Indian J. Pharm. Biol. Res. 2026; 14(3):346-356

ISSN: 2320-9267

Indian Journal of Pharmaceutical and Biological Research (IJPBR)

Journal homepage: www.ijpbr.in

RESEARCH ARTICLE

Early Cardiovascular Changes in Subclinical Hypothyroidism: Evidence from Clinical and Echocardiographic Evaluation

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is characterized by elevated thyroid-stimulating hormone (TSH) levels with normal free thyroid hormone concentrations and is increasingly recognized as a risk factor for cardiovascular dysfunction. This study aimed to evaluate early cardiovascular changes in SCH using clinical, biochemical, electrocardiographic, and echocardiographic parameters.

Methods: A hospital-based cross-sectional observational study was conducted over two years (2019–2021) at the Department of General Medicine, Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla, Odisha. A total of 210 adults with SCH were enrolled and categorized into mild SCH (TSH 4.5–9.9 mIU/L; n=170) and severe SCH (TSH >10 mIU/L; n=40). Clinical assessment, lipid profile, inflammatory markers, electrocardiography (ECG), and two-dimensional echocardiography were performed. Statistical analysis was carried out using SPSS version 11.5.

Results: Severe SCH patients showed significantly higher serum creatinine, anti-thyroid peroxidase positivity, and elevated C-reactive protein levels compared to mild SCH ($p<0.05$). Significant dyslipidemia was observed in severe SCH with increased total cholesterol, triglycerides, LDL, and VLDL levels ($p=0.001$). ECG abnormalities such as ST-segment depression, low-voltage complexes, prolonged QT interval, and conduction defects were more frequent in severe SCH. Echocardiographic evaluation revealed significantly reduced ejection fraction, increased posterior wall thickness, reduced E velocity, decreased E/A ratio, and prolonged isovolumetric relaxation time in severe SCH, indicating both systolic and diastolic dysfunction.

Conclusion: Severe SCH is associated with significant metabolic abnormalities and early cardiovascular dysfunction, including electrophysiological and echocardiographic alterations. Early cardiovascular evaluation in SCH patients may help identify high-risk individuals and prevent future cardiovascular complications.

Keywords: Subclinical Hypothyroidism, Diastolic dysfunction, Echocardiography

Indian J. Pharm. Biol. Res. (2026): https://doi.org/10.30750/ijpbr.14.3.53

INTRODUCTION

Subclinical hypothyroidism is a metabolic disorder defined by serum thyroid-stimulating hormone (TSH) levels above the reference range in the presence of normal free triiodothyronine (FT3) and free thyroxine (FT4) concentrations, reflecting a state of subtle thyroid dysfunction [1]. Several factors contribute to its development, including thyroid tissue damage, exposure to goitrogenic substances such as antithyroid medications, lithium, and iodine, as well as autoimmune conditions like thyroiditis. Physiologically, TSH is secreted by the anterior pituitary under the control of thyrotropin-releasing hormone (TRH) from the hypothalamus and stimulates the thyroid gland to produce T3 and T4 [2]. In primary hypothyroidism, reduced circulating thyroid hormones lead to a compensatory increase in TSH, whereas elevated T3 and T4 suppress TSH secretion via negative feedback [3].

However, elevated TSH concentrations do not always indicate intrinsic thyroid dysfunction; they may also reflect an altered homeostatic set point within the hypothalamic–pituitary–thyroid axis. Factors such as bacterial infections, systemic inflammation, environmental stressors, and chronic psychological stress can shift this set point, resulting in higher TSH levels despite unchanged peripheral thyroid hormone concentrations [4]. Growing evidence suggests that subclinical hypothyroidism is associated with an increased risk of adverse cardiovascular outcomes. Thyroid hormones play a critical role in cardiac function, particularly through regulation of calcium handling in cardiomyocytes. The sarcoplasmic reticulum calcium adenosine triphosphatase (SERCA2) is essential for myocardial contraction and relaxation by facilitating calcium reuptake into the sarcoplasmic reticulum [5]. Triiodothyronine (T3) enhances cardiac contractility by upregulating SERCA2 expression. In contrast, TSH interaction with cardiac membrane receptors activates

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How to cite this article: Athira TK, Tripathy S, Patel NK, Kumar RGN, Biswas P, Sahu AK, Baitharu I. Early Cardiovascular Changes in Subclinical Hypothyroidism: Evidence from Clinical and Echocardiographic Evaluation. Indian J. Pharm. Biol. Res. 2026;14(3):346-356.

Source of support: Nil

Conflict of interest: None.

Received: 02/07/2026 **Revised:** 15/07/2026 **Accepted:** 28/07/2026 **Published:** 17/08/2026

the cAMP–protein kinase A (PKA) signaling pathway, leading to phosphorylation of SERCA2 and disruption of calcium homeostasis. This process impairs both systolic and diastolic ventricular function and contributes to ventricular remodeling. Clinically, this dysfunction may manifest as a reduced peak filling rate (PFR), indicating impaired diastolic relaxation.

In addition to its cardiac effects, TSH influences lipid metabolism. Hydroxymethylglutaryl-CoA (HMG-CoA) reductase, a key enzyme in cholesterol synthesis, is regulated by its phosphorylation state, with phosphorylation inactivating and dephosphorylation restoring its activity [6]. TSH promotes cholesterol synthesis by enhancing the transcription of the low-density lipoprotein receptor (LDL-R) gene and increasing hepatic HMG-CoA reductase expression. This effect is partly mediated through inhibition of AMP-activated protein kinase (AMPK), a metabolic sensor that normally phosphorylates and suppresses HMG-CoA reductase activity. Reduced AMPK activity leads to increased cholesterol synthesis and dyslipidemia. Elevated LDL levels promote lipid accumulation in arterial walls, accelerating atherosclerosis and increasing cardiovascular risk. Furthermore, TSH may enhance lipid peroxidation and platelet activation, contributing to atherothrombotic processes. The sterol regulatory element-binding protein 2 (SREBP-2), a transcription factor central to cholesterol homeostasis, is also influenced by TSH signaling [7]. Vascular dysfunction is another important feature of subclinical hypothyroidism, characterized by impaired smooth muscle relaxation due to reduced availability of endothelial nitric oxide. Over time, subclinical hypothyroidism may progress to overt hypothyroidism, particularly in individuals with higher baseline TSH levels and the presence of anti-thyroid peroxidase (anti-TPO) antibodies [8].

Given these pathophysiological mechanisms, an important clinical question arises: whether early treatment of subclinical hypothyroidism can mitigate or prevent the development of cardiovascular complications. This study aims to examine the relationship between subclinical hypothyroidism and cardiovascular risk, with a focus on underlying mechanisms and therapeutic implications.

MATERIAL AND METHODS

Study settings

A hospital-based cross-sectional observational study was conducted for 2 years from November 2019 to November 2021 in the Department of General Medicine, Veer Surendra Sai Institute of Medical Sciences and Research (VIMSAR), Burla, a tertiary-care referral center serving Western Odisha and neighboring areas of Chhattisgarh.

Study Population

The study includes subjects with age ≥18 years admitted with subclinical hypothyroidism i.e. having elevated TSH level (>4.5 ml U/L) and normal T3 and T4 levels were included. Patients with pre-existing cardiovascular disease, overt hypothyroidism, chronic kidney disease, pregnancy, patient who were on thyroid medication within last 3 months, diabetes, hypertension, acute illness, obesity, and those who declined to provide consent were excluded.

Sample Size and Sampling

The sample size was determined by taking prevalence of cardiovascular abnormality in subclinical hypothyroidism as 20%, as reported from previous medical records, precision 5%, and confidence interval of 95%, the sample size was estimated to about 210 and patient's selection was done by nonprobability convenience sampling.

Procedure for data collection

A total of 210 participants were enrolled using a

nonprobability convenience sampling method after obtaining informed consent form and meeting the case definition. Comprehensive case histories were recorded using a semi-structured, close ended proforma following a detailed explanation of the study. Basic demographic and lifestyle information, including age, sex, life-style and previous medical history (history of hypertension and other comorbid conditions) were collected from all participants. A thorough general physical examination was performed for each participant. For analysis, all patients were categorized into two study groups viz. mild subclinical hypothyroidism (TSH:4.5-9.9 ml U/L) and severe subclinical hypothyroidism (TSH >10 ml U/L).

Clinical Measurements

After the subject had rested for at least five minutes, Arm supine blood pressure was using a sphygmomanometer. Two readings were obtained at an interval of five minutes, and the average of these readings was taken as the final blood pressure value. Hypertension was defined either by a documented history of antihypertensive medication use or by a blood pressure reading greater than 130/80 mmHg, in accordance with the Joint National Committee-7 (JNC-VII) criteria [9]. Heart rate and pulse rate was measured using clinically validated pulse oximeter (Zacurate, U.S., 500DL, 2024).

Sample collection and Analysis

The puncture site was thoroughly cleaned and sanitized before blood collection. Three different types of vacutainer tubes such as plain tubes, EDTA containing tubes, and Fluoride tubes were used for collection of peripheral venous blood samples. The estimation of biochemical and hematological parameters such as lipid profile, thyroid profile, kidney function tests, hemoglobin levels, complete blood count, erythrocyte sedimentation rate and random blood glucose were performed with samples allocated to the appropriate tubes for each analysis. Inflammatory markers such as C-Reactive protein (CRP) was also analyzed. ELISA Kit was employed for estimation of Anti-thyroid peroxidase (anti-TPO) antibodies. All samples were collected from the study participants and analyzed at the Regional Diagnostic Center, Veer Surendra Sai Institute of Medical Science and Research, Burla, Odisha, India. The sample processing and testing were performed on the same day as collection. The blood sample was centrifuged at 3000 rpm for 10 minutes at 4oC for separation of serum. Random blood glucose and biochemical parameters such as renal function test and lipid profile, thyroid profile test, CRP were measured using Transasia XL 1000 autoanalyzer. Hemoglobin concentration and complete blood count were determined using photometric methods on the Mindray BC 1000 six-part hematology analyzer. All chemical reagents used were of analytical grade and procured from recognized commercial sources.

Electrocardiography

A standard 12-lead electrocardiogram (ECG) was recorded for all study participants under resting conditions following established clinical guidelines. Recordings were obtained using a calibrated digital ECG machine with a paper speed of 25 mm/s and a gain of 10 mm/mV. Participants were instructed to avoid caffeine, smoking, and strenuous physical activity for at least 30 minutes prior to the procedure. All ECGs were performed in the supine position after a rest period of 10 minutes in a quiet, temperature-controlled environment to minimize physiological variability. Limb and precordial leads were placed according to standard anatomical positions. ECG parameters including heart rate, PR interval, QRS duration, QT interval, and corrected QT (QTc) interval were measured. QTc was calculated using Bazett's formula. All recordings were independently reviewed and interpreted by two experienced cardiologists at Department of Cardiology, Veer Surendra Sai Institute of Medical Science and Research, Burla, Odisha, India to ensure accuracy and reduce observer bias, and any discrepancies were resolved by consensus.

2D Echocardiography

Two-dimensional (2D) echocardiography was performed in all participants using a commercially available ultrasound system equipped with a phased-array transducer (2.5–3.5 MHz), following the recommendations of the American Society of Echocardiography. Examinations were conducted with the subject in the left lateral decubitus position after adequate rest. Standard parasternal long-axis, short-axis, apical four-chamber, and apical two-chamber views were obtained. Systolic function was assessed by measuring left ventricular ejection fraction (LVEF) using the modified Simpson's biplane method, along with fractional shortening and left ventricular dimensions. Diastolic function was evaluated using pulsed-wave Doppler across the mitral valve to obtain early (E) and late (A) transmitral flow velocities, E/A ratio, deceleration time (DT), and isovolumetric relaxation time (IVRT). Tissue Doppler imaging (TDI) was used to measure early diastolic (e′) velocity at the septal and lateral mitral annulus, and the E/e′ ratio was calculated as an estimate of left ventricular filling pressure. All measurements were averaged over three consecutive cardiac cycles to minimize beat-to-beat

variability. Echocardiographic recordings were analyzed offline by two independent cardiologists blinded to clinical data, and discrepancies were resolved by consensus to ensure reproducibility and reduce observer bias.

Statistical Analysis

All the data were analyzed using SPSS software (version 11.5). Quantitative variables were presented as mean and standard deviation, while categorical variables were presented as frequencies and percentages. Student's t – test was applied to assess differences between the mean values of two continuous variables, and the chi square test was used to compare categorical variables across groups. p value of less than 0.05 was considered statistically significant.

RESULT

The comparative analysis of clinical and demographic variables between mild and severe subclinical hypothyroidism (SCH) groups reveals several noteworthy patterns. Gender distribution differed significantly between the groups, with females predominating however, the proportion of females was significantly higher in the mild SCH group (89.4%) compared to the severe group (72.5%), while males were relatively more represented in the severe group, though this difference was not statistically significant ($p = 0.115$). The mean age of participants was comparable between mild (38.98 ± 13.27 years) and severe SCH (38.66 ± 8.85 years), indicating no age-related bias. Vital parameters, including heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP), did not show statistically significant differences between the two groups ($p > 0.05$), suggesting that SCH severity may not markedly influence baseline cardiovascular parameters in this cohort. Similarly, biochemical parameters such as hemoglobin, urea, random blood sugar (RBS), erythrocyte sedimentation rate (ESR), and most renal indices were comparable across groups. However, serum creatinine levels were significantly higher in the severe SCH group (0.97 ± 0.31 mg/dL) compared to the mild group (0.88 ± 0.23 mg/dL) ($p = 0.044$), which may indicate subtle renal function alterations with increasing disease severity.

A striking finding was the strong association of thyroid autoimmunity with disease severity. Anti-thyroid peroxidase (anti-TPO) positivity was significantly higher in severe SCH (90.0%) compared to mild SCH (10.6%) ($p = 0.001$), while anti-TPO negativity was predominantly observed in mild cases. This suggests that autoimmune mechanisms play a crucial role in the progression to severe SCH. Inflammatory status, as indicated by C-reactive protein (CRP), also differed significantly between groups. A majority of severe SCH patients had elevated CRP levels (>10 mg/L, 90.0%), whereas most mild cases had CRP <10 mg/L (70.0%), with both comparisons being statistically

Table 1: Clinical and demographics details

Variable	*Mild SCH (n=170)*	*Severe SCH (n=40)*	*p-value*
Male n(%)	18 (10.6)	11 (27.5)	0.115$
Female n(%)	152 (89.4)	29 (72.5)	0.001$
Age	38.98 ± 13.27	38.66 ± 8.85	0.352
Heart Rate (bpm)	74.43 ± 7.41	76.05 ± 4.76	0.189
SBP (mmHg)	119.16 ± 14.71	116.10 ± 14.88	0.238
DBP (mmHg)	73.38 ± 9.21	73.50 ± 6.32	0.936
Hemoglobin (g/dL)	11.03 ± 1.99	11.47 ± 1.60	0.199
Urea (mg/dL)	20.76 ± 6.26	20.53 ± 6.15	0.831
Creatinine (mg/dL)	0.88 ± 0.23	0.97 ± 0.31	**0.044**
RBS (mg/dL)	89.91 ± 15.19	93.23 ± 22.14	0.260
Anti-TPO + ve n(%)	18 (10.6)	36 (90.0)	0.001
Anti-TPO - ve n(%)	152 (89.4)	4 (10.0)	0.001
ESR (mm/hr)	19.92 ± 11.84	18.00 ± 14.15	0.394
CRP <10 n(%)	119 (70.0)	4 (10.0)	0.001
CRP >10 n(%)	51 (30.0)	36 (90.0)	0.012

*Data represented in Mean SD unless indicated. p-value indicated with $ is obtained by Chi-square test and rest by

Table 2: Lipid Profile

Parameter	*Mild SCH (n=170) Mean ± SD*	*Severe SCH (n=40) Mean ± SD*	*p-value*
Total Cholesterol (mg/dL)	169.81 ± 45.90	234.73 ± 29.52	**0.001**
Triglycerides (mg/dL)	153.79 ± 39.48	223.38 ± 32.15	**0.001**
VLDL (mg/dL)	24.83 ± 7.67	32.25 ± 11.02	**0.001**
LDL (mg/dL)	120.43 ± 29.81	162.25 ± 42.29	**0.001**
HDL (mg/dL)	37.66 ± 10.09	35.25 ± 9.58	0.171

*Data represented in Mean SD, Student's t – test was applied to test the significance

significant (p = 0.012 and p = 0.001, respectively). This indicates a possible link between systemic inflammation and SCH severity. Overall, while most demographic and routine clinical parameters remain similar between mild and severe SCH, the significant differences in creatinine levels, anti-TPO positivity, and CRP concentrations highlight the potential roles of renal involvement, autoimmunity, and systemic inflammation in the progression and severity of subclinical hypothyroidism.

The comparison of lipid profile parameters between mild and severe subclinical hypothyroidism (SCH) demonstrates a clear and statistically significant deterioration in lipid metabolism with increasing disease severity. Patients with severe SCH exhibited markedly higher levels of total cholesterol (234.73 ± 29.52 mg/dL) compared to those with mild SCH (169.81 ± 45.90 mg/dL), with a highly significant difference (t = 8.529, p = 0.001). Similarly, triglyceride levels were substantially elevated in the severe group (223.38 ± 32.15 mg/dL) relative to the mild group (153.79 ± 39.48 mg/dL), indicating pronounced hypertriglyceridemia (t = 10.362, p = 0.001).

Consistent with these findings, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) levels were also significantly higher in severe SCH patients (VLDL: 32.25 ± 11.02 mg/dL; LDL: 162.25 ± 42.29 mg/dL) compared to mild cases (VLDL: 24.83 ± 7.67 mg/dL; LDL: 120.43 ± 29.81 mg/dL), with both differences reaching strong statistical significance (p = 0.001). These elevations in atherogenic lipid fractions underscore an increased cardiovascular risk burden associated with severe SCH. In contrast, high-density lipoprotein (HDL) levels were slightly lower in the severe group (35.25 ± 9.58 mg/dL) than in the mild group (37.66 ± 10.09 mg/dL); however, this difference was not statistically significant (t = 1.374, p = 0.171), suggesting that HDL may not be substantially influenced by SCH severity in this cohort. Overall, the findings indicate that severe SCH is strongly associated with an adverse lipid profile characterized by elevated total cholesterol, triglycerides, LDL, and VLDL levels, while HDL remains relatively unchanged. This pattern highlights the potential role of worsening thyroid dysfunction in promoting dyslipidemia and emphasizes the need for early monitoring and management of lipid abnormalities to mitigate cardiovascular risk in SCH patients.

The electrocardiographic (ECG) findings observed among patients with mild and severe subclinical hypothyroidism (SCH) demonstrated a wide spectrum of cardiac abnormalities, indicating progressive cardiovascular involvement with increasing severity of thyroid dysfunction. A normal ECG pattern was observed in the majority of patients with mild SCH [76 cases (44.7%)], whereas only 8 patients (20%) with severe SCH had normal ECG findings. This reduction in normal ECG patterns among severe SCH patients suggests greater cardiac electrical abnormalities with increasing thyroid dysfunction severity. Among the ECG abnormalities, sinus bradycardia was one of the most common findings in mild SCH, observed in 25 patients (14.7%), compared to only 3 patients (7.5%) in severe SCH. Bradycardia is a well-recognized manifestation of hypothyroid states due to reduced sympathetic activity and decreased metabolic demand. Additional bradyarrhythmic manifestations such as sinus bradycardia with ST depression and low-voltage complexes with sinus bradycardia were also exclusively noted in mild SCH patients.

ST-segment depression emerged as the most prominent abnormality in severe SCH, being present in 10 patients (25%), compared with only 4 patients (2.35%) in mild SCH. This finding may indicate myocardial repolarization abnormalities, subclinical ischemic changes, or impaired ventricular function associated with worsening thyroid dysfunction. Furthermore, severe SCH patients also demonstrated advanced conduction and structural abnormalities including first-degree heart block with prolonged QT interval (5%), poor R-wave progression (7.5%), and left anterior hemiblock (LAHB) associated with low-voltage complexes and axis deviation. Low-voltage complexes were relatively frequent in both groups, occurring in 10% of mild SCH patients and 15% of severe

Table 3: ECG Findings

ECG Finding	*Mild SCH n (%)*	*Severe SCH n(%)*
Normal	76(44.70)	8(20)
Right Bundle Branch Block	3(1.76)	0(0)
Atrial Fibrillation	3(1.76)	0(0)
Bigemini	3(1.76)	0(0)
Biphasic T wave with 2nd degree AV block	2(1.17)	0(0)
Sinus trachicardia, T wave inverstion ST depression and systolic dysfunction	3(1.76)	0(0)
Low voltage complex	17 (10)	6(15)
Low voltage complex with diastolic dysfunction	2(1.17)	0(0)
Low voltage complex with sinus bradycardia	3(1.76)	0(0)
Poor R wave progression, axis deviation, premature atrial complex	3(1.76)	0(0)
Sinus Bradycardia	25(14.70)	3(7.5)
Sinus Bradycardia with ST depression	3(1.76)	0(0)
ST depression	4(2.35)	10(25)
ST depression with T wave inversion	1(4.11)	0(0)
ST depression, T wave inversion and mild pericardial effusion	2(1.17)	0(0)
T wave inversion	10(5.88)	2(5)
Ventricular premature complex	10(5.88)	2(5)
1ST degree heart block with prolonged QT	0(0)	2(5)
Low voltage in left axis, LAHB, poor progression of R wave	0(0)	2(5)
Low voltage in left axis, LAHB, poor progression of R wave, moderate pericardial effusion	0(0)	2(5)
Poor R wave Progression	0(0)	3(7.5)

SCH patients. The higher prevalence in severe SCH may reflect increased myocardial edema, pericardial effusion, or reduced myocardial contractility commonly associated with hypothyroid states. Notably, moderate pericardial effusion accompanied by low-voltage complexes and conduction abnormalities was observed only in severe SCH, indicating more advanced cardiac involvement. T-wave inversion and ventricular premature complexes (VPCs) were observed in both mild and severe SCH groups, though their frequencies were relatively similar. These abnormalities may represent altered ventricular repolarization and increased myocardial irritability secondary to thyroid hormone deficiency. Several uncommon ECG findings, including right bundle branch block (RBBB), atrial fibrillation, bigeminy, biphasic T waves with second-degree AV block, and combined systolic dysfunction patterns, were seen exclusively in mild SCH cases. Although these findings were infrequent, they indicate that even mild SCH may occasionally present with significant electrophysiological disturbances.

The comparison of systolic 2D echocardiographic parameters between mild and severe subclinical hypothyroidism (SCH) reveals selective but clinically meaningful alterations in cardiac structure and function with increasing disease severity. Left ventricular end-systolic diameter (LVESD) and interventricular septal thickness (IVST) were comparable between the two groups ($p = 0.865$ and $p = 0.761$, respectively), indicating no significant difference in these baseline structural dimensions. However, posterior wall thickness (PWT) was significantly higher in the severe SCH group (10.18 ± 2.70 mm) compared to the mild group (9.19 ± 2.07 mm) ($p = 0.012$), suggesting early concentric remodeling or increased myocardial wall thickness associated with more advanced thyroid dysfunction. Notably, left ventricular systolic performance showed significant impairment in severe SCH, as evidenced by a markedly reduced ejection fraction ($55.15 \pm 7.23\%$) compared to mild SCH ($64.60 \pm 7.34\%$) ($p = 0.001$). This reduction indicates compromised global systolic function with increasing severity of SCH. In contrast, fractional

Table 4: Systolic 2D Echo Variables

Variable	*Mild SCH Mean ± SD*	*Severe SCH Mean ± SD*	*p-value*
LVESD	27.70 ± 5.51	27.53 ± 7.20	0.865
IVST	10.49 ± 5.02	10.25 ± 1.35	0.761
PWT	9.19 ± 2.07	10.18 ± 2.70	**0.012**
Ejection Fraction (%)	64.60 ± 7.34	55.15 ± 7.23	**0.001**
Fractional Shortening (%)	34.85 ± 4.40	40.65 ± 3.08	**0.015**
PAFV	8.25 ± 1.49	10.50 ± 1.17	**0.021**

* Data represented in Mean SD, Student's t – test was applied to test the significance.

shortening (FS) was paradoxically higher in the severe group (40.65 ± 3.08%) than in the mild group (34.85 ± 4.40%) (p = 0.015). This apparent inconsistency may reflect compensatory myocardial mechanics, geometric alterations, or methodological variability, and warrants cautious interpretation alongside other systolic indices.

Additionally, peak atrial flow velocity (PAFV) was significantly elevated in severe SCH patients (10.50 ± 1.17) compared to mild cases (8.25 ± 1.49) (p = 0.021), suggesting altered atrial contribution to ventricular filling or early diastolic dysfunction accompanying systolic changes. Overall, while some structural parameters remain unchanged, severe SCH is associated with increased myocardial wall thickness and significant alterations in systolic function, particularly reduced ejection fraction and increased PAFV. These findings highlight the potential subclinical cardiac involvement in SCH progression and underscore the importance of echocardiographic evaluation in patients with more severe disease.

The analysis of diastolic 2D echocardiographic parameters demonstrates significant impairment of left ventricular relaxation and filling dynamics in patients with severe subclinical hypothyroidism (SCH) compared to mild cases. The early diastolic filling velocity (E wave) was markedly reduced in the severe SCH group (0.52 ± 0.04) compared to the mild group (0.72 ± 0.21), with a highly significant difference (p = 0.001), indicating impaired early ventricular relaxation. In contrast, late diastolic filling (A velocity) was slightly higher in severe SCH (0.79 ± 0.08) than in mild SCH (0.75 ± 0.13), although this difference did not reach statistical significance (p = 0.092), suggesting a compensatory increase in atrial contribution to ventricular filling. Consequently, the E/A ratio was significantly reduced in the severe group (0.65 ± 0.05) compared to the mild group (0.97 ± 0.31) (p = 0.001), which is a hallmark of diastolic dysfunction, particularly impaired relaxation. However, the categorical distribution of E/A ratios presents an apparent inconsistency: all severe SCH patients were reported to have E/A >1 (100%), whereas none had E/A <1, which contradicts the observed lower mean E/A ratio (<1). This discrepancy suggests a possible data entry or classification error that should be carefully verified before drawing firm conclusions from the categorical analysis.

Table 5: Diastolic 2D Echo Variables

Variable	*Mild SCH*	*Severe SCH*	*p-value*
E velocity	0.72 ± 0.21	0.52 ± 0.04	0.001
A velocity	0.75 ± 0.13	0.79 ± 0.08	0.092
E/A ratio	0.97 ± 0.31	0.65 ± 0.05	0.001
E/A <1 n(%)	76 (44.7)	0 (0.0)	0.001
E/A >1 n(%)	94 (55.3)	40 (100)	0.001
IRT (ms)	91.69 ± 14.89	115.82 ± 10.73	0.001

*Data represented in Mean SD unless indicated, Student's t – test was applied to test the significance.

Furthermore, isovolumetric relaxation time (IRT) was significantly prolonged in severe SCH (115.82 ± 10.73 ms) compared to mild SCH (91.69 ± 14.89 ms) (p = 0.001), reinforcing the presence of delayed myocardial relaxation and diastolic dysfunction. Overall, the findings strongly indicate that severe SCH is associated with significant diastolic dysfunction characterized by reduced early filling velocity, decreased E/A ratio, and prolonged relaxation time. These alterations reflect impaired ventricular compliance and relaxation, underscoring the impact of thyroid dysfunction on cardiac diastolic performance. However, the inconsistency in E/A categorical data warrants further validation to ensure accurate interpretation.

DISCUSSION

The present study comprehensively assessed cardiovascular, metabolic, inflammatory, and echocardiographic characteristics in patients with subclinical hypothyroidism and compared findings between mild and severe forms of

the disease. The results demonstrated that progression to severe SCH was accompanied by more pronounced lipid abnormalities, increased inflammatory activity, enhanced autoimmune responses, and greater impairment of cardiac function. These findings suggest that SCH is not merely a biochemical abnormality but rather a condition with important systemic and cardiovascular implications, which is in agreement with earlier observations [10].

Female patients constituted the majority of the study population, particularly among individuals with mild SCH. This pattern corresponds with epidemiological evidence demonstrating a greater susceptibility of women to thyroid disorders, largely attributable to hormonal influences and the higher prevalence of autoimmune diseases in females [11, 12]. In addition, anti-thyroid peroxidase antibody positivity was significantly more common in patients with severe SCH, further emphasizing the contribution of autoimmune mechanisms to disease progression. Previous investigations have shown that the presence of anti-TPO antibodies is strongly associated with ongoing thyroid injury and an increased likelihood of developing overt hypothyroidism [13].

An important finding of the present study was the presence of enhanced systemic inflammatory activity in severe SCH, reflected by significantly elevated CRP levels. Recent evidence has increasingly recognized low-grade chronic inflammation as a characteristic feature of SCH, with potential implications for endothelial dysfunction and atherosclerotic processes [14]. Similar observations have been reported by Tuzcu et al. [15], suggesting that inflammatory mechanisms may contribute to the increased cardiovascular risk associated with thyroid dysfunction. Although most renal function parameters were comparable between the groups, serum creatinine levels were significantly higher among patients with severe SCH. This finding may indicate subtle impairment of renal function secondary to reduced thyroid hormone activity, which has previously been shown to influence renal blood flow and glomerular filtration [16].

Among the metabolic abnormalities identified, dyslipidemia represented one of the most clinically significant abnormalities. Individuals with severe SCH exhibited higher concentrations of total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol compared with those with mild disease. These findings are consistent with previous studies demonstrating reduced LDL receptor activity and impaired lipoprotein clearance in hypothyroid states [17]. Experimental evidence has also shown that elevated TSH levels may directly stimulate cholesterol synthesis through activation of HMG-CoA reductase and SREBP-2-mediated pathways [18]. No significant differences in HDL cholesterol were observed between groups, a finding that concurs with previous reports indicating inconsistent effects of SCH on HDL metabolism [14].

Electrocardiographic abnormalities were frequently encountered and became increasingly evident with greater severity of thyroid dysfunction. Patients with mild SCH more often exhibited normal electrocardiographic patterns, whereas conduction abnormalities and repolarization disturbances were observed more commonly in severe SCH. Sinus bradycardia represented one of the predominant findings and is consistent with the reduced chronotropic responsiveness associated with diminished thyroid hormone activity [19]. Low-voltage complexes observed predominantly in severe disease may be related to myocardial edema or the presence of pericardial effusion, findings previously described by Klein and Ojamaa [20]. Moreover, abnormalities such as ST-segment depression, prolonged QT interval, first-degree atrioventricular block, left anterior hemiblock, and poor R-wave progression were more frequent in severe SCH, indicating significant alterations in ventricular conduction and repolarization. Similar observations have been reported in studies demonstrating an association between elevated TSH levels and increased cardiovascular morbidity [21]. These electrocardiographic changes are biologically plausible because thyroid hormones exert important regulatory effects on cardiac ion channels and electrophysiological function [22]. Therefore, cardiovascular assessment appears warranted even in patients with apparently mild thyroid dysfunction.

Echocardiographic findings also revealed evidence of structural and functional cardiac alterations. Although no significant differences were noted in LVESD and interventricular septal thickness, posterior wall thickness was increased among patients with severe SCH, suggesting the presence of early myocardial remodeling. In addition, left ventricular ejection fraction was significantly lower in severe disease, indicating impaired systolic function. These observations are supported by previous studies showing that thyroid hormone deficiency adversely affects myocardial contractility through disturbances in calcium handling and reduced expression of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2) [23]. The paradoxical increase in fractional shortening despite reduced ejection fraction may be attributable to compensatory changes in ventricular geometry or methodological factors, highlighting the

importance of interpreting echocardiographic parameters collectively rather than individually [24].

Diastolic dysfunction emerged as one of the most prominent abnormalities associated with severe SCH. Lower E-wave velocity, reduced E/A ratio, and prolonged IVRT collectively indicate impaired ventricular relaxation and decreased compliance. Previous investigators have similarly identified diastolic dysfunction as an early manifestation of cardiac involvement in SCH [25]. Since thyroid hormones are essential for calcium reuptake and myocardial relaxation, even subtle hormonal alterations may adversely affect diastolic performance. Nevertheless, the categorical distribution of E/A ratios observed in the present study warrants further evaluation because the reported proportions appear inconsistent with the calculated mean values, suggesting the possibility of data classification errors.

Taken together, the coexistence of dyslipidemia, systemic inflammation, thyroid autoimmunity, and impaired cardiac performance highlights the multifactorial nature of cardiovascular risk in SCH. Elevated LDL cholesterol, increased CRP concentrations, and deterioration of myocardial function may collectively create a pro-atherogenic and pro-thrombotic environment, thereby predisposing patients to coronary artery disease and heart failure, particularly in those with markedly elevated TSH levels [21].

From a clinical standpoint, the findings of the present study underscore the importance of early identification and appropriate risk stratification in individuals with SCH. Although traditionally considered a relatively benign condition, the present results demonstrate that increasing disease severity is accompanied by significant metabolic and cardiovascular abnormalities [1]. Routine evaluation of thyroid function, including serum TSH and anti-TPO antibody levels, may therefore be particularly useful in individuals presenting with dyslipidemia, obesity, cardiovascular risk factors, or a family history of thyroid disease. Early recognition of severe SCH may facilitate timely intervention and potentially prevent progression to overt hypothyroidism and irreversible cardiovascular complications.

The higher prevalence of anti-TPO antibody positivity among patients with severe disease suggests that antibody assessment may provide valuable prognostic information regarding disease progression. Patients with positive thyroid autoantibodies may require closer surveillance and more frequent follow-up. Although the management of mild SCH remains a matter of debate, the substantial metabolic and cardiovascular abnormalities observed in severe SCH support an individualized approach to therapy, particularly in patients with markedly elevated TSH levels, positive anti-TPO antibodies, and coexisting cardiovascular risk factors. Overall, the findings emphasize that SCH should be regarded as a condition with clinically significant systemic effects and highlight the importance of comprehensive cardiovascular evaluation and long-term monitoring to improve patient outcomes.

LIMITATIONS

This study has several limitations that should be considered when interpreting the findings. First, the cross-sectional design limits the ability to establish temporal or causal relationships between subclinical hypothyroidism and the observed metabolic, inflammatory, and cardiovascular alterations. Second, the use of non-probability convenience sampling may have introduced selection bias and may limit the generalizability of the results to the broader population. Third, the relatively smaller number of participants in the severe SCH group may have reduced the statistical power for certain subgroup analyses. Finally, potential confounding factors such as duration of SCH, lifestyle characteristics, dietary habits, and medication use were not comprehensively evaluated. Future prospective, multicenter studies with larger sample sizes and longitudinal follow-up are needed to confirm these findings.

CONCLUSION

In summary, the present study demonstrates that increasing severity of subclinical hypothyroidism is associated with significant dyslipidemia, systemic inflammation, autoimmune activation, and both systolic and diastolic cardiac dysfunction. These findings underscore the need for comprehensive cardiovascular evaluation in SCH patients and highlight the potential benefits of early intervention in preventing adverse cardiovascular outcomes.

ACKNOWLEDGMENT

The authors acknowledge the Regional Diagnostic Center (RDC), Veer Surendra Sai Institute of Medical Science and Research (VIMSAR), Burla, for providing the essential laboratory facilities and technical support required for sample analysis. We extend our sincere thanks to the Dean and Superintendent, VIMSAR, for their valuable administrative approval and continuous encouragement throughout the study. The authors also express their deep appreciation to the Head, faculty members, and staff of the Department of General Medicine, and Department of Cardiology VIMSAR, for their consistent cooperation,

insightful guidance, and assistance during the execution of this research work.

DISCLOSURE STATEMENT

The authors report there are no competing interests to declare.

DATA AVAILABILITY STATEMENT

All data are available in the manuscript.

CONSENT TO PARTICIPATE

Written inform consents were obtained from all the participants and their legal attendants.

FUNDING DECLARATION

Not Applicable

CLINICAL TRIAL NUMBER

Not Applicable

ETHICS DECLARATION

This study was conducted in accordance with the Declaration of Helsinki and was approved by Veer Surendra Sai Institute of Research and Ethics Committee, vide letter number 19234/I-S-T/250/19 dated, 30-11-2019.

AI DECLARATION

The authors declare that artificial intelligence (AI) tools were used only for language improvement, grammar correction, formatting assistance, and enhancement of readability during the preparation of this manuscript. The scientific content, study design, data analysis, interpretation of results, and conclusions were conceived and completed solely by the authors. All authors take full responsibility for the accuracy, originality, and integrity of the work presented in this manuscript.

CONSENT TO PUBLISH

All participants provided written informed consent for the publication of anonymized data.

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