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Study of association between subclinical hypothyroidism on diastolic function of the heart

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Abstract

Background: Thyroid dysfunction is known problem in Indian population, vary from hypothyroidism to hyperthyroidism. 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. Our study aimed to study the association between subclinical hypothyroidism on diastolic function of the heart. **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. Present study involved 31 Subclinical hypothyroid and 31 normal individuals with normal thyroid profile. **Results:** 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 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. 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 significantly associated with symptomatic with NYHA GRADE 2 breathlessness as well as left ventricular diastolic Dysfunction. Evaluation by 2D echocardiography in patients with subclinical hypothyroidism helps for early detection, treatment & follow-up.

Keywords: Subclinical hypothyroidism, left ventricular diastolic Dysfunction, 2D echocardiography, TSH.

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Introduction

Thyroid dysfunction is known problem in Indian population, vary from hypothyroidism to hyperthyroidism. Clinically, apparent illness in the extreme two disorders can easily seek medical attention. 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. The problem exists with subclinical dysfunctions as patient

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remain asymptomatic for long period of times. Thus, it is diagnosed on the basis of laboratory test results.[1,2]

Patients with subclinical hypothyroidism may present with nonspecific symptoms suggestive of hypothyroidism, but difficult to identify clinically. Cardiovascular effects of thyroid hormones are well know 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, other effects include increased capillary permeability leads to pericardial effusion, increased systemic vascular resistance causing hypertension. [3,4]

Our study aimed to study the association between subclinical hypothyroidism on diastolic function of the heart. On the other hand, some authors clearly deny any association of cardiac dysfunction in subclinical hypothyroidism.[5] There is no established guideline regarding treatment plan of these patients. Some favor treatment with levothyroxine whereas others do not agree. Because of this dilemma, the study was conducted to find out whether cardiac dysfunction exists in subclinical hypothyroid patients and establish a clear relationship between left ventricular diastolic function and subclinical hypothyroid Indian patients.

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.

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 to patients in local language & written consent was taken for participation & study. Present study was a case control study involving 31 Subclinical hypothyroid and 31 normal individuals with normal thyroid profile. After a period of overnight fasting, venous blood samples will be collected in both controls and cases. Thyroid profile will be assessed using chemiluminescence immune assay technique

All patients underwent echocardiogram using Phillips model CX50 for determination of parameters

a. Peak E-early mitral flow rate
b. Peak A-late mitral flow rate
c. E/A ratio
d. DT-deceleration time
e. E/E'-early mitral flow velocity/mitral valve tissue velocity

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

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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.

Results

There was no statistically significant difference found between cases and controls with respect to age, P value 1.00, There was no statistically significant difference found between cases and controls with respect to sex. There was a statistically significant difference found between cases and controls with respect to Total Cholesterol, There was no statistically significant difference found between cases and controls with respect to Triglyceride, LDL, HDL, VLDL

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 and controls with respect to TSH. There was no statistically significant difference found between cases and controls 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 between cases and controls

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

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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

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

In contrast to overt symptomatic thyroid disease, subclinical hypothyroid disease implies the absence of classic hypothyroid related symptoms in patients with thyroid dysfunction. The definition has been further refined to include the demonstration of an abnormal TSH level (1-4 mU/I) in the face of normal serum level Free T4.[6] On the basis of the known effects of thyroid hormone on the heart, it is reasonable to expect adverse cardiac effects in subclinical thyroid dysfunction.

Subclinical hypothyroidism especially with S.TSH < 10.0 mU/l is associated with increased risk of heart failure in older patients. The most consistent cardiac abnormality recognized with subclinical hypothyroidism is left ventricular diastolic dysfunction characterized by slowed myocardial relaxation and impaired ventricular filling, both at rest and with exercise.[7] This is often associated with a variable impairment in left ventricular systolic function at rest, which becomes more consistent on exercise. There is also a strong

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association between subclinical hypothyroidism and atherosclerotic coronary artery disease with ischemic heart failure more common in this subset with dyslipidemia, increased arterial stiffness and endothelial dysfunction.[8]

In our study, the case and control population, each consisting of 31 individuals, were matched for age and 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.

In a study by Uzunlulu et al.[9] prevalence of dyslipidemia in females with SCH was higher than that of the healthy ones (16.4% versus 8.5%).[92] In our current study total cholesterol was high among the cases(197±36.3 vs 177±31.33,p-value=0.024) of which (41% in cases and 25% in controls) with a statistically significant (P-value 0.024).There was no statistically significant difference found between cases and controls with respect to Triglyceride, LDL, HDL, VLDL with (P-value 0.096,0.515,0.350,0.210) respectively.

Meta-analysis study of Sixteen observational studies done by Xiao Li et al,.[10] suggested that the serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and total triglyceride levels were significantly increased in patients with subclinical hypothyroidism compared with euthyroidism individuals; the WMD were 12.17 mg/dl, 7.01 mg/dl, and 13.19 mg/dl, respectively (P<0.001 for all).

Nag C et al.,[11] observed that there was significant left ventricular diastolic dysfunction as measured by increased mitral peak A velocity (66.3 ± 8.4 mm/s in case vs. 52.4 ± 4.8 mm/s in control, $P < 0.001$), decreased E/A ratio (0.90 ± 0.08 in case vs. 1.31 ± 0.36 in control, $P < 0.001$), prolonged isovolumetric relaxation time (120 ± 13 ms in case vs. 76 ± 9 ms in control, $P = 0.035$), increased Tei index (0.29 ± 0.13 in case vs. 0.22 ± 0.10 in control, $P = 0.015$). Similarly in our study it was found that there was significant diastolic dysfunction among case with an increased mitral peak A velocity(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) and decreased E/A ratio (0.89 ± 0.50 in case vs. 1.47 ± 0.28 in control, $P < 0.002$) suggestive of diastolic dysfunction among cases compared to controls.

Nag C et al.,[11] concluded that there was significant diastolic dysfunction in patients with subclinical hypothyroidism. SH have impaired endothelial function and impaired calcium homeostatis in the myocardial tissue, normal/depressed systolic function, left ventricular diastolic dysfunction at rest, and systolic and diastolic dysfunction on effort, which may result in poor physical exercise capacity. There is also a tendency to increase diastolic blood pressure as a result of increased systemic vascular resistance

Biondi et al.,[12] 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.,[13] 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.[14] 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.[15,16] 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.

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Conclusion

Subclinical hypothyroidism is significantly associated with symptomatic with NYHA GRADE 2 breathlessness as well as left ventricular diastolic Dysfunction. Evaluation by 2D echocardiography in patients with subclinical hypothyroidism helps for early detection, treatment & follow-up.

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