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Left Ventricular Diastolic Dysfunction in Patients with Subclinical Hypothyroidism: A Single South Indian Tertiary Care Centre Study

Anurag S. Kuchulakanti[1] Raghava Sharma[1] Basavaraj Utagi[2]

[1] Department of General Medicine, K.S. Hegde Medical Academy, Karnataka, India
[2] Department of Cardiology, K.S. Hegde Medical Academy, Karnataka, India

Address for correspondence Anurag S. Kuchulakanti, MD, L-701, Bearys Turning Point, Deralakatte, Mangalore, Dakshina Kannada, Karnataka 575022, India (e-mail: anuragkuchulakanti@gmail.com).

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Abstract

Context Subclinical hypothyroidism (SCH) has been implicated in left ventricular diastolic dysfunction (LVDD).

Aims To study the association between SCH and LVDD.

Objectives To analyze the association between SCH and LVDD. To correlate the amount of LVDD with the serum thyroid-stimulating hormone (TSH) levels.

Settings and Design Single-center case–control study.

Methods and Material A case–control study was conducted between January 2020 and June 2021. A total of 36 cases of SCH were enrolled in the study and 36 age- and gender-matched euthyroid controls were included. Each individual's LV diastolic functioning was assessed by 2D echocardiography. LVDD was graded and compared between cases and controls.

Statistical Analysis Used The sample size was calculated to be 72 based on previous studies. Statistical analysis was performed using the IBM SPSS software version 20. A *p*-value of less than 0.05 was considered significant.

Results SCH was more commonly seen among females (75%) as compared with males (25%). Among cases, a majority of them (75%) had grade 1 SCH (i.e., TSH $<$ 10 mU/L) and 25% of them had grade 2 SCH (i.e., TSH $\geq$ 10 mU/L). Among all the parameters assessed for LV diastolic function, the isovolumetric relaxation time and septal E/e' ratio was found to be significantly higher in cases than in controls and mitral E wave deceleration time (DT) significantly lower in cases. A statistically significant majority (72.2%) of the patients with SCH had some form of LVDD as compared with controls (30.5%)

Conclusions Walk-in outpatient department patients who opt for health check-up packages should be screened for SCH. SCH is statistically significantly associated with higher grades of LVDD as compared with age- and gender-matched euthyroid controls.

Keywords
- subclinical hypothyroidism
- left ventricular diastolic dysfunction
- 2D echocardiography

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Key Messages

Patients with subclinical hypothyroidism have statistically significant left ventricular diastolic dysfunction.

Introduction

Subclinical hypothyroidism (SCH) is a thyroid disorder defined by elevated serum thyroid-stimulating hormone (TSH) and normal serum free thyroxine (FT4). It affects 4 to 20% of the adult population and may progress to overt hypothyroidism in approximately 2 to 5% of cases annually.[1,2] The prevalence of SCH rises with age and is more common in females.

Overt hypothyroidism is known to cause various abnormalities of the cardiac system, including pericardial effusion and heart failure.[3] Overt hypothyroidism is associated with an increase in peripheral resistance and reduced left ventricular (LV) diastolic functioning. There have been no prior published studies done on the south Indian population. The presence of LV diastolic dysfunction (LVDD) is associated with increased morbidity and mortality and hence its presence in SCH has important implications for timely intervention. This study was done to assess LV diastolic function in patients with SCH.

Aim

To study the association between SCH and LVDD.

Objectives

- To assess the LV diastolic function in patients with SCH.
- To analyze the association between SCH and LVDD.
- To correlate the amount of LVDD with the serum TSH levels.

Patients and Methods

Ethics: The study was approved by the Institutional Ethics Committee. Written informed consent was taken for each of the study participants.

Study design: Case–control study.
Study duration: From January 2020 to June 2021.
Sample size: Expecting similar results to a study done by Meena et al at 90% accuracy at a 95% confidence interval with a case–control ratio of 1:1, the sample size was calculated to be 36 cases and 36 controls using the formula $N = 2S^2(Z_{1-\alpha/2}+Z_{1-\beta})^2 / \mu d_2$, where S is the standard deviation and μ is the mean deviation.

***Inclusion criteria*:**

- Elevated TSH levels (>4 mU/L) with normal FT4 levels (9–16 pmol/L) and normal T3 levels (0.85–2.02 ng/mL).[4,5]
- Age >18 years.

***Exclusion criteria*:**

- Age > 65 years.
- Known cases of diabetes mellitus, systemic hypertension, dyslipidemia, thyroid disorders, cardiac disorders including valvular heart diseases, and ischemic heart disease (IHD).
- Known alcoholics.
- Patients on drugs known to affect the thyroid hormone equilibrium such as Levothyroxine.

Method of Data Collection

Walk-in outpatient department patients who have opted for the health check-up package that includes the thyroid function tests were selected. Patients with SCH were identified by the use of Cobas E 411 fully automated analyzer that uses electrochemiluminescence technology, which showed elevated TSH values > 4 mU/L, normal FT4 levels between 9 and 16 pmol/L, and normal T3 levels of 0.85 to 2.02 ng/mL. Patients with SCH were then included/excluded in the study based on the inclusion and exclusion criteria. Based on the TSH levels, cases were categorized into grade 1 (TSH levels, 4–10 mU/L) and grade 2 (TSH levels ≥ 10 mU/L). Appropriately age- and sex-matched euthyroid patients were included in the control arm of the study. The cases and controls were then subjected to a 2D echocardiography scan, in which various parameters of LV diastolic function namely, the transmitral flow velocities (early diastolic filling velocity [E], late diastolic filling velocity [A], mitral E/A ratio, mitral E wave deceleration time [DT], and isovolumetric relaxation time [IVRT]) and mitral annular velocities (systolic velocity [S'], early diastolic velocity [E'], late diastolic velocity [A']), were assessed. The mitral annular velocities were assessed by using the tissue Doppler imaging mode of the 2D echocardiography and were assessed for both lateral and septal velocities. The E/e' ratio was calculated. Left atrial volume index (LAVI) was also considered using Simpson's method.

Grading of LVDD[6]

Grading of LVDD was done per the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging. ►**Fig. 1** depicts the flowchart used for grading LVDD.

Statistics

Quantitative data were interpreted by mean, median, and mode. Qualitative data were interpreted by frequency and proportion. Analysis of the data was done by standard

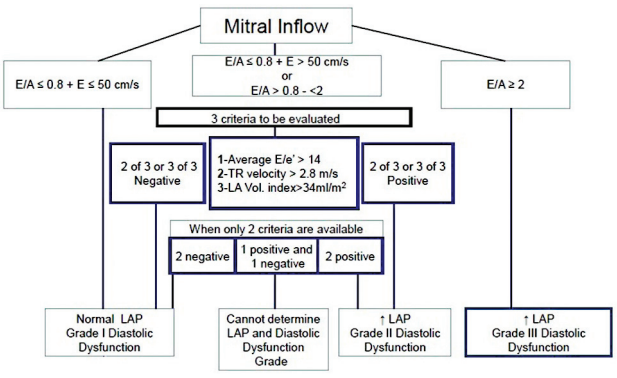

Fig. 1 Flow chart depicting the criteria used to grade LVDD using 2D echocardiographic parameters. (Adapted from Nagueh et al.[6])

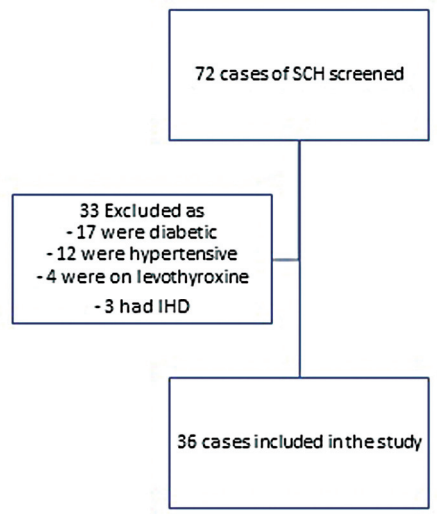

Fig. 2 Flowchart depicting the selection of cases for the study.

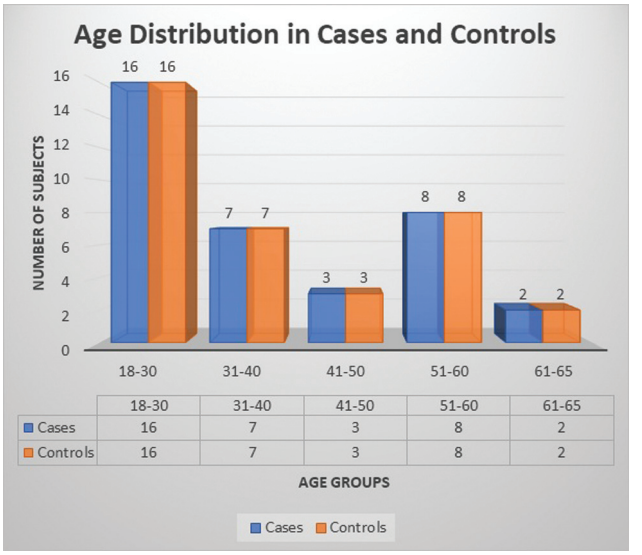

Fig. 3 Chart depicting the age distribution among the study patients stratified into various categories of age. Note that the controls were matched with the same age as that of the cases.

deviation, unpaired *t*-test, chi-square test, Pearson's correlation, and Fischer's exact test. Statistical analysis was performed using the IBM SPSS software version 20. A *p*-value less than 0.05 was considered significant.

Results

►**Fig. 2** depicts the selection of cases for the study.

The study included 36 cases and 36 controls with a total study population of 72 individuals. The gender and age of the control group were matched appropriately to those of the cases.

►**Table 1** depicts the baseline characteristics of the study population.

The gender distribution in the study was found to have a female predominance, with 75% of the study population being females, i.e., 27 of the 36 participants in cases and controls. Nine of the 36 participants in both cases and controls were men and contributed to 25% in each group.

The age distribution of the study population is depicted in ►**Fig. 3**. It was found that maximum representation was seen in the 18 to 30 years age group, with 16 cases and controls contributing to 44% of the study population.

Thyroid Profile in the Study Population

TSH

Nine of the 36 cases, i.e., 25% of the cases, had TSH values above 10 mU/L.

The remaining 75% of the cases had TSH levels between 4 and 10 mU/L.

Table 1 Baseline characteristics of the study population

Characteristic	Mean value		Standard deviation		95% confidence interval		*p*-Value
	Case, $n=36$	Control, $n=36$	Case, $n=36$	Control, $n=36$	Lower	Upper	
Height (cm)	162.0	162.78	7.97	8.14	−4.56	3.00	0.683
Weight	59.58	60.58	7.71	7.83	−4.65	2.56	0.587
BMI	22.95	23.21	2.38	2.62	−1.44	0.91	0.653
HR	79.66	82.89	9.52	12.4	−8.41	1.98	0.220
SBP	120.80	118.05	14.62	9.77	−3.09	8.59	0.351
DBP	76.33	79.42	18.67	13.15	−10.67	4.50	0.421
TSH	8.76	2.02	6.72	0.93	4.48	8.99	**0**
FT4	1.23	1.30	0.21	0.23	−0.165	0.044	0.253
T3	1.24	1.37	0.30	0.37	−0.287	0.026	0.102
T4	8.28	8.25	2.01	2.22	−0.98	1.02	0.965

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FT4, free thyroxine; HR, hazard ratio; SBP, systolic blood pressure; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.
Note: *p*-value < 0.005 was considered significant.

Table 2 Comparison of the various parameters used to assess the LV diastolic function compared between cases and controls

Parameter	Group	*N*	Mean ± SD	*t*-Value	Mean difference	95% confidence interval	*p*-Value
E	Case	36	76.33 ± 28.88	1.69	9.14	(−1.62 to 19.91)	0.09
	Control	36	67.18 ± 14.68				
A	Case	36	77.93 ± 25.48	1.21	7.63	(−4.91 to 20.18)	0.22
	Control	36	70.30 ± 27.86				
DT	Case	36	184.97 ± 32.99	−1.33	−8.27	(−20.64 to 4.08)	**0.001**
	Control	36	193.25 ± 17.17				
IVRT	Case	36	106.86 ± 18.20	3.45	12.94	(5.46–20.42)	**0.001**
	Control	36	93.92 ± 13.21				
E/A	Case	36	1.03 ± 0.38	0.02	0.001	(−0.14 to 0.15)	0.98
	Control	36	1.02 ± 0.23				
Medial E/e'	Case	36	10.91 ± 4.28	1.98	1.64	(−0.004 to 3.286)	**0.005**
	Control	36	9.2722 ± 2.47				
Medial e'/a'	Case	36	0.94 ± 0.19	−0.83	−0.03	(−0.12 to 0.05)	0.40
	Control	36	0.98 ± 0.18				
Lateral E/e'	Case	36	9.37 ± 2.99	−0.46	−0.30	(−1.60 to 1.00)	0.64
	Control	36	9.67 ± 2.53				
Lateral e'/a'	Case	36	1.06 ± 0.33	1.20	0.07	(−0.04 to 0.20)	0.23
	Control	36	0.98 ± 0.17				
Average E/e'	Case	36	10.14 ± 3.49	0.67	0.48	(−0.95 to 1.92)	0.50
	Control	36	9.65 ± 2.55				
LAVI	Case	36	26.78 ± 7.44	0.79	1.19	(−1.82, 4.20)	0.43
	Control	36	25.58 ± 5.17				

Abbreviations: A, late diastolic filling velocity; DT, deceleration time; E, early diastolic filling velocity; IVRT, isovolumetric relaxation time; LAVI, left atrial volume index; SD, standard deviation.
Note: *p*-value < 0.05 is considered significant.

The mean TSH level in the cases was 8.75 ± 6.6 mU/L, compared with the mean TSH level of 2.02 ± 0.9 mU/L in controls.

FT4

The mean FT4 value in the case arm of the study was 1.23 ± 0.20 ng/dL and in the control arm of the study was 1.30 ± 0.23 ng/dL. All the patients had FT4 values in the normal range, as mentioned in the inclusion criteria. The SCH group had lower FT4 levels compared with that of the controls but was of no statistical significance.

T3

The mean T3 value in the case arm of the study was 1.23 ± 0.29 ng/dL and in the control arm of the study was 1.36 ± 0.36 ng/dL. The T3 levels were lower in the cases than that in the controls but both were well within the normal range.

Echocardiographic parameters were used for the assessment of LVDD. All the 2D echocardiographic variables used for assessing LVDD were compared in cases and controls using unpaired *t*-test (►**Table 2**). LV hypertrophy on echocardiography was seen only in one patient among cases. Among all the parameters used, DT, IVRT, and medial E/e' showed statistical significance.

Grades of LVDD in the Study Population

►**Fig. 4** depicts the different grades of LVDD in the study population.

In this study, a total of 35 individuals had no LV dysfunction, i.e., 48% of the entire study population had a normal LV

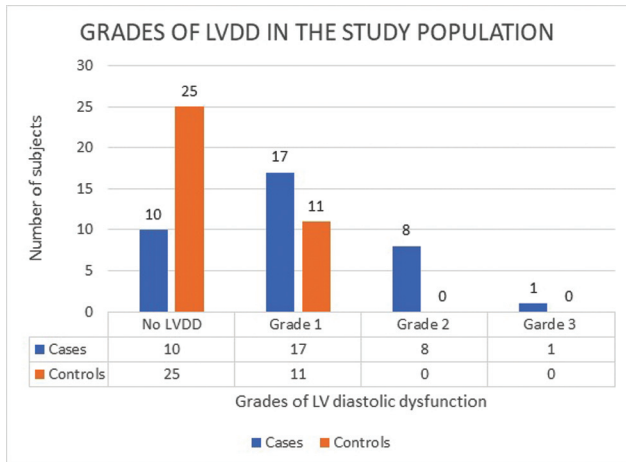

Fig. 4 A column chart showing the study population categorized into the different grades of diastolic dysfunction.

Table 3 Cross-tabulation of the grade of diastolic dysfunction and the case/control groups of the study

			Groups		Total
			Case	Control	
Diastolic dysfunction grade	Grade 1	Count	17	11	28
		% within group	47.2%	30.6%	38.9%
	Grade 2	Count	8	0	8
		% within group	22.2%	0.0%	11.1%
	Grade 3	Count	1	0	1
		% within group	2.8%	0.0%	1.4%
	Normal	Count	10	25	35
		% within group	27.8%	69.4%	48.6%
Total		Count	36	36	72
		% within group	100.0%	100.0%	100.0%

diastolic function. A total of 28 individuals (38.9%) had grade 1, 8 individuals (11.1%) had grade 2, and 1 individual (1.4%) had grade 3 LVDD. In the case arm of the study, 17 individuals (47.2% of cases) had grade 1 LVDD, 8 individuals (22.2% of cases) had grade 2 LVDD, 1 individual (2.8% of cases) had grade 3 LVDD, and 10 individuals (27.8% of all cases) had no LVDD.

In the control arm of the study, 25 individuals (69.4% of controls) had no LVDD. The remaining 11 individuals (30.6% of controls) had grade 1 LVDD. There was no grade 2 or grade 3 LVDD observed in the controls.

►**Table 3** depicts the comparisons between the grades of LVDD in cases and controls.

Fisher's exact test was used for the statistical analysis of the grades of LVDD in cases and controls and has a *p*-value of 0.001 implying high statistical significance. In other words, there is a statistically significant association between SCH and the development of LVDD.

Comparison of TSH Levels and Grades of LVDD

►**Table 4** depicts the comparison of TSH levels and grades of LVDD.

To compare the TSH level groups with that of grades of LVDD, Fisher's exact test was conducted and showed a *p*-value of 0.03, which implies high statistical significance. In other words, the higher the TSH levels, the higher the probability of developing LVDD.

Discussion

The mean age of the study group was 37.5 ± 13.4 years, which was lesser than most other studies[7–9] but was higher than the mean age in the studies by Biondi et al[10] and Malhotra et al.[11] In this study, only individuals between 18 and 65 years were considered, as previous studies have reported that with increasing age, there will be a worsening of the LV diastolic function. Age-related LVDD has been demonstrated by using conventional Doppler studies by Miyatake et al.[12] Hence, individuals above 65 years were excluded to remove the confounding effect of age on LVDD.

In this study, there was a significant female preponderance, with the female-to-male ratio being 3:1. In the study by Meena et al,[7] females were 76.66% and males were 23.33%. Most other studies have also reported a female preponderance, with females accounting for at least 75% of the study population.[10,11,13] The reason for female preponderance is still unclear but estrogen has been implicated in a study done on postmenopausal women by Arafah,[14] which showed hormone replacement therapy increased TSH. In the Whickham survey,[9] elder women above the age of 45 years showed

Table 4 Cross-tabulation between the TSH levels and grades of diastolic dysfunction

			Diastolic dysfunction grade				Total
			Grade 1	Grade 2	Grade 3	Normal	
TSH level groups	TSH level < 9.9	Count	25	5	0	34	64
		% within diastolic dysfunction grade	89.3%	62.5%	0.0%	97.1%	88.9%
	TSH level ≥ 10	Count	3	3	1	1	8
		% within diastolic dysfunction grade	10.7%	37.5%	100.0%	2.9%	11.1%
Total		Count	28	8	1	35	72
		% within diastolic dysfunction grade	100.0%	100.0%	100.0%	100.0%	100.0%

Abbreviation: TSH, thyroid-stimulating hormone.

a higher prevalence of SCH. The thyroid antibodies have been demonstrated to be more frequent in females as compared with males and were more frequent as age increases in a cross-sectional study by Pedersen et al.[15]

The mean body mass index (BMI) of cases in this study was 22.9 ± 2.3 kg/m^2, which was in the normal range for the Indians as per the consensus statement for diagnosing obesity for Asian Indians.[16] This was contrary to the study conducted by Malhotra et al[11] in which the mean BMI was 26.13 ± 3.67 kg/m^2, which was lower compared with other studies they compared with. A significant association is noted between BMI and SCH, but in their study, no such association between BMI and LVDD was found.

The serum TSH levels were significantly higher in the cases than in controls, as expected, since high TSH levels were the inclusion criteria for the case arm of the study. The mean TSH level was 8.75 ± 6.6 mU/L in the cases compared with 2.02 ± 0.9 mU/L in controls. The mean FT4 value in the case arm of the study was 1.23 ± 0.20 ng/dL and in the control arm of the study was 1.3 ± 0.23 ng/dL. All the patients had FT4 values in the normal range, as mentioned in the inclusion criteria. The SCH group had lower FT4 levels compared with that of the controls but within the normal range and is comparable to other studies.[10,11,13,17] In this study, the mean T3 value in the case arm of the study was 1.23 ± 0.29 ng/dL and in the control arm of the study was 1.36 ± 0.36 ng/dL. The T3 levels were lower in the cases than that in the controls but both were well within the normal range and are similar to other studies.[10,13]

Among the parameters used for measuring and grading the LVDD in this study, DT, IVRT, and medial E/e' ratio were found to have statistical significance.

The mean peak E wave velocity value was 76.33 ± 28.88 cm/s in cases and 67.18 ± 14.68 cm/s in controls. The mean peak E wave velocity in this study was higher in cases than in controls but was not of statistical significance ($p = 0.09$). This was in contrast to other studies,[7,13] where there was a statistically significant lower peak E wave velocity in cases compared with controls.

The mean peak A wave velocity value was 78.7 ± 25.1 cm/s in cases and 70.3 ± 27.4 cm/s in controls. The mean peak A wave velocity was higher in cases compared with controls but was not of statistical significance. In similar studies, the mean peak A wave velocities not only were higher but also were of statistical significance.[7,10,11]

In this study, the mean DT was 184.9 ± 32.99 ms in cases and 193.25 ± 17.17 ms in controls. The DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening, and LV stiffness.[6] In this study, the DT in cases was significantly shorter than that of the controls and was similar to the results of other studies.[17,18] However, in the study by Malhotra et al,[11] the DT was longer in cases when compared with that of controls, although it was not of statistical significance.

The mean IVRT was 106.86 ± 18.20 ms in cases and 93.92 ± 13.21 ms in controls in this study. The IVRT was significantly higher in cases than in controls, similar to other studies.[10,18] IVRT is a measure of myocardial relaxation and is the time taken from the closure of the aortic valve to the opening of the mitral valve. The longer the duration, the poorer the myocardial relaxation.

The E/A ratio was higher in the cases as compared with the controls in this study (1.03 ± 0.38 vs 1.02 ± 0.23) and was not of statistical significance ($p = 0.98$) and this was in concordance with one study[7] and was contradictory to other studies.[11,13,19]

The ratio of early diastolic transmitral flow velocity and early diastolic mitral annular flow velocity septal (E/e') ratio in this study was 10.91 ± 4.28 in cases and 9.27 ± 2.47 in controls. This ratio can be used for predicting the LV filling pressures as the e' velocity can be used to correct for the effect of LV relaxation on mitral E velocity.[6]

In this study, the septal E/e' ratio was significantly higher in cases as compared with controls ($p = 0.005$), similar to the study conducted by Malhotra et al.[11] No further literature was found comparing the E/e' ratio in SCH and controls and hence an accurate conclusion cannot be drawn.

The lateral E/e' ratio was lower in cases as compared with controls (9.37 ± 2.99 vs 9.67 ± 2.53) and was not statistically significant ($p = 0.64$). The average E/e' ratio of the septal and lateral wall, however, was higher in cases when compared with controls (10.14 ± 3.49 vs 9.65 ± 2.55), albeit not statistically significant ($p = 0.50$). The average E/e' ratio values of < 8 usually indicate normal LV filling pressure and values > 14 have high specificity for increased LV filling pressures.[6]

The LAVI was higher in cases when compared with controls (26.78 ± 7.44 vs 25.58 ± 5.17) in this study and was not of statistical significance ($p = 0.43$). This was also seen in other studies.[11,20] The effects of LV filling pressure over time will be reflected by the maximal LA volume index. LAVI is an independent predictor of death, heart failure, atrial fibrillation, and stroke.[6]

Nearly half of the cases with SCH (17 of the 36; 47.2%) had grade 1 LVDD. Eight cases of the total 36 cases (22.2%) and one out of the total 36 cases (2.8%) have grade 3 LVDD. However, there were no euthyroid individuals with grade 2 or grade 3 LVDD. In this study, a statistically significant association was found between SCH and the development of LVDD ($p = 0.001$). This is consistent with other studies,[7,10,11,13,17,19] which have proved an association between SCH and the development of LVDD. Furthermore, there was statistically significant LVDD in individuals with TSH ≥ 10 mU/L ($p = 0.03$). We followed strict exclusion criteria in the patient selection of the study to exclude patients with other potential factors contributing to LVDD such as those who are having diabetes, systemic hypertension, preexisting thyroid disorders on treatment, IHD, and those on medication that can affect the thyroid hormone balance. Thus, we can safely attribute the findings of this study that LVDD in cases is due to SCH and more so due to TSH hormone.

Limitations of This Study

This study has a few limitations. As this is a single-center study done with a relatively small sample size, the findings of this study cannot be generalized to the public. There was no randomization nor blinding done to minimize bias. Incidence

TSH, T3, and FT4 levels were measured and no serial follow-ups were done to ascertain the duration of SCH. Assessment of biochemical markers like brain natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NTBNP) was not done in this study. Electrocardiogram findings were not used as part of the inclusion/exclusion criteria. Reversibility of the diastolic dysfunction with thyroxin supplementation was not attempted as this was an observational study.

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Conflict of Interest
None declared.

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