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Epicardial Adipose Tissue Thickness as a Tool for Cardiovascular Risk Assessment in Overt Hypothyroidism

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Abstract: ***Epicardial adipose tissue (EAT) is an emerging cardiometabolic risk marker that may play a role in cardiovascular risk assessment among hypothyroid patients. This cross-sectional study compared EAT thickness and carotid intima-media thickness (CIMT) in 40 overt hypothyroid and 10 euthyroid subjects. EAT thickness was measured via non-contrast cardiac CT at three ventricular levels, while CIMT was assessed using carotid Doppler. Hypothyroid subjects showed significantly higher mean EAT and CIMT values, with positive correlations between EAT thickness, serum TSH levels, CIMT, and disease duration. These results highlight EAT thickness as a potential marker for early cardiovascular risk detection in overt hypothyroidism, warranting further large-scale validation.***

Keywords: Epicardial adipose tissue; carotid intima-media thickness; hypothyroidism; cardiovascular risk; TSH levels

1. Introduction

Hypothyroidism, one of the most prevalent endocrine disorders, possesses high cardiovascular risks. According to Unnikrishnan et al, prevalence of overt hypothyroidism and subclinical hypothyroidism in India is 3.9% and 9.4% respectively [1]. Hypothyroidism, both overt and subclinical, has been associated with atherosclerosis, coronary artery disease and heart failure.

Epicardial adipose tissue (EAT), located between the visceral pericardium and myocardium, is a specialized visceral adipose tissue in which the coronary arteries are embedded [2]. Epicardial adipocytes are anatomically, morphologically and functionally different from other fat depots like subcutaneous adipose tissue and visceral adipose tissue. It extends from the epicardial surface into the myocardium, often following the adventitia of the coronary artery branches, thus may interact locally and modulate the coronary arteries through paracrine or vasocrine secretion [3,4]. EAT produces numerous proinflammatory and proatherogenic mediators like tumor necrosis factor–α, resistin, monocyte chemoattractant protein–1, interleukin-6, visfatin, nerve growth factor, leptin, angiotensinogen and plasminogen activator inhibitor–1 that might promote the initiation and progression of coronary atherosclerosis [2,5-11]. Previous studies have reported that increased EAT volume and thickness is associated with coronary artery disease, metabolic syndrome, obesity and diabetes [12,13].

Hypothyroidism often leads to dyslipidemia, weight gain, and visceral fat accumulation, specifically in EAT, by influencing adipocyte differentiation and function [14,15]. Genes involved in thyroid hormone receptors, adipokine production and inflammatory cytokines may directly affect EAT accumulation in hypothyroid individuals [15]. Autoimmune thyroid disorders has also been postulated to modulate EAT thickness through enhanced systemic inflammation (TNF alpha, interleukin-6) [5].

An increasing number of evidences state that EAT measurement may play a role in the stratification and prediction of the cardiometabolic risk in hypothyroid patients and tailoring treatment plans based on an individual's specific risk profile, including their EAT levels, thyroid hormone status, and other metabolic markers [3]. This study aimed to evaluate EAT thickness in overt hypothyroidism and explore its association with TSH levels, disease duration, and CIMT to determine its potential as a cardiovascular risk marker. By establishing the diagnostic value of EAT thickness, this research may provide clinicians with an additional, non-invasive marker to stratify cardiovascular risk in overt hypothyroidism, particularly in the Indian population.

2. Materials and Methodology

Data Source and Study Design

A single-centered cross-sectional study was conducted over 12 months from September 2023 till August 2024, in the Department of Medicine, Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi, after clearance from Institutional Ethics Committee. This study adhered to the ethical standards of the responsible institutional review board for research involving human participants.

Study Population

Patients with hypothyroidism attending the Endocrinology clinic, Medicine outpatient department in Lok Nayak Hospital, New Delhi were enrolled for the study based on the inclusion and exclusion criteria.

Inclusion Criteria
Patients with age between 18-70 years having hypothyroidism diagnosed for more than 5 years were included in the study.

Exclusion Criteria
Patients with obesity (BMI ≥ 25 kg/m^2), diagnosed coronary artery disease, diabetes mellitus, chronic liver disease, chronic kidney disease, endocrinopathies like Cushing syndrome, Polycystic Ovary Disease were excluded. Pregnant and HIV positive patients were also excluded as well as those receiving steroids, or oral contraceptive pills.

Study outcome
EAT thickness measurement in hypothyroidism and euthyroid subjects and its correlation with duration of hypothyroidism, TSH levels and Carotid Intima-media thickness in hypothyroid subjects.

Study Sample
We enrolled 40 hypothyroid subjects in our study. We also additionally measured EAT and CIMT thickness in 10 age and sex matched euthyroid subjects, in whom NCCT of chest was done for other purposes, to further strengthen our results.

3. Methodology

- A detailed history was taken from each subject regarding the duration, treatment of the disease, any comorbidities and clinical examination was done in each case. Routine investigations including thyroid profile were done in all subjects along with ultrasound of the neck and Anti Thyroperoxidase(Anti TPO) antibodies on case-to-case basis.
- EAT thickness was measured using Non-contrast cardiac CT scanning through which multiplanar reconstructions of the raw data was obtained in the ventricular short axis and horizontal long axis view at the basal, mid ventricular and apical levels. The mean of these three measurements (basal, mid ventricular and apical) was used for the analysis. Bilateral carotid artery doppler was done to evaluate Carotid artery intima-media thickness, PSV (Peak Systolic Velocity), EDV (End diastolic velocity) and direction of flow in external carotid artery, internal carotid artery and common carotid artery. Figure 1 summarizes the study design and parameters that were analyzed.

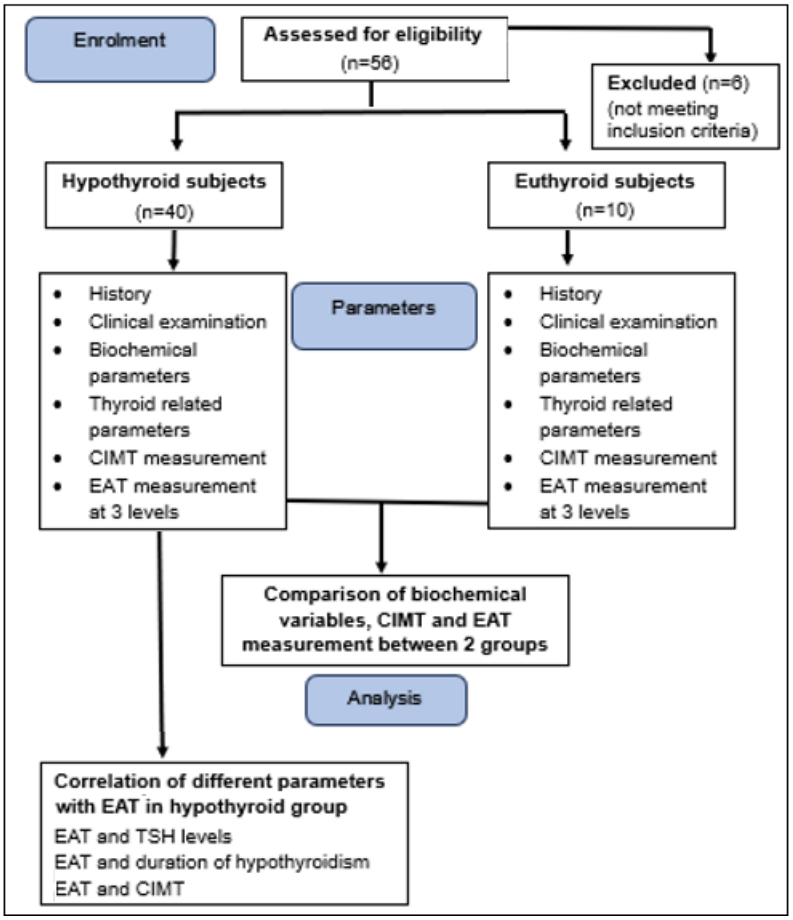


Figure 1: Flowchart showing study design including enrolment, parameters and analysis

Statistical Analysis
Following statistics was used to analyse the data gathered:

1) Continuous variables were presented as mean ± standard deviation or medians with Inter-quartile range and were compared by Student's T test/ANOVA or Mann Whitney/Kruskall Wallis.
2) Categorical variables were presented as frequencies and percent values and were compared by Chi Square or Fisher's Exact Test.
3) Correlations between continuous variables were analysed using Pearson's correlation for normally

distributed variables and Spearman's rank correlation for non-normally distributed variables.

4) The p-value < 0.05 was considered to be significant and all the data gathered was processed by SPSS (Statistical Package for the Social Sciences) version 23.

4. Results and Observations

Demographic, clinical and laboratory variables of the subjects

Both the groups - hypothyroid (Mean age 42.48 ± 10.97 years) as well as euthyroid (Mean age 39.7 ± 4.24 years) had a comparable age and gender distribution and there was a female predominance in both the groups (95.0% in hypothyroid and 90.0% in euthyroid respectively). Various other clinical and laboratory variables of the two groups has been consolidated in table 1. ECG also didn't show any significant abnormality in all the subjects, further ruling out any contributory cardiovascular risk factor.

Table 1: Comparing the demographic, clinical and laboratory variables of the study subjects. (a=Student's T Test, b=Fisher's Exact Test, c=Mann Whitney U Test, n=number, BMI= Body Mass Index, SD= Standard Deviation, BP=Blood Pressure, Hb = Hemoglobin, TLC = Total Leukocyte Count, FBS = Fasting Blood Sugar, PPBS = Postprandial Blood Sugar, Urea = Urea, Creat = Creatinine, T. bil = Total Bilirubin, AST = Aspartate Aminotransferase, ALT = Alanine Aminotransferase, HDL = High-Density Lipoprotein, LDL = Low-Density Lipoprotein)

Characteristic	Hypothyroid subjects (n=40)	Euthyroid subjects (n=10)	P- value
Demographic characteristics			
Age distribution			
Mean(yrs)	42.48 ± 10.97	39.7 ± 4.24	0.439a
<30 Years-n(%)	4 (10.0%)	0 (0.0%)	0.174b
30 to 39 Years-n(%)	11 (27.5%)	4 (40.0%)	0.174b
40 to 49 Years-n(%)	14 (35.0%)	5 (50.0%)	0.174b
≥50 Years-n(%)	11 (27.5%)	1 (10.0%)	0.174b
Sex			
Female sex- n(%)	38 (95.0%)	9 (90.0%)	0.496b
Physical Examination			
BMI (kg/m2) (SD)	21.05 (1.51)	21.22 (1.42)	0.746a
Pulse Rate-Mean (SD)	76.25 (5.73)	79.2 (7.13)	0.226c
Systolic BP-Mean (SD)	125.65 (5.65)	119.6 (5.23)	0.004a
Diastolic BP-Mean (SD)	79.2 (3.43)	77.25 (4.36)	0.374c
Laboratory parameters			
Hb-Mean (SD)	12.26 (1.27)	13.09 (1.35)	0.035c
TLC-Mean (SD)	7794.15 (1680.62)	7214.0 (1509.71)	0.325a
FBS-Mean (SD)	98.6 (8.41)	97.3 (4.74)	0.642a
PPBS-Mean (SD)	113.18 (16.49)	115.4 (17.48)	0.536c
Urea-Mean (SD)	30.8 (9.4)	27.0 (7.23)	0.24a
Creat-Mean (SD)	0.85 (0.21)	0.85 (0.17)	1.0a
T. bil-Mean (SD)	0.77 (0.13)	0.79 (0.1)	0.581c
AST-Mean (SD)	30.0 (7.55)	27.9 (4.53)	0.406a
ALT-Mean (SD)	36.78 (9.01)	38.6 (7.55)	0.558a
Total Protein (g/dL)	7.48 (0.36)	7.68 (0.35)	0.154c
Serum Albumin (g/dL)	4.0 (0.13)	4.03 (0.17)	0.68c
Calcium (mg/dL)	9.07 (0.42)	9.06 (0.46)	0.921a
Phosphorus (mg/dL)	3.97 (0.41)	4.08 (0.27)	0.422a
Triglyceride (mg/dL)	112.92 (10.92)	103.0 (19.88)	0.052c
Total cholesterol (mg/dL)	166.62 (14.21)	118.7 (25.39)	<0.001c
HDL (mg/dL)	32.75 (6.62)	41.9 (3.81)	<0.001a
LDL (mg/dL)	111.29 (16.62)	56.2 (26.13)	<0.001c

Exploratory Outcome

Thyroid related parameters and Comparison of EAT and CIMT between hypothyroid and euthyroid subjects

All the hypothyroid subjects were on thyroid hormone replacement therapy and mean duration of hypothyroidism was 7 years. Thyroid parameters, EAT and CIMT thickness in hypothyroid and euthyroid subjects has been concluded in table 2.

The evaluation of EAT thickness revealed significantly higher values in hypothyroid subjects compared to euthyroid subjects across all levels as shown in bar plot 1 - Apex (Mean 6.82 mm in hypothyroid versus 4.77 mm in euthyroid, p value 0.017), Mid Ventricular Wall (Mean 6.19 mm in Hypothyroid versus 4.33 mm in Euthyroid, p value 0.022) as well as Base (Mean 6.18 mm Hypothyroid versus 4.81 mm in Euthyroid, p value 0.201)). The Mean EAT Thickness was also higher in the hypothyroid group (Mean 6.4 mm in Hypothyroid versus 4.63 mm in Euthyroid, p value 0.004). Figure 2 is showing an image of non-contrast cardiac CT of a hypothyroid subject showing increased EAT thickness of 6.72 mm from our study.

Table 2: Thyroid parameters, EAT and CIMT thickness among hypothyroid and euthyroid subjects. (a=Student's T Test, b =Mann Whitney U Test, fT3 = Free Triiodothyronine, fT4 = Free Thyroxine, TSH = Thyroid Stimulating Hormone, Anti TPO = Anti-Thyroid Peroxidase Antibodies, CIMT = Carotid Intima-Media Thickness, CCA = Common Carotid Artery, ECA = External Carotid Artery, ICA = Internal Carotid Artery)

Variable	Hypothyroid subjects(n=40)	Euthyroid subjects(n=10)	P-value
Thyroid related parameters			
fT3 (pmol/L)	3.24 (0.76)	6.18 (1.31)	<0.001b
fT4 (pmol/L)	7.88 (1.85)	15.9 (3.48)	<0.001b
TSH (mIU/mL)	18.24 (6.38)	3.34 (0.72)	<0.001b
Anti TPO (IU/mL)	81.47 (39.0)	18.1 (8.41)	<0.001b
Carotid doppler related parameters			
CIMT in CCA (mm)	0.73 (0.16)	0.53 (0.12)	0.001a
Peak Systolic Velocity in ECA (cm/s)	53.92 (14.05)	57.3 (9.98)	0.32b
Peak Systolic Velocity in ICA (cm/s)	68.9 (14.26)	70.3 (13.11)	0.779a
Peak Systolic Velocity in CCA (cm/s)	57.24 (9.13)	56.44 (7.89)	0.801a
End Diastolic Velocity in ECA (cm/s)	20.16 (6.99)	15.44 (3.17)	0.044a
End Diastolic Velocity in ICA (cm/s)	29.27 (6.15)	26.7 (8.17)	0.28b
End Diastolic Velocity in CCA (cm/s)	29.62 (5.58)	28.9 (3.35)	0.697a
EAT thickness using NCCT			
EAT Thickness at Apex (mm)	6.82 (2.54)	4.77 (1.03)	0.017a
EAT Thickness at Mid Ventricular Wall (mm)	6.19 (2.42)	4.33 (0.89)	0.022a
EAT Thickness at Base (mm)	6.18 (2.15)	4.81 (0.82)	0.201b
Mean EAT Thickness (mm)	6.4 (1.81)	4.63 (0.68)	0.004a

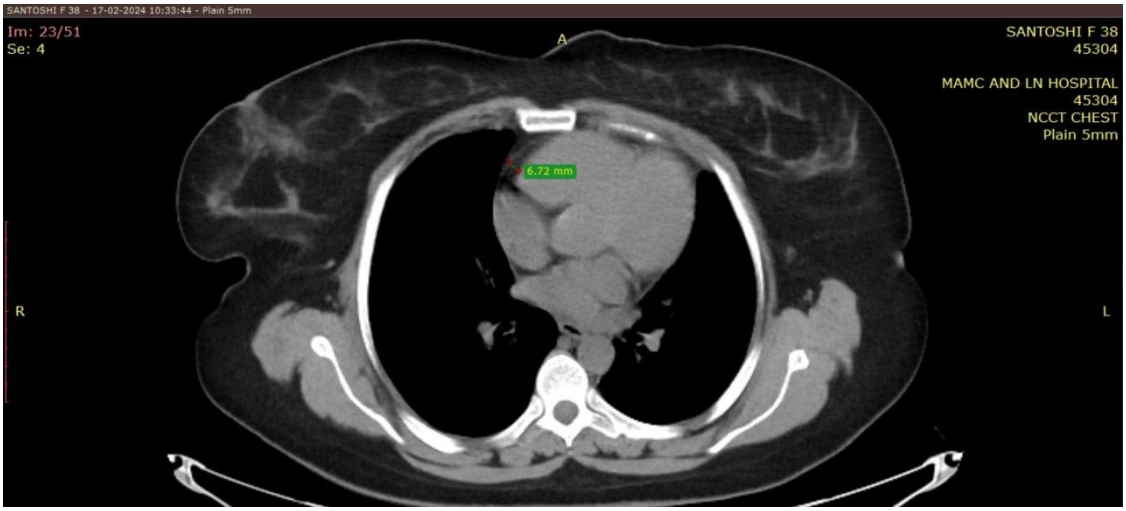
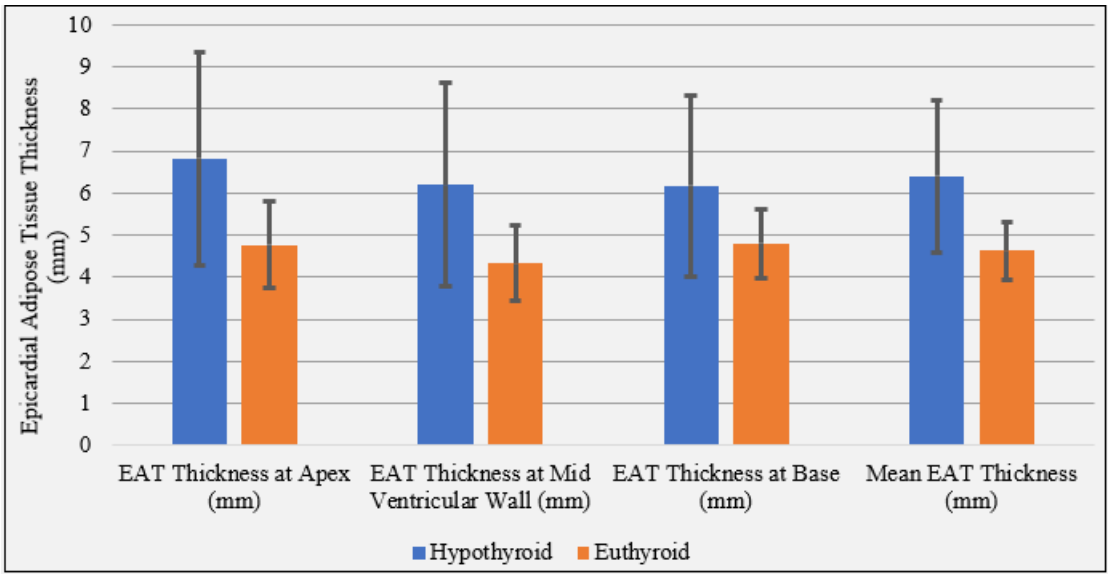


Figure 2: Non-contrast cardiac CT image showing increased epicardial adipose tissue of 6.72 mm(marked double line arrow) thickness in one of the hypothyroid subjects from our study.



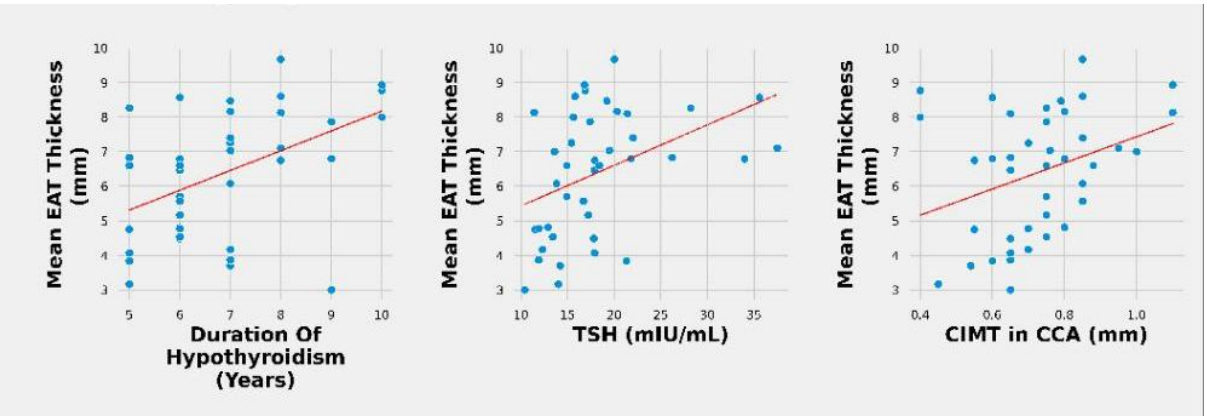
Bar Plot 1: Showing mean EAT Thickness (mm), at Apex (mm), at Mid Ventricular Wall (mm), at Base (mm) and their mean in the two groups

Correlations of the EAT thickness with different variables in hypothyroid subjects

A statistically significant positive correlation was found between mean EAT thickness and CIMT in the CCA (correlation coefficient=0.37, p = 0.02), with serum TSH levels (correlation coefficient=0.47, p = 0.002) and duration of hypothyroidism (correlation coefficient=0.48, p = 0.002) in hypothyroid subjects as summarized in table 3. EAT thickness at apex, mid ventricular and basal level showed positive correlation with above mentioned parameters and EAT thickness at base showed maximum significance amongst all.

Table 3: Correlation between EAT thickness(mm) and TSH levels(mIU/mL), duration of hypothyroidism (Years) and CIMT in CCA (mm). (a: Spearman Rank Correlation, TSH = Thyroid stimulating hormone, CIMT = Carotid Intima-Media Thickness)

Parameter	Correlation Coefficient (a)	P Value
At Apex		
EAT versus Duration	0.29a	0.069
EAT versus TSH	0.23a	0.15
EAT versus CIMT	0.29a	0.073
At mid- ventricular wall		
EAT versus Duration	0.37a	0.019
EAT versus TSH	0.45a	0.004
EAT versus CIMT	0.11a	0.517
At Base		
EAT versus Duration	0.45a	0.003
EAT versus TSH	0.42a	0.007
EAT versus CIMT	0.47a	0.002
Mean EAT		
EAT versus Duration	0.48a	0.002
EAT versus TSH	0.47a	0.002
EAT versus CIMT	0.37a	0.02



Scatter Plot 1: Correlation between mean EAT thickness with TSH, duration of hypothyroidism and CIMT in CCA in hypothyroid subjects.

5. Discussion

EAT is a metabolically active visceral fat depot surrounding the heart, distinct in its smaller adipocyte size and unique biochemical profile. Hypothyroidism, both overt and subclinical, is increasingly recognized as a contributor to EAT accumulation and associated cardiovascular risk. It promotes visceral fat deposition, including in EAT, through effects on adipocyte differentiation and metabolism [14,15]. Elevated EAT thickness in hypothyroid patients is linked with cardiac remodeling, including left ventricular hypertrophy, atrial enlargement, and impaired diastolic function, likely driven by a pro-inflammatory, pro-fibrotic EAT milieu [16,17]. Genetic pathways involving thyroid hormone receptors and cytokines may directly influence EAT development in this population [15].

In this study, we excluded various comorbidities that could influence EAT thickness including diabetes and studied relationship between hypothyroidism and EAT independent of insulin resistance or metabolic syndrome, as insulin resistance also promotes EAT deposition independently. The higher Anti-TPO antibody levels in the hypothyroid group as evident in table 2 reflects the autoimmune nature of thyroid dysfunction in most subjects in our study.

The hypothyroid group exhibited significantly higher SBP(Mean 125.65 ± 5.65 mm Hg in Hypothyroid vs 119.6 ± 5.23 mm Hg Euthyroid group), lower hemoglobin levels(Mean 12.26 ± 1.27 g/dL in Hypothyroid vs 13.09 ± 1.35 g/dL in Euthyroid), higher total cholesterol(Mean 166.6 mg/dL in Hypothyroid versus 118.7 mg/dL in Euthyroid), higher LDL (Mean 111.29 mg/dL in Hypothyroid versus 56.2 mg/dL in Euthyroid), and lower HDL (Mean 32.75 mg/dL in Hypothyroid versus 41.9 mg/dL in Euthyroid) as compared to euthyroid group. These findings are consistent with existing literature and they signify higher cardiovascular risk in hypothyroid subjects through dyslipidemia and further increasing the risk of heart failure if anemia and hypertension are not managed effectively in these patients.

The CIMT in the CCA was significantly higher in the hypothyroid subjects compared to the euthyroid subjects (Mean 0.73 ± 0.16 mm in hypothyroid vs 0.53 ± 0.12 mm in euthyroid, P = 0.001), indicating a heightened cardiovascular risk of developing subclinical atherosclerosis in them. In a review by Aziz et al, CIMT was found to be higher in

subclinical hypothyroid subjects as compared to euthyroid subjects and after treatment with thyroxine, there was a statistically significant decrease in CIMT (pooled weighted mean difference of CIMT decrease was -0.32 mm). This study also showed added benefit of decrease in TC, TG and LDL after receiving treatment with thyroxine [18]. Another study by Takamura et al found that higher TSH (even within the normal reference range) was significantly associated with CIMT which suggests an increased cardiovascular risk in subjects with low normal thyroid function [19]. While PSV remained comparable in our subjects, the elevated EDV in the ECA may suggest early signs of increased vascular stiffness in hypothyroid patients.

A significant increase in EAT thickness (Mean 6.4 mm in Hypothyroid versus 4.63 in Euthyroid, p value 0.004 respectively) was found in hypothyroid subjects. These findings are consistent with previous literature, for instance, in a study by Erdal Belen et al, mean EAT thickness was increased in the subclinical hypothyroid group compared to the control group (6.7 ± 1.4mm vs 4.7 ± 1.2, P<0.001) and also showed positive correlation with TSH level [20]. In another study by Karoli et al, and it was concluded that EAT thickness, measured using ECHO, was significantly higher in hypothyroid subjects than controls (5.6 ± 0.7 and 3.5 ± 0.6, P=0.001) and EAT had positive correlation with serum TSH levels [21]. However, a study by Arpaci et al found no difference between EAT thickness of SCH patients and healthy controls (Mean 4.61 mm vs 4.51 mm, p value 0.532) and found no correlation between EAT and TSH or LDL or anti-TPO levels [22]. It is important to note that most studies have compared patients of SCH with healthy controls, unlike our study which was conducted on patients of overt hypothyroidism.

Significant correlation between EAT thickness and other parameters in hypothyroid patients was found as shown in bar plot 1, suggesting that higher EAT thickness values may be linked with higher values of TSH, CIMT as well as longer duration of hypothyroidism and this correlation might be influenced by the measurement site of the EAT. Finally, EAT accumulation at the base or the mean of EAT thickness measured at 3 levels might serve as a better indicator for assessment. Karkamaz et al also found that there was a significant positive correlation between EAT and TSH in SCH patients ($r = 0.31$, $p = 0.014$) and higher EAT was found in subjects with TSH ≥ 10 mU/l [23]. A study by Yazici et al, found positive correlation between EAT thickness and CIMT in SCH group ($r = 0.39$, $p = 0.01$) and restoration of euthyroid state with thyroid hormone replacement was associated with significant decrease in EAT thickness and CIMT [24].

The measurement of EAT thickness in hypothyroid patients has potential clinical applications, particularly in stratifying cardiovascular risk and tailoring patient management. Incorporating EAT thickness as a routine parameter could aid in early identification of hypothyroid patients at high cardiovascular risk, potentially guiding more aggressive lipid-lowering and anti-inflammatory treatments.[3] Although EAT thickness has significant potential as a clinical marker, its integration into routine practice requires further standardization of measurement techniques, validation of threshold values, and a better understanding of its interactions with thyroid-specific factors.

This study has several limitations that may affect the generalizability of its findings. The relatively small sample size of 40 subjects, single-center design, and female predominance may introduce selection bias. The cross-sectional nature restricts insights into long-term effects of thyroid hormone therapy on EAT thickness and its cardiovascular implications. Additionally, the predominance of autoimmune hypothyroidism, as indicated by elevated Anti-TPO levels, raises the need for studies evaluating non-autoimmune cases.

6. Conclusion

This study demonstrates a robust association between EAT thickness and cardiovascular risk markers in overt hypothyroidism, underscoring its value as a non-invasive diagnostic tool. Standardized measurement protocols and large-scale validation studies are essential before routine clinical adoption.

Conflict of Interest Statement
None declared

Financial disclosure
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Acknowledgments
None to declare.

Informed Consent
Informed consent was obtained from all participants, who were also informed about the purpose of the study and their right to exit at any time. All patient information was handled with the utmost confidentiality

Author Contributions
Muskan Garg conducted the entire research, including sample and data collection, analytical calculations, numerical simulations, and result interpretation. She also drafted the manuscript with support from the contributors listed below. Sandeep Garg conceptualized and designed the study, encouraged the investigation, supervised the research, verified the analytical methods, and assisted with manuscript preparation. Sunita Aggarwal, Harpreet Singh, and Sapna Singh provided guidance throughout the investigation, supervised the findings, and verified the analytical approaches. Lovish Garg helped in data analysis and result interpretation. Manidipa Mondal and Pujan Acharya assisted with sample collection.

Data Availability
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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