (at $t = 6$ months, 4, i.e., 66.7% mildly remained reduced others became normal), 5 (9.8%) patients had moderately reduced (at $t = 6$ months, 2, that is, 33.3% remained moderately reduced, others became normal) and 38 (74.5%) patients had normal and in the control group, 2 (3.9%) patients had mildly reduced and 49 (96.1%)

patients had normal. All patients EF at $t = 0$ in normal, remained in the normal group at $t = 6$ months suggesting no change in EF after treatment. The association of EF at $t = 0$ vs EF at $t = 6$ months was statistically significant ($p < 0.0001$).

When compared with the values of LVMI in the case group, at $t = 0$ and $t = 6$ months, LVMI at $t = 0$ mildly increased, and all 4 (100%) came into normal category at $t = 6$ months. Among moderately increased category at $t = 0$, 3 (60.0%) patients remained in moderately increased categories at $t = 6$ months. And among the severely increased category at $t = 0$, only 1 (20%) remained in severely increased category. At $t = 6$ months, 42 (97.7%) had normal LVMI. The association of LVMI at $t = 0$ vs LVMI at $t = 6$ months was statistically significant ($p < 0.0001$). Left ventricular mass index at $t = 0$ and at $t = 6$ months in the control group, all patients had normal category.

Positive correlation was found between E/E´ at $t = 6$ months vs FT4 at $t = 6$ months and it was not statistically significant ($p = 0.504$).

Positive correlation was found between EF at $t = 6$ months vs FT4 at $t = 6$ months and it was statistically significant ($p = 0.055$).

Negative correlation was found between LVMI at $t = 6$ months vs FT4 at $t = 6$ months and it was not statistically significant ($p = 0.576$). Negative correlation was found between TSH at $t = 6$ months vs FT4 at $t = 6$ months and it was not statistically significant ($p = 0.348$).

Discussion

We were prompted to undertake this study on account of an increasing number of patients who were seen at hospital with hypothyroidism in adult subjects. After excluding other comorbidities, the study included only cases of primary hypothyroidism. The prevalence of primary hypothyroidism was around 11%. In addition, about 8% of patients were diagnosed to have SCH (normal serum-free T4 and TSH > 5.50 µIU/mL).[1]

Age- and sex-matched healthy controls were taken for comparison. The mean age of the study group was 44.57 ± 10.53 years among cases. In case arm, and 28 (54.9%) patients were males and 23 (45.1%) were females. Male–female ratio was approximately 1.2:1. In the study by Unnikrishnan and Menon[2] females were found to be more affected than males ~ 3 times (15.86% vs 5.02%). In the hospital-based study, we found a Male:Female ratio of ~ 1.2. But from this, any conclusion regarding gender predisposition cannot be drawn. In the mentioned study, older individuals than younger ones (13.11% vs 7.53%) were found to be more affected. In our study, 4 (7.8%) patients between 61 and 70 years of age, and the most commonly affected group was 41–50 years (37.3%). Among young individuals less than 30 years of age, 4 (7.8%) were found to be suffering from primary hypothyroidism. In a changing scenario from an iodine-depleted to iodine-replete state, this finding may be noteworthy. In other study by R Varma et al.,[3] the age range of the study was between 21 and 60 years. The age groups of 31–40 years contributed to the highest proportion of patients. Female preponderance was seen in between 31 and 40 years. About 75% of the total was contributed to by the female population.

In our study, we found abnormal E/E´ suggestive of diastolic dysfunction in 24 out of 51 (47.1%) subjects. In the study by Bengel et al. [4] up to 25% were found to have diastolic dysfunction In the study by William F. Crowley Jr et al.[5] LV function was found to be abnormal in severe primary hypothyroid patients. In the study, the mean serum thyroxine level was 0.8 µg/100 ml, and mean TSH level was 160 µIU/ml. They noticed a negative correlation of change in the pre-ejection period (ΔPEP) with serum TSH level ($p < 0.001$), and a positive correlation with serum T4 level ($p < 0.001$). In a study by Varma R et al.,[3] no abnormality was found in echocardiographic findings in 32.5% cases. Pericardial effusion was observed in 11 (27.5%) cases. Diastolic dysfunction was seen in 27.5%. Among them mild dysfunction was found majority of cases. Severe diastolic dysfunction was not documented in any of the cases. Systolic dysfunction was seen in 7.5% of patients. Forfar JC, et al.[6] and Yamada H et al.,[7] have described low systolic function indices in hypothyroid patients. Rawat and Satyal[8] showed no systolic dysfunction.

Multiple studies are there in support of the reversibility of diastolic dysfunction after correction of hypothyroid state. Ripoli et al.[9] observed that in comparison with the controls, patients with SCH had reduced stroke volume, end-diastolic volume, and cardiac index. Similar conclusions were drawn regarding unchanged LV ejection fraction among patients of SCH.[10–12] Karki P et al.[13]and Ilic S et al.[14] carried out similar studies which showed that SCH is a reversible cause of diastolic dysfunction. The study by Crowley Jr et al.[5] concluded that an appropriately adjusted dose of thyroxin is required in hypothyroidism for optimum left ventricular function. The study by A Gauna et al.[15] concluded that left ventricular diastolic dysfunction is more or less similar in all hypothyroid patients off T4 vs healthy controls or the same patients on T4. In the study by Monzani et al.,[16] it was concluded that myocardial abnormalities were reversible by levothyroxine replacement therapy.

In the present study, about 47% were found to have diastolic dysfunction which is higher in comparison with other studies. But with treatment, the significant change in E/E´ suggests reversibility of diastolic dysfunction which goes in conjunction with other studies as mentioned above. Although data on systolic dysfunction is controversial in various studies, in our studies, we found mild impairment in LVEF among 15.7%, and moderate among 9.8% of patients and EF was normal in 74.5% of the patients with primary hypothyroidism. As none of the subjects were evaluated by coronary angiography or a more sensitive method for the detection of other structural heart disease or coronary artery disease, this finding may not reflect the real scenario. Still, the association of EF at $t = 0$ vs EF at $t = 6$ months was statistically significant ($p < 0.0001$). The association of LVMI at $t = 0$ vs LVMI at $t = 6$ months was found statistically significant ($p < 0.0001$).

At $t = 6$ months there was found to be a negative correlation between TSH and EF value, not statistically significant ($p = 0.57$). The positive correlation of TSH with E/E´ was not statistically significant ($p = 0.48$). A negative correlation of TSH with LVMI was also statistically not significant ($p = 0.89$).

Conclusion

Primary hypothyroidism is linked with diastolic dysfunction, left ventricular systolic dysfunction, and abnormal left ventricular mass. The most affected age group is the 5th decade or above. Diastolic dysfunction is more severe than systolic dysfunction. Levothyroxine supplementation can potentially revert these dysfunctions. It takes at least 6 months for cardiac function to reverse. Early diagnosis of hypothyroidism and levothyroxine supplementation can prevent potentially dangerous complications of cardiovascular system including heart failure. Close monitoring every 4–6 weeks

is essential to rapidly establish euthyroid status. Whether rapid correction alters the change in cardiac function is unclear.

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