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Metabolic Phenotypes of Hypothyroidism: A Cluster Analysis of Obesity, Atherogenic Dyslipidemia, and Dysglycemia

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Abstract: ***Background:*** Hypothyroidism is associated with multiple metabolic abnormalities that increase cardiovascular risk. However, these metabolic disturbances are heterogeneous, and the relative contributions of obesity, dyslipidemia, and dysglycemia vary among affected individuals. ***Objectives:*** To characterize metabolic phenotypes of hypothyroidism with respect to obesity, atherogenic dyslipidemia, and glycemic status, and to evaluate the predictive utility of the atherogenic index of plasma (AIP), waist circumference, and body mass index (BMI). ***Methods:*** This cross-sectional analytical study was performed on 100 hypothyroid patients and 100 age and gender matched controls in GMCH Srinagar. Anthropometric measurements including BMI and waist circumference were recorded. Fasting blood glucose and lipid profile were assessed, and AIP was calculated as $\log_{10}$(triglycerides/HDL cholesterol). Statistical analysis included non-parametric tests, multivariable logistic regression and Receiver operating characteristic (ROC) curve analysis. ***Results:*** Hypothyroid subjects demonstrated higher BMI and waist circumference compared with euthyroid controls. Triglyceride levels and AIP were significantly elevated in the hypothyroid group, whereas fasting blood glucose levels did not differ significantly. On multivariable analysis, AIP emerged as the strongest independent predictor of hypothyroidism after adjustment for age, BMI, and waist circumference. ROC analysis demonstrated superior discriminatory ability of AIP compared with BMI and waist circumference, with an optimal cut-off of approximately 0.58. ***Conclusion:*** Hypothyroidism is associated with distinct metabolic phenotypes characterized predominantly by atherogenic dyslipidemia and central obesity rather than dysglycemia. The atherogenic index of plasma is an independent and superior predictor of hypothyroidism compared with conventional anthropometric measures and may serve as a practical tool for cardiometabolic risk stratification.

Keywords: Hypothyroidism, obesity, atherogenic index of plasma (AIP), body mass index (BMI), waist circumference

INTRODUCTION

Hypothyroidism is one of the most prevalent endocrine disorders worldwide and is associated with a broad spectrum of metabolic derangements that contribute substantially to cardiovascular morbidity and mortality [1]. While the classical metabolic consequences of overt hypothyroidism include weight gain, hypercholesterolemia, and reduced basal metabolic rate, clinical observations increasingly suggest that metabolic manifestations of hypothyroidism are heterogeneous and not uniform across affected individuals [2]. This heterogeneity is particularly evident in patients with subclinical or mild thyroid dysfunction, in whom traditional markers of metabolic syndrome may not be consistently present.

Thyroid hormones exert profound effects on lipid metabolism through regulation of hepatic lipid synthesis, cholesterol absorption, and lipoprotein clearance [3]. Reduced thyroid hormone activity leads to diminished expression of low-density lipoprotein (LDL) receptors, impaired clearance of triglyceride-rich lipoproteins, and increased oxidative modification of lipids, thereby promoting an atherogenic lipid profile [4,5]. These lipid

abnormalities may occur independently of changes in body mass index (BMI), highlighting the limitations of BMI as a sole indicator of cardiometabolic risk in hypothyroid patients.

Central obesity, reflected by increased waist circumference, has been increasingly recognized as a more reliable marker of cardiometabolic risk than BMI in endocrine disorders [6]. However, even measures of central adiposity may fail to fully capture qualitative abnormalities in lipid metabolism that are characteristic of hypothyroidism. In contrast, alterations in glucose metabolism are less consistently observed, with several studies reporting normal fasting glucose levels despite significant dyslipidemia [7]. This raises the possibility that hypothyroidism is associated with a distinct metabolic phenotype rather than a uniform metabolic syndrome.

The atherogenic index of plasma (AIP), calculated as the logarithm of the triglyceride-to-high-density lipoprotein (HDL) cholesterol ratio, has emerged as a robust surrogate marker of atherogenic dyslipidemia and small dense LDL particles [8,9]. AIP integrates both pro-atherogenic and protective lipid fractions and has been shown to correlate strongly with cardiovascular risk across diverse populations [10-13]. Studies in the Indian population, though scanty, have yielded convincing results.[14-15] Despite its potential relevance, data examining the role of AIP in characterizing metabolic risk in hypothyroidism remain limited.

The present study was designed to characterize metabolic phenotypes in hypothyroidism by examining patterns of obesity, atherogenic dyslipidemia, and dysglycemia in a noth Indian tertiary care centre. We further evaluated the relative utility of AIP, waist circumference, and BMI as predictors of hypothyroidism using multivariable regression and receiver operating characteristic (ROC) analysis.

MATERIAL AND METHODS

This cross-sectional analytical study included adult participants undergoing evaluation for thyroid dysfunction at departments of Medicine and Biochemistry, Government Medical College Srinagar . Individuals were classified as hypothyroid or euthyroid based on serum thyroid-stimulating hormone (TSH) and thyroid hormone levels measured using standardized immunoassays, in accordance with established laboratory reference ranges [16]. 100 hypothyroid patients and 100 euthyroid age and gender matched controls were taken for the sudy. The study was approved by the institutional ethics committee and was performed in accordance with ethical standards laid down in Helsinki declaration of 1964.

Anthropometric measurements were obtained using standardized protocols. Height and weight were measured with subjects wearing light clothing and no footwear, and BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Blood pressure was recorded in the seated position after adequate rest.

After an overnight fast, venous blood samples were collected for estimation of fasting blood glucose, total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol using enzymatic methods. Triglyceride and HDL cholesterol values were converted to molar concentrations, and AIP was calculated as log10(TG/HDL).

Statistical analysis was performed using non-parametric methods due to skewed distribution of metabolic variables. Continuous data were expressed as mean ± standard deviation. Between-group comparisons were performed using the Mann–Whitney U test. Multivariable logistic regression analysis was conducted to identify independent predictors of hypothyroidism after adjusting for potential confounders. ROC curves were constructed to assess discriminatory performance, and optimal cut-off values were derived using the Youden index. A p value <0.05 was considered statistically significant.

RESULTS

A total study population comprising hypothyroid and euthyroid individuals was analyzed. Hypothyroid subjects demonstrated higher BMI and waist circumference compared with euthyroid controls (Table 1). Triglyceride levels were significantly elevated in the hypothyroid group, while HDL cholesterol levels showed a trend toward reduction. In contrast, fasting blood glucose levels did not differ significantly between the two groups.

The atherogenic index of plasma (AIP) was significantly higher in hypothyroid subjects, placing a substantial proportion of these individuals in the high-risk AIP category. (Fig 1) This finding underscores the predominance of atherogenic dyslipidemia in hypothyroidism, even in the absence of overt hyperglycemia. AIP and waist circumference showed a positive correlation substantiating the fact that central obesity contributes to cardiovascular risk via dyslipidemia, reflected by higher AIP (Fig 2). On multivariable logistic regression analysis, AIP emerged as the strongest independent predictor of hypothyroidism after adjustment for age, BMI, and waist

circumference (Table 2). Anthropometric indices lost statistical significance in the adjusted model, highlighting the dominant contribution of lipid abnormalities.

ROC curve analysis demonstrated that AIP had superior discriminatory ability compared with BMI and waist circumference. An AIP cut-off value of approximately 0.58 provided the optimal balance of sensitivity and specificity for identifying hypothyroid individuals (Table 3, Figure 3).

Tables and figures

Parameter	Euthyroid (Mean ± SD)	Hypothyroid (Mean ± SD)	p-value
BMI (kg/m²)	24.48 ± 5.62	26.53 ± 6.99	**0.035**
Waist Circumference (cm)	85.91 ± 11.06	91.23 ± 12.03	**0.002**
Fasting Blood Glucose (mg/dL)	94.62 ± 19.82	92.80 ± 15.44	0.859
Triglycerides (mg/dL)	145.05 ± 61.83	184.41 ± 101.88	**0.015**
HDL Cholesterol (mg/dL)	43.78 ± 12.12	40.63 ± 9.98	0.097
LDL Cholesterol (mg/dL)	95.19 ± 33.71	104.05 ± 34.25	0.055
Atherogenic Index of Plasma	0.50 ± 0.24	0.61 ± 0.27	**0.006**

Table 1 Baseline Characteristics of cases and controls

Variable	Adjusted OR	95% CI	p-value
Atherogenic Index of Plasma	4.07	1.22 – 13.56	**0.022**
Waist Circumference (per cm)	1.02	0.99 – 1.05	0.147
BMI (kg/m²)	1.03	0.97 – 1.08	0.354

Table 2 Multivariable Logistic Regression Analysis of atherogenic index of plasma, waist circumference and BMI

Marker	AUC	Optimal Cut-off	Sensitivity (%)	Specificity (%)
Atherogenic Index of Plasma	0.61	**0.58**	**52**	**69**
Waist Circumference (cm)	0.63	93	44	78
BMI (kg/m²)	0.59	21.3	80	37

Table 3 ROC Analysis and Youden Index of atherogenic index of plasma, waist circumference and BMI

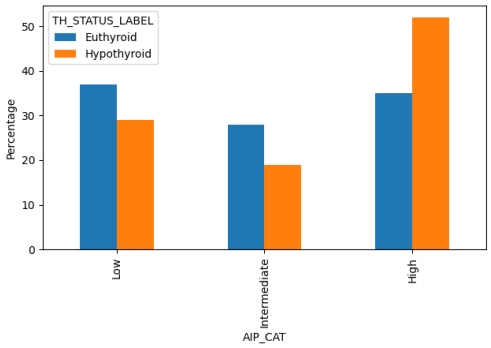

Figure 1 Bar Chart showing atherogenic index of plasma (AIP) categories as per thyroid status

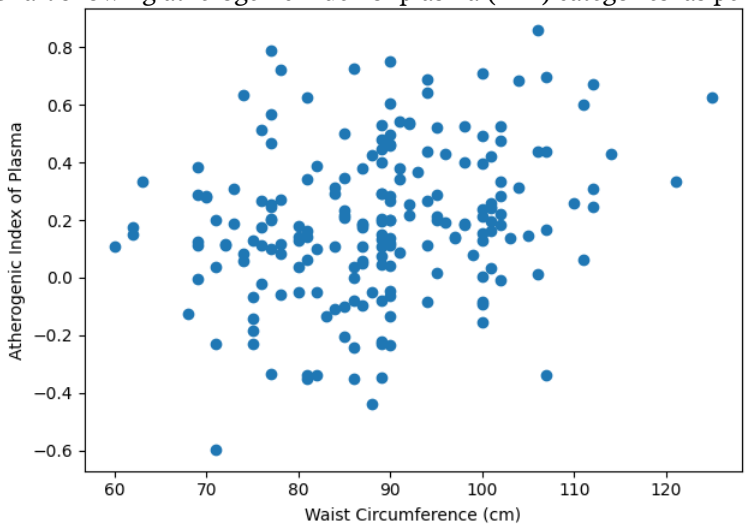

Figure 2 Scatter Plot showing relationship between waist circumference and Atherogenic Index of Plasma (AIP)

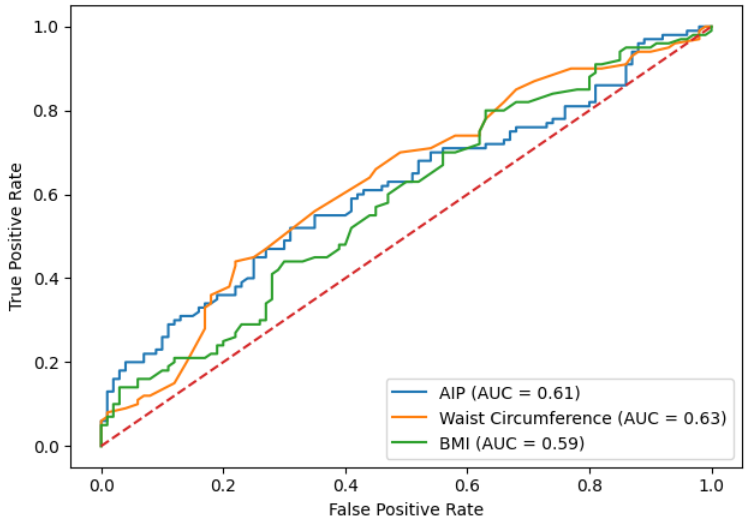

Figure 3 ROC Curves of Atherogenic index of plasma (AIP), waist circumference and BMI for predicting hypothyroidism

DISCUSSION

The present study demonstrates that hypothyroidism is associated with distinct metabolic phenotypes characterized predominantly by atherogenic dyslipidemia and central obesity rather than dysglycemia. These findings challenge the traditional view that hypothyroidism uniformly mirrors the metabolic syndrome and instead support a more nuanced phenotypic classification, wherein lipid abnormalities play a more prominent role than disturbances in glucose metabolism [17]. This heterogeneity in metabolic expression underscores the importance of moving beyond a "one-size-fits-all" cardiometabolic risk assessment in hypothyroid individuals.

In the current cohort, hypothyroid subjects exhibited significantly elevated triglyceride levels and higher values of the atherogenic index of plasma (AIP), indicating qualitative lipid abnormalities that are not fully captured by conventional lipid parameters alone. This observation is concordant with prior studies by Jungare et al (2017) and Prasad et al(2024) [18-19]. AIP reflects the balance between triglyceride-rich lipoproteins and protective HDL cholesterol and has been shown to correlate closely with the presence of small dense LDL particles, a lipoprotein fraction with high atherogenic potential.

The pathophysiological basis for these findings can be explained by the central role of thyroid hormones in lipid metabolism. Thyroid hormone deficiency leads to reduced activity of lipoprotein lipase and hepatic lipase, impaired clearance of triglyceride-rich

lipoproteins, and decreased expression of LDL receptors, resulting in accumulation of atherogenic lipoprotein particles [20-21]. These mechanisms contribute to qualitative dyslipidemia even when absolute cholesterol levels are only modestly elevated, highlighting why composite indices such as AIP may be superior to isolated lipid measurements in hypothyroid populations.

Notably, fasting blood glucose levels did not differ significantly between hypothyroid and euthyroid individuals in this study, suggesting that dysglycemia is not a universal feature of hypothyroidism. This finding aligns with earlier reports indicating preserved glucose homeostasis in hypothyroid individuals in the absence of severe insulin resistance, long-standing disease, or marked obesity [22]. While thyroid hormone deficiency can influence insulin sensitivity through alterations in glucose transport and hepatic gluconeogenesis, these effects may be context-dependent and less pronounced in early or mild disease, reinforcing the concept that hypothyroidism-associated metabolic risk is primarily lipid-driven rather than glycemia-driven.

Among the evaluated markers, AIP consistently outperformed body mass index and waist circumference as a predictor of hypothyroidism. Although central obesity was more prevalent among hypothyroid subjects, anthropometric measures alone may underestimate cardiovascular risk, particularly in individuals with normal or only mildly elevated BMI. This observation is consistent with emerging evidence emphasizing the limitations of BMI as a surrogate for metabolic health and the superior predictive value of visceral adiposity and lipid-based indices [19,23]. The modest discriminatory performance of BMI in the present analysis further supports the need for integrating biochemical markers into risk assessment models for hypothyroid patients.

From a clinical perspective, the incorporation of AIP into routine metabolic evaluation may facilitate early identification of hypothyroid individuals at increased cardiovascular risk, even in the absence of overt hyperglycemia or severe obesity. Given its simplicity, low cost, and reliance on routinely available lipid parameters, AIP represents a practical and scalable tool for risk stratification, particularly in resource-limited settings where advanced lipid testing may not be feasible. Adoption of such an approach could allow for earlier lifestyle or therapeutic interventions aimed at mitigating long-term cardiovascular risk in this population.

Taken together, these findings support the concept of metabolic phenotyping in hypothyroidism and emphasize the predominance of atherogenic dyslipidemia as a key determinant of cardiometabolic risk. Future longitudinal studies are warranted to evaluate whether incorporation of AIP into clinical decision-making improves cardiovascular outcomes and to determine the impact of thyroid hormone replacement on these distinct metabolic phenotypes.

CONCLUSION

Hypothyroidism is associated with heterogeneous metabolic phenotypes, with a predominance of atherogenic dyslipidemia and central obesity rather than dysglycemia. The atherogenic index of plasma is an independent and superior predictor of hypothyroidism compared with conventional anthropometric indices. These findings support the use of AIP as a practical marker for cardiometabolic risk assessment in hypothyroid patients.

REFERENCES

1. Spartalis M, Spartalis E, Paschou SA, et al. The Thyroid-cardiac Axis: Thyroid Function, Cardiac Rhythmology, and Sudden Cardiac Death. Endocr Metab Immune Disord Drug Targets. 2024;24(10):1127-1130.
2. Biondi B, Cooper DS, Cappola AR, et al. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008 Feb;29(1):76–131.
3. Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. Eur Thyroid J. 2013 Dec;2(4):215–28.
4. Pingitore A, Gaggini M, Mastorci F et al. Metabolic Syndrome, Thyroid Dysfunction, and Cardiovascular Risk: The Triptych of Evil. Int J Mol Sci. 2024 Oct 2;25(19):10628.
5. Razvi S, Jabbar A, Pingitore A, et al. Thyroid Hormones and Cardiovascular Function and Diseases. J Am Coll Cardiol. 2018 Apr 24;71(16):1781-1796
6. Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR Working Group on Visceral Obesity. Nat Rev Endocrinol. 2020;16(3):177–189.
7. Taylor PN, Razvi S, Pearce SH, et al. Consequences of variation in thyroid function. J Clin Endocrinol Metab. 2013;98(9):3562–3571.
8. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). Clin Biochem. 2001 Oct;34(7):583-8
9. Mahmoodi MR, Najafipour H. Associations between serum vitamin D3, atherogenic indices of plasma and cardiometabolic biomarkers among patients with diabetes in the KERCADR study. BMC Endocr Disord. 2022 May 12;22(1):126.

10. Onat A, Can G, Kaya H et al. "Atherogenic index of plasma" (log10 triglyceride/high-density lipoprotein-cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol. 2010 Mar-Apr;4(2):89-98.
11. Alifu J, Xiang L, Zhang W, et al. Association between the atherogenic index of plasma and adverse long-term prognosis in patients diagnosed with chronic coronary syndrome. Cardiovasc Diabetol. 2023;22:255
12. Fernandez-Macías JC, Ochoa-Martínez AC, Varela-Silva JA, et al. Atherogenic Index of Plasma: Novel Predictive Biomarker for Cardiovascular Illnesses. Arch Med Res. 2019 Jul;50(5):285-294.
13. Kammar-García A, Lopez-Moreno P, Hernández-Hernandez ME, et al. Atherogenic index of plasma as a marker of cardiovascular risk factors in Mexicans aged 18 to 22 years. Proc (Bayl Univ Med Cent). 2020 Aug 21;34(1):22-27.
14. Raaj I, Thalamati M, Gowda M N V, et al. The Role of the Atherogenic Index of Plasma and the Castelli Risk Index I and II in Cardiovascular Disease. Cureus. 2024 Nov 28;16(11):e74644.
15. Bugge SK. Atherogenic Index of Plasma in Acute Coronary Syndrome: An Observational Study in a Tertiary Care Hospital. Indian J Med Biochem 2023; 27 (1):14-17.
16. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults. Thyroid. 2012;22(12):1200–1235.
17. Biondi B, Cappola AR, Cooper DS, et al. Cardiovascular effects of mild hypothyroidism. Eur J Endocrinol. 2019;180(2):R59–R67.
18. Jungare SA, Jungare AD, Ghorpade KS, et al. Atherogenic index of plasma and lipid profile in hypothyroidism. Indian J Appl Res. 2017;7(1):970-72
19. Prasad NS, Hanumantharaya R, Sannamadhu M, et al. Atherogenic indices as early predictors of cardiovascular diseases among patients with subclinical and overt hypothyroidism in a tertiary care hospital, Karnataka: a cross-sectional study. Natl J Lab Med. 2024;13(1):BO04–BO09.
20. Pearce EN, Yang Q, Benjamin EJ, et al. Thyroid hormone and lipid metabolism. Endocr Rev. 2012;33(3):464–493.
21. Brenta G, Berg G, Arias P, et al. Lipoprotein abnormalities in hypothyroidism and the effect of levothyroxine therapy. J Clin Endocrinol Metab. 2011;96(4):E654–E658.
22. Maratou E, Hadjidakis DJ, Kollias A, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol. 2009;160(5):785–790.
23. Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical practice: a consensus statement. Nat Rev Endocrinol. 2020;16(3):177–189.

