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Echocardiographic evaluation of diastolic dysfunction in patients with subclinical hypothyroidism

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Abstract

Background: Cardiovascular effects of thyroid hormones are well known and abnormalities well documented and have attracted a great deal of importance. Present study was aimed to study echocardiographic evaluation of diastolic dysfunction in patients with subclinical hypothyroidism. **Material and Methods:** Present study was single-center, case control study, conducted patients more than 18 years age, had elevated TSH level higher than the upper limit range 4mU/L but below 10mU/l and normal levels of T3 and T4 without any clinical features of hypothyroidism. **Results:** In present study, 62 patients were included, 31 cases & 31 controls. There was no statistically significant difference found between cases and controls with respect to age, sex, Triglyceride, LDL, HDL & VLDL. There was a statistically significant difference found between cases and controls with respect to Total Cholesterol, There was a statistically significant difference found between cases (6.70 ± 1.49) and controls (1.70 ± 0.83) with respect to TSH. There was no statistically significant difference found between cases (1.37 ± .37) and controls (1.44 ± 0.34) with respect to free T4. There was a statistically significant difference found between cases and controls with respect to Peak E-early mitral flow rate, Peak A-late mitral flow rate, .E/A ratio, E/E'-early mitral flow velocity/mitral valve tissue velocity. Among those who have sub clinical hypothyroidism 45.2% have abnormal peak E value when compared to 3.2% among controls and this was found to be statistically significant. Similirly 25% of the cases were found to have abnormal peak and 3.2% of the cases were found to be statistically significant. E/A ratio was significant in cases when compared to controls with 29% being abnormal in cases and 3.2% in the controls. DT and E/E' was not significant. **Conclusion:** Subclinical hypothyroidism is associated with left ventricular diastolic dysfunction.

Keywords: Subclinical hypothyroidism, Left Ventricular Diastolic Dysfunction, 2D echocardiography, cardiovascular morbidity.

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Introduction

Thyroid dysfunction is known problem in Indian population. Subclinical hypothyroidism is defined biochemically as a normal serum free thyroxine (T4) concentration in the presence of an elevated serum thyroid-stimulating hormone (TSH) concentration. Patients with subclinical hypothyroidism may present with nonspecific symptoms suggestive of hypothyroidism, but difficult to identify clinically. The prevalence of subclinical hypothyroidism amongst the suspected cases. Prevalence of subclinical hypothyroidism is

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about 10% among individuals over age 60 years, with a higher prevalence in women[1,2]

Cardiovascular effects of thyroid hormones are well known and abnormalities well documented and have attracted a great deal of importance. The most common cardiac abnormality observed in patients with hypothyroidism is left Ventricular (LV) diastolic function, which is due to abnormally slowed myocardial relaxation and impaired early ventricular filling. In almost all cases these cardiovascular changes are reversible when the underlying thyroid disorder is recognized and treated promptly. [3,4]

Doppler echocardiography has been used to evaluate left ventricular systolic and diastolic function in patients with subclinical hypothyroidism. Abnormalities 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] Present study was aimed to study echocardiographic evaluation of diastolic dysfunction in patients with subclinical hypothyroidism

Material And Methods

Present study was single-center, case control study, conducted in department of Medicine, M S Ramaiah Medical College, Bangalore, India. Study duration was of 2 years (October 2017 to August 2019). Study approval was obtained from institutional ethical committee.

62 asymptomatic patients underwent echocardiographic evaluation for diastolic dysfunction.

Inclusion criteria – Patients more than 18 years age, had elevated TSH level higher than the upper limit range 4mU/L but below 10mU/l and normal levels of T3 and T4 without any clinical features of hypothyroidism, willing to participate in present study

Exclusion criteria

Diabetes, Hypertension, Known cardiac disease, Hypothyroid patients on treatment, Harmful alcohol consumption, Patients receiving drugs which alter thyroid function & patients with any other structural or functional abnormality detected during 2D echocardiography were excluded from the study.

CASE - A case defined as the one who satisfies the following inclusion and exclusion criteria with a normal fT4 levels and TSH between 4mU/L to 10mU/L.

CONTROL - A control is defined as the one who satisfies the inclusion criteria and exclusion criteria with a normal thyroid profile.

Study was explained & written consent was taken from patients. Relevant history was noted & physical examination done. Relevant investigations such as FBS, PPBS, Renal function tests, including electrolytes, urine routine and microscopy, ECG, Chest x-ray & Echocardiography were done in all patients.

Conventional echocardiography. Standard and pulsed wave Doppler echocardiograms were obtained in all diabetic patients. All subjects were examined in the left lateral decubitus position, using a commercially available ultrasound system Phillips model CX50 (Bothell, WA, USA) S5-1 phased-array transducer with M-mode, two-dimensional, pulsed and continuous wave, color-flow, and tissue Doppler capabilities. In Echocardiography ejection fraction, E-peak velocity of early mitral flow, E-peak velocity of late mitral flow, E/A ratio & Left atrial size was calculated in all patients. E/A <1 and increase in LA size was considered as the evidence of left ventricular Diastolic Dysfunction.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

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Results

In present study, 62 patients were included, 31 cases & 31 controls. There was no statistically significant difference found between cases and controls with respect to age, sex, Triglyceride, LDL, HDL & VLDL. There was a statistically significant difference found between cases and controls with respect to Total Cholesterol,

Table 1: General characteristics

Characteristics	**Cases**	**Controls**	**P value**
Mean age (mean ± SD)	41.83 ± 9.72	42.60 ± 8.56	0.747
Gender			
Female (n=32)	16 (50 %)	16 (50 %)	--
Male (n=28)	14 (50 %)	14 (50 %)	--
Lipid profile (mg/dl)			
Cholesterol	197.80 ± 36.26	177.47 ± 31.35	**0.024**
Triglyceride	133.97 ± 67.69	166.40 ± 80.19	0.096
HDL	46.70 ± 12.71	49.87 ± 23.19	0.515
LDL	110.73 ± 37.19	102.80 ± 27.28	0.350
VLDL	26.57 ± 13.76	30.70 ± 11.38	0.210

There was a statistically significant difference found between cases (6.70 ± 1.49) and controls (1.70 ± 0.83) with respect to TSH. There was no statistically significant difference found between cases (1.37 ± .37) and controls (1.44 ± 0.34) with respect to free T4

Table 2: Comparison of TSH and T4 between cases and controls

Characteristics	**Cases**	**Controls**	**P value**
TSH	6.70 ± 1.49	1.70 ± .83	<0.001
fT4	1.37 ± .37	1.44 ± .34	0.407

There was no statistically significant difference found between cases and controls with respect to HB, Blood pressure, RBS and serum creatinine

Table 3: Comparison of HB, Blood pressure, RBS and serum creatinine

Characteristics	**Cases**	**Controls**	**P value**
HB	13.83 ± 1.63	13.86 ± 1.75	0.945
Serum Creatinine	0.76 ± 0.20	0.72 ± 0.14	0.414
RBS	112.87 ± 32.85	108.47 ± 15.51	0.510
SBP	126.07 ± 11.50	124.53 ± 11.52	0.608
DBP	80.90 ± 8.09	80.87 ± 8.43	0.988

There was a statistically significant difference found between cases and controls with respect to Peak E-early mitral flow rate, Peak A-late mitral flow rate, .E/A ratio, E/E'-early mitral flow velocity/mitral valve tissue velocity. There was no statistically significant difference found between cases and controls with respect to DT-deceleration time.

Table 4: Comparison of Echocardiographic parameters between cases and controls

Echocardiographic parameters	**Cases**	**Controls**	**P value**
PEAK E	0.71 ± .22	0.96 ± .15	0.001
PEAK A	0.88 ± .22	0.67 ± .14	0.002
E/A	0.89 ± .50	1.47 ± .28	0.003
DT	203.08 ± 21.57	206.89 ± 17.12	0.595
E/E'	9.40 ± 2.98	6.94 ± .90	0.016

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Among those who have sub clinical hypothyroidism 45.2% have abnormal peak E value when compared to 3.2% among controls and this was found to be statistically significant. Similirly 25% of the cases were found to have abnormal peak and 3.2% of the cases were found to be statistically significant. E/A ratio was significant in cases when compared to controls with 29% being abnormal in cases and 3.2% in the controls. DT and E/E' was not significant.

Table 5: Comparison of Echocardiographic parameters between cases and controls

Echocardiographic parameters		**Cases n(%)**	**Controls n(%)**	**P value***
PEAK E	Abnormal value	14(45.2)	1(3.2)	**0.0002**
	Normal value	17(54.8)	30(96.8)	
PEAK A	Abnormal value	8(25)	1(3.2)	**0.0261**
	Normal value	23(74)	30(96.8)	
E/A	Abnormal value	9(29)	1(3.2)	**0.0125**
	Normal value	22(70)	30(96.8)	
DT	Abnormal value	6(19)	4(13)	0.731
	Normal value	25(81)	27(87)	
E/E'	Abnormal value	4(14)	0	1
	Normal value	27(87)	31(100)	

*Fischer exact test-unpaired t-test

Discussion

As per American Thyroid Association guidelines, Subclinical hypothyroidism is defined as a FreeT4 in normal range with slightly high TSH that ranges from 4.0 to 10mU/L. Other terms for this condition are mild hypothyroidism, early thyroid failure, preclinical hypothyroidism and decreased thyroid reserve.[6]

Studies have shown that Subclinical Hypothyroidism is associated with hyperlipidemia, myocardial dysfunction and decrease in quality of life.[5] Mechanism of LV diastolic dysfunction in Subclinical Hypothyroidism patients is mainly due to under expression of SERCA 2A ,which regulates the rate of calcium release and its uptake into the SR, which is an important determinant of systolic contractility and diastolic relaxation.[7] The most common reported alteration in diastolic function are prolonged isovolumetric relaxation time and abnormal time-to-peak filling rate on echocardiography.[2]

In our study, the case and control population, each consisting of 31 individuals, were matched for age and gender. The mean age of the case was 41.83 ± 9.72 years and of the control population was 42.6 ± 8.56 years. There was no statistically significant difference found between cases and controls with respect to age & gender. On comparison of the lipid profile among the two groups, serum cholesterol was found to be higher in case group when compared to controls (197±36.3 vs 177±31.33,p-value=0.024) and was statistically significant. Triglycerides, HDL, LDL and VLDL were not significant among cases and control.

Hueston et al,[8] showed increased levels of total cholesterol in patients with SCH versus the control group higher mean cholesterol levels (226 vs 217 mg/dL, $P = .003$) and rates of elevated cholesterol levels (74.2% vs 63.9%, $P = 0.02$) than the euthyroid control group,. Similarly in our study it was found that total cholesterol was (197±36.3 vs 177±31.33,p-value=0.024) with a prevalence of (41% in cases and 25% in controls). No significant difference was observed between the 2 groups regarding lipid panel.

Study done by Erkan G et al.,[9] noted that, tissue Doppler-derived mitral annular E' velocities were significantly lower in the SH group. A moderate but significant improvement

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was observed in E' velocities after Thyroid Hormone Replacement Therapy (13.2+/- 3.87 versus 14.53 +/- 2.75,P=0.04).It was observed that Isovolumetric relaxation time (IVRT) is prolonged and pulsed Doppler-derived transmitral A wave velocity is increased in SH. These findings of diastolic dysfunction (DD) are normalized after T4 replacement therapy. Time-to-peak filling rate is prolonged and normalized after T4 replacement in a radionuclide ventriculographic study, reflecting the reversal of diastolic dysfunction in SH.

In our study it was found that Peak E(early mitral flow velocity) was significantly reduced among cases (0.71 +/- 0.22 versus 0.96 +/- 0.15 with p value =0.001) and increased Peak A(Late mitral flow velocity) between cases and controls (0.88 +/- 0.22 versus 0.67 +/- 0.14 p value=0.003) suggestive of diastolic dysfunction among cases compared to controls.

A study done by Malhotra et al.,[10] SCH patients had a higher prevalence of LVDD than controls (13.43% versus 1.49%; p = 0.017). E velocity, E' velocity, A' velocity, iso-volumetric relaxation time (IVRT), E/A, and E'/A' ratios were significantly lower, while A velocity, deceleration time (DT), E/E' ratio, left atrial (LA) volume index, and peak tricuspid regurgitation (TR) velocity were significantly higher in cases than controls ($p < 0.05$ each).. Echocardiographic indices for LVDD showed significant improvement after 6 months of L-thyroxine therapy ($p < 0.05$ each).

Biondi et al.,[11] found subclinical hypothyroidism to be associated with left ventricular systolic and diastolic dysfunction and enhanced risk for atherosclerosis and myocardial infarction based on the fact that heart responds to minimal, but persistent changes in blood level of thyroid hormone that is typical for subclinical hypothyroidism. Hak et al.,[12] had similar observation that it is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly woman. There is also evidence regarding increased arterial stiffness in this disorder.[13] A number of studies demonstrated diastolic dysfunction in subclinical hypothyroidism, and, based on their observation, they recommended to treating these patient as levothyroxine may reverse this diastolic dysfunction over the period of time.[14,15]

In our study it has been observed that the patients with subclinical hypothyroidism are found to have left ventricular diastolic dysfunction. Out of 31 cases 14 (45%) patients were found to have diastolic dysfunction. Out of 14 patients, 8 (57%) patients had Grade 1 dysfunction, 5(35%) patients had Grade 2 dysfunction and 1 (3%) patient had Grade 3 dysfunction. Out of the 14 patients 8 (57%) were female and 6 (43%) were male.1 patient in the control group had grade 1 diastolic dysfunction and probable reason would be age related after excluding other known causes. Further studies including larger population are needed to establish a possible correlation ship. Studies involving the effect of thyroxine treatment on the diastolic dysfunction would further strengthen the relationship which would help us reduce the mortality and morbidity associated with subclinical hypothyroidism.

Conclusion

Subclinical hypothyroidism is associated with Left Ventricular Diastolic Dysfunction. Early detection of Left ventricular diastolic dysfunction using 2D echocardiography would help guide us the therapy associated with Subclinical hypothyroidism and reduce the cardiovascular morbidity.

Conflict of Interest: None to declare

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