Original Article

DOI: 10.7860/NJLM/2024/63416.2788

Biochemistry Section

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

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ABSTRACT

Introduction: Hypothyroidism is a common health issue that decreases the functional ability of life. It is strongly associated with altered levels of serum lipids, leading to an increased risk of Cardiovascular Disease (CVD). Lipid profile and Atherogenic Indices (AIs) can serve as better markers for evaluating CVD risk.

Aim: The aim of this cross-sectional study is to evaluate the role of dyslipidaemia and AIs as predictors of CVD risk among patients with Subclinical Hypothyroidism (SCH) and Overt Hypothyroidism (OH) compared to euthyroid controls.

Materials and Methods: The present cross-sectional study was conducted at the Clinical Biochemistry Section of Mandya Institute of Medical Sciences in Mandya, Karnataka, India from August to September 2019. A total of 150 subjects aged between 25-60 years were enrolled. Fasting lipid profile and Thyroid Function Test (TFT) were analysed. Based on TFT results, subjects were categorised into SCH, OH, and euthyroid groups. Data on anthropometry {(height, weight, Body Mass Index (BMI), and Blood Pressure (BP)}, lipid profile, Atherogenic Index of Plasma (AIP), Castelli Risk Index-I (CRI-I), CRI-II, and Atherogenic Coefficient (AC) were collected. Statistical analysis was performed using Pearson's correlation and Receiver Operating Characteristic (ROC) curve analysis.

Results: Out of the 150 subjects, 104 (69.3%) were females and 46 (30.7%) were males, with a mean age of 41.08±11.24 years. Both the SCH and OH groups showed statistically significant dyslipidaemic changes and elevated AIs compared to euthyroid controls. Among OH patients, there was a statistically significant positive correlation between TSH and Total Cholesterol (TC) (r=0.463), Low-Density Lipoprotein cholesterol (LDL-c) (r=0.448), CRI-I (r=0.414), CRI-II (r=0.412), and AC (r=0.411). Conversely, there was a statistically significant negative correlation between fT3 and TC (r=-0.393), LDL-c (r=-0.363), CRI-I (r=-0.300), CRI-II (r=-0.301), and AC (r=-0.298). Among the AIs, AIP showed the maximum Area Under the Curve (AUC) in both the SCH (0.707) and OH (0.747) groups.

Conclusion: AIs aid in the better assessment of dyslipidaemia and CVD risk compared to lipid profile alone in hypothyroid subjects. Incorporating AIs enables early prediction of high-risk individuals for CVD risk.

Keywords: Atherosclerosis, Blood pressure, Dyslipidaemia, Thyroid disorder

INTRODUCTION

The global prevalence of hypothyroidism is 4.6%, while in India, it is documented to be around 10.95% [1]. A population-based study conducted in Cochin found the prevalence of hypothyroidism to be around 3.9%, with SCH contributing to 9.4% [2]. An epidemiological study conducted in eight cities across India showed that 8.02% of the entire population had SCH [3]. Thyroid disorders constitute the most common endocrine abnormality and pose a major public health challenge. In hyperthyroidism, there is a negative feedback mechanism on the hypothalamus in response to raised Triiodothyronine (T3) and Thyroxine (T4), resulting in reduced Thyroid-Stimulating Hormone (TSH) levels. Conversely, there is an increased TSH level in hypothyroidism due to low levels of plasma T3 and T4. SCH refers to an increase in the level of TSH with concurrent normal levels of free thyroid hormones, without clinical symptoms or with mild symptoms [4]. Decreased levels of free T3 (fT3) and free T4 (fT4) with a concurrent increase in TSH are reported in OH [5]. Existing studies on the prevalence of hypothyroidism have shown a wide range of variabilities due to differences in age group, geographical location, ethnicity, genetic predisposition, and environmental factors such as dietary iodine and goitrogen intake [6-8]. In hypothyroidism, thyroid hormones have a significant effect on lipid metabolism, causing varied effects on lipid profile parameters. Several changes in the synthesis, metabolism, and mobilisation of lipids result in elevated TC and LDL-c. Thyroid hormones, through their action on hepatic lipase, alter High-Density Lipoprotein cholesterol (HDL-c). Lipoprotein lipase lowers Triglyceride (TG) levels, and its activity is increased by thyroid hormones. Therefore, hypothyroidism may lead to hypertriglyceridemia [9]. Hypothyroidism leads to dyslipidaemia, endothelial dysfunction, atherosclerosis, and hypertension, thereby increasing the risk of CVD. Even small changes in thyroid hormone levels within the reference range can affect the severity of atherosclerosis [10]. AIs have been found useful to assess atherogenic risk and are considered better predictors than parameters of lipid profile alone. In recent times, lipid profile parameters in association with newer indices such as AIP, CRI-I, CRI-II, and AC have been proposed as markers to predict the risk of CVD [11]. The contribution of each of these indices, AIP, CRI-I, CRI-II, and AC, towards the prediction of the risk of CVD was 30%, 20%, 13%, and 16%, respectively [12].

AIs are precursors to cardiovascular and cerebrovascular diseases. Therefore, the calculation of these indices could provide avenues

for early diagnosis and rigorous management of dyslipidaemia and associated CVD risk in patients with SCH and OH. With the widespread availability and increased affordability of Thyroid Function Tests (TFT), the frequency of disease diagnosis has increased. Various researchers have proposed the use of newer AIs such as AIP, CRI-I, CRI-II, and AC to predict the risk of CVD in hypothyroid patients, in addition to the conventional TFT in laboratories [13,14]. However, there have been only a few studies conducted in South India [15,16] that consider all the AIs, and most of these studies have been done in patients with SCH. The present study incorporated all the AIs in both subclinical and OH, and it could serve as a trendsetter for further research on the association between hypothyroidism and CVD risk. Therefore, this study aimed to determine the use of AIs as early predictors of the risk of CVD by correlating individual lipid profile parameters and AIs with fT3, fT4, and TSH levels among patients with SCH and OH in a tertiary care hospital in Karnataka, India.

MATERIALS AND METHODS

This cross-sectional study was carried out for a period of two months, from August to September 2019, in the Clinical Biochemistry Section of the Central Diagnostic Laboratory at Mandya Institute of Medical Sciences in Mandya, Karnataka, India. The study was approved by the Institutional Scientific and Ethics Committee (IEC No: MIMS/IEC/2019/3180), and informed written consent was obtained from each participant before the commencement of the study.

Inclusion criteria: The study included patients with SCH and OH, aged between 25-60 years. Age-matched healthy subjects without any history of thyroid disorder were included as controls.

Exclusion criteria: Subjects with a history of type-2 diabetes mellitus, hypertension, renal and hepatic failure, a history of thyroidectomy, radiotherapy, radioactive iodine therapy, primary or secondary dyslipidaemia, and patients on statins and other drugs known to cause hypothyroidism (such as amiodarone, sulfonylureas, and lithium) were excluded from the study.

Sample size: A total of 150 subjects were enrolled in the study using convenience sampling. Based on the values of TFT, the subjects were categorised into three groups: SCH, OH, and euthyroid controls, with 50 subjects in each group. Euthyroid controls were classified as individuals with normal serum fT3 levels (1.71-3.71 pg/mL), fT4 levels (0.70-1.48 ng/mL), and TSH levels (0.35-5 µIU/mL). Participants with normal fT3, fT4, and TSH levels between 5-15 µIU/mL were classified as SCH, while those with decreased fT3 (<1.71 pg/mL) and fT4 (<0.70 ng/mL) and TSH values beyond 5 µIU/mL were considered as OH [17].

Data collection: A participant proforma was used to collect information regarding their age, family history, personal history, past medical history, anthropometric measurements, and biochemical investigations.

Anthropometric measurements: Anthropometric measurements, such as height (cm) and weight (kg), were measured using a stadiometer and an analogue weighing scale, respectively. BMI was calculated as weight (kg) divided by height (m) squared. BP was measured using a mercury sphygmomanometer (mmHg).

Biochemical parameters: The participants were informed in advance about the requirement for 8-10 hours of overnight fasting for the biochemical investigations. The next morning, after confirming their fasting status and following all aseptic precautions, 3 mL of venous blood was drawn into a plain non-vacuum vacutainer. These tubes were allowed to stand for about 10-15 minutes and then subjected to centrifugation at 3500 rpm for 15-20 minutes. The separated serum was used to estimate fT3, fT4, TSH, TC, TG, and HDL-c. fT3, fT4, and TSH were analysed using a two-step immunoassay method using Chemiluminescent Microparticle Immunoassay (CMIA). Lipid profile parameters such as TC were determined using the Cholesterol Oxidase Peroxidase (CHOD-POD) method, TG using the Glycerol Phosphate Oxidase (GPO) method, and HDL-c using the direct homogeneous enzymatic method [17].

The blood samples were analysed using fully automated Abbott Architect analysers, ensuring that both normal and pathological levels of quality control materials were assayed and within range before analysing patient samples. LDL-c was calculated using Friedewald's equation: LDL-c=(TC)-(HDL-c)-(TG/5). The factor (TG)/5 was used to estimate VLDL-c concentration, based on the average ratio of TG to cholesterol in VLDL. Friedewald's equation is not suitable for LDL-c calculation if TG value >400 mg/dL; in such cases, a direct homogeneous enzymatic assay was performed [18]. The test results were analysed, and the participants were informed about their reports along with appropriate advice. Furthermore, AIs such as AIP, CRI-I, CRI-II, and AC were calculated using the values of lipid profile parameters as given in [Table/Fig-1] [17,19,20].

Atherogenic Indices (AIs) and biochemical parameters	Method of analysis (Formula)	Cut-off range
AIP	Log (TG/HDL-c) [19]	<0.11: Low CVD risk 0.11-0.21: Intermediate CVD risk >0.21: Increased CVD risk
CRI-I	TC/HDL-c [20]	≥5.0: Increased CVD risk
CRI-II	LDL-c/HDL-c [20]	≥3.3: Increased CVD risk
AC	(TC-HDL-c)/HDL-c [20]	≥3: Increased CVD risk
TC	Cholesterol oxidase peroxidase method [17]	<200 mg/dL: Desirable 200-239 mg/dL: Borderline ≥240 mg/dL: High
TG	Glycerol phosphate oxidase method [17]	<150 mg/dL: Desirable 150-199 mg/dL: Borderline 200-499 mg/dL: High >500 mg/dL: Very high
HDL	Direct homogenous enzymatic method [17]	40-60 mg/dL
LDL	Friedewald's equation [17]	<100 mg/dL: Desirable
fT3	Chemiluminescent microparticle Immunoassay [17]	1.71-3.71 pg/mL
FT4	Chemiluminescent microparticle Immunoassay [17]	0.70-1.48 ng/mL
TSH	Chemiluminescent microparticle Immunoassay [17]	0.35-4.94 µIU/mL

[Table/Fig-1]: Reference ranges of AIs and biochemical parameters [17,19,20].
AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient; TC: Total cholesterol; TG: Triglyceride; HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; fT3: Free Triiodothyronine; fT4: Free thyroxine; TSH: Thyroid stimulating hormone

STATISTICAL ANALYSIS

The collected data were entered into a Microsoft Excel sheet and analysed using descriptive and inferential statistics with SPSS 22.0 and R-environment version 3.2.2. Microsoft Word and Excel were used to generate graphs and tables. Results are presented as Mean±SD for continuous variables and as number (%) for categorical measurements. Analysis of Variance (ANOVA) and Chi-square/Fisher-Exact test were used to determine the significance of study parameters on a categorical scale between two or more groups. The strength of association between study variables was determined using Pearson's correlation and other relevant statistics. A value close to +1 indicates a strong positive correlation, while a value close to -1 indicates a strong negative correlation. A p-value <0.05 was considered statistically significant. ROC curve analysis and the area under the ROC curve (AUC of ROC) were used to predict the outcome.

RESULTS

The study population consisted of 150 consenting subjects who were categorised into three groups: 50 age-matched euthyroid controls, 50 subclinical hypothyroid, and 50 overt hypothyroid

based on their values of TFT. The mean age of the study population was 41.08±11.24 years. In the present study, the majority of subjects in each group were females [Table/Fig-2].

Gender	Euthyroid controls	SCH	OH	Total
Females	31 (62%)	34 (68%)	39 (78%)	104 (69.3%)
Males	19 (38%)	16 (32%)	11 (22%)	46 (30.7%)
Total	50 (100%)	50 (100%)	50 (100%)	150 (100%)

[Table/Fig-2]: Distribution of the study population according to gender.
p=0.215, Not Significant, Chi-square test
SCH: Subclinical hypothyroid; OH: Overt hypothyroid

The mean values of BMI, Systolic Blood Pressure (SBP), and Diastolic Blood Pressure (DBP) were significantly higher in Subclinical Hypothyroid (SCH) and Overt Hypothyroid (OH) patients compared to euthyroid controls. The mean values of TSH, fT3, and fT4 showed statistically significant differences in both SCH and OH groups compared to euthyroid controls. Additionally, lipid profile parameters such as TC, TG, and LDL-c were significantly higher, while HDL-c was significantly lower among SCH and OH groups compared to euthyroid controls. Similarly, the mean values of AIs such as AIP, CRI-I, CRI-II, and AC were increased in both SCH and OH groups compared to euthyroid controls, and the difference was statistically significant with a p-value <0.001 [Table/Fig-3].

Correlation analysis between TFT parameters (TSH, fT3, and fT4) and anthropometric measurements such as BMI, SBP, and DBP did not show any statistical significance [Table/Fig-4].

Among OH patients, TSH showed a statistically significant positive correlation with lipid profile parameters such as TC (r=0.463; p=0.001**) and LDL-c (r=0.448; p=0.001**). Similarly, when TSH was correlated with AIs, a statistically significant positive correlation was observed with CRI-I (r=0.414; p=0.003**), CRI-II (r=0.412; p=0.003**), and AC (r=0.411; p=0.003**). There was no significant correlation found between TSH, fT3, fT4, lipid parameters, and AIs among euthyroid and subclinical hypothyroid subjects [Table/Fig-5].

It was noted that there was a statistically significant negative correlation between fT3 and TC (r=-0.393; p=0.005**) as well as fT3 and LDL-c (r=-0.363; p=0.010) among patients in the Overt Hypothyroid (OH) group. When fT3 was correlated with AIs, a statistically significant negative correlation was observed with CRI-I (r=-0.300; p=0.035*), CRI-III (r=-0.301; p=0.033**), and AC (r=-0.298; p=0.036**) among OH group patients. This indicates that as fT3 decreases, the values of lipid profile parameters and AIs increase [Table/Fig-6].

[Table/Fig-7] shows the correlation analysis of fT4 with lipid profile parameters and AIs. It was observed that there was no statistically significant correlation between fT4 and the study variables.

ROC analysis was performed to predict the outcome. Among the Subclinical Hypothyroid (SCH) group, the AUC for AIP was 0.707, while for CRI-I and CRI-II, it was 0.699 and 0.658, respectively [Table/Fig-8,9]. AIP had a higher AUC compared to other indices, making it an important marker for predicting the risk of CVD among SCH patients.

Variables	Euthyroid controls (n=50)	SCH (n=50)	OH (n=50)	Total study population (N=150)	p-value
BMI (kg/m^2)	24.99±3.99	25.97±4.44	28.13±3.24	26.36±4.11	<0.001*
SBP (mmHg)	121.06±16.22	132.10±17.83	133.26±11.64	128.81±16.31	<0.001*
DBP (mmHg)	82.49±10.65	88.82±9.79	85.88±10.16	85.73±10.46	0.009**
TSH (µIU/mL)	1.99±0.92	8.87±4.69	97.62±76.87	36.16±62.13	<0.001**
fT3 (pg/mL)	2.77±0.34	2.59±0.39	1.69±0.56	2.35±0.65	<0.001**
fT4 (ng/mL)	0.96±0.14	0.84±0.09	0.52±0.20	0.77±0.24	<0.001**
TC (mg/dL)	180.24±39.88	193.68±37.55	212.86±64.58	195.59±50.38	0.004**
TG (mg/dL)	146.32±48.88	193.24±92.89	211.40±108.91	183.65±91.00	0.001**
HDL-c (mg/dL)	39.55±6.61	35.40±7.56	34.84±4.39	36.60±6.63	<0.001**
LDL-c (mg/dL)	112.20±35.97	122.28±36.52	142.89±64.62	125.79±49.00	0.005**
AIP	0.55±0.17	0.71±0.24	0.74±0.21	0.67±0.22	<0.001**
CRI- I	4.67±1.23	5.69±1.53	6.17±1.91	5.51±1.69	<0.001**
CRI- II	2.93±1.06	3.59±1.29	4.15±1.90	3.55±1.53	<0.001**
AC	3.67±1.23	4.69±1.53	5.18±1.91	4.51±1.69	<0.001**

[Table/Fig-3]: Comparison of baseline characteristics among study subjects.
*Moderately significant (p-value: 0.01<p<0.05)** Strongly significant (p-value: p<0.01) by ANOVA test
SCH: Subclinical hypothyroid; OH: Overt hypothyroid; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TSH: Thyroid stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine; TC: Total cholesterol; TG: Triglyceride; HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient

	Euthyroid controls		SCH		OH	
Pair	r-value	p-value	r-value	p-value	r-value	p-value
TSH vs BMI	0.259	0.069	-0.098	0.496	-0.049	0.737
TSH vs SBP	-0.067	0.644	0.023	0.872	0.192	0.172
TSH vs DBP	-0.068	0.641	0.065	0.652	0.183	0.202
fT3 vs BMI	-0.043	0.769	0.005	0.975	-0.006	0.965
fT3 vs SBP	-0.110	0.445	-0.088	0.543	-0.159	0.270
fT3 vs DBP	0.031	0.828	-0.150	0.299	-0.299	0.035*
fT4 vs BMI	0.078	0.592	0.165	0.254	0.230	0.108
fT4 vs SBP	0.193	0.179	-0.094	0.515	-0.135	0.348
fT4 vs DBP	-0.024	0.867	-0.002	0.986	-0.268	0.059

[Table/Fig-4]: Pearson correlation between TFT parameters (TSH, fT3 and fT4) versus anthropometric measurements.
*Moderately significant (p-value: 0.01<p<0.05)** Strongly significant (p-value: p<0.01)
SCH: Subclinical hypothyroid; OH: Overt hypothyroid; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TSH: Thyroid stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine

Pair	Euthyroid controls		SCH		OH	
	r-value	p-value	r-value	p-value	r-value	p-value
TSH vs TC	0.079	0.586	-0.151	0.295	0.463	0.001**
TSH vs TG	-0.064	0.660	-0.186	0.197	0.079	0.586
TSH vs HDL-c	0.133	0.357	-0.207	0.148	0.084	0.562
TSH vs LDL-c	0.031	0.833	-0.028	0.848	0.448	0.001**
TSH vs AIP	-0.028	0.847	-0.128	0.377	0.034	0.816
TSH vs CRI-I	-0.011	0.942	0.023	0.874	0.414	0.003**
TSH vs CRI-II	-0.025	0.866	0.078	0.590	0.412	0.003**
TSH vs AC	-0.011	0.940	0.023	0.874	0.411	0.003**

[Table/Fig-5]: [Table/Fig-5]: Pearson correlation of TSH with lipid profile parameters and AIs.
**Strongly significant (p-value: p<0.01)
SCH: Subclinical hypothyroid; OH: Overt hypothyroid; TSH: Thyroid stimulating hormone; TC: Total cholesterol; TG: Triglyceride; HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient

Pair	Euthyroid controls		SCH		OH	
	r-value	p-value	r-value	p-value	r-value	p-value
fT3 vs TC	-0.056	0.700	0.034	0.817	-0.393	0.005**
fT3 vs TG	0.012	0.937	-0.069	0.633	-0.143	0.323
fT3 vs HDL-c	-0.076	0.600	0.090	0.534	-0.209	0.146
fT3 vs LDL-c	-0.046	0.750	0.091	0.530	-0.363	0.010**
fT3 vs AIP	-0.020	0.890	-0.086	0.551	-0.090	0.535
fT3 vs CRI-I	-0.016	0.915	-0.028	0.848	-0.300	0.035*
fT3 vs CRI-II	-0.025	0.864	0.046	0.748	-0.301	0.033*
fT3 vs AC	-0.016	0.911	-0.028	0.848	-0.298	0.036*

[Table/Fig-6]: Pearson correlation of fT3 with lipid profile parameters and AIs.
*Moderately significant (p-value: 0.01<p<0.05) **Strongly significant (p-value: p<0.01)
SCH: Subclinical hypothyroid; OH: Overt hypothyroid; TSH: Thyroid stimulating hormone; fT3: Free T3; TC: Total cholesterol; TG: Triglyceride; HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient

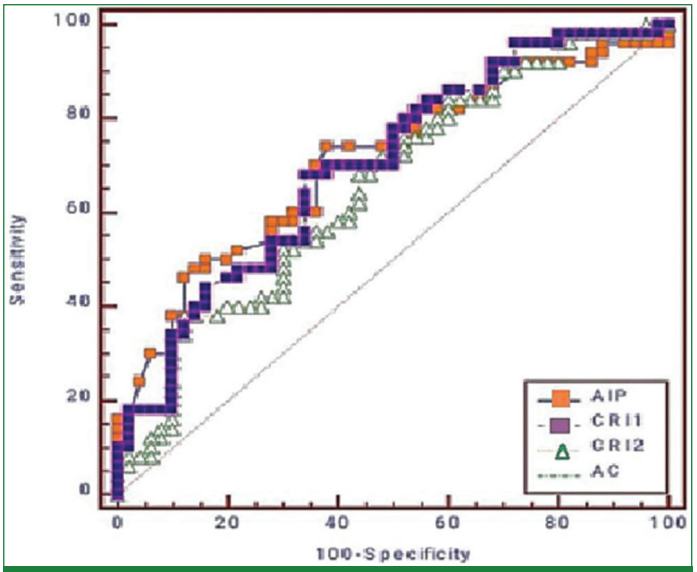
Pair	Euthyroid controls		SCH		OH	
	r-value	p-value	r-value	p-value	r-value	p-value
fT4 vs TC	0.032	0.823	0.043	0.768	-0.213	0.138
fT4 vs TG	-0.031	0.831	-0.128	0.376	-0.075	0.606
fT4 vs HDL-c	0.217	0.134	0.162	0.262	-0.047	0.748
fT4 vs LDL-c	-0.010	0.946	0.012	0.932	-0.180	0.210
fT4 vs AIP	-0.039	0.785	-0.180	0.212	-0.087	0.548
fT4 vs CRI-I	-0.075	0.606	-0.112	0.440	-0.187	0.193
fT4 vs CRI- II	-0.076	0.598	-0.121	0.403	-0.160	0.268
fT4 vs AC	-0.075	0.606	-0.112	0.440	-0.186	0.195

[Table/Fig-7]: Pearson correlation of fT4 with lipid profile parameters and AIs.
SCH: Subclinical hypothyroid; OH: Overt hypothyroid; TSH: Thyroid stimulating hormone; fT4: Free T4; TC: Total cholesterol; TG: Triglyceride; HDL-c: High density lipoprotein cholesterol; LDL-c: Low density lipoprotein cholesterol; AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient

Atherogenic Indices (AI)	Area Under the Curve (AUC)	Standard Error (SE)	Confidence Interval (CI)
AIP	0.707	0.0522	0.608 to 0.794
CRI-I	0.699	0.0522	0.599 to 0.787
CRI-II	0.658	0.0547	0.556 to 0.750
AC	0.699	0.0522	0.599 to 0.787

[Table/Fig-8]: Area under the ROC curve of AIs in subclinical hypothyroid patients.
AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient

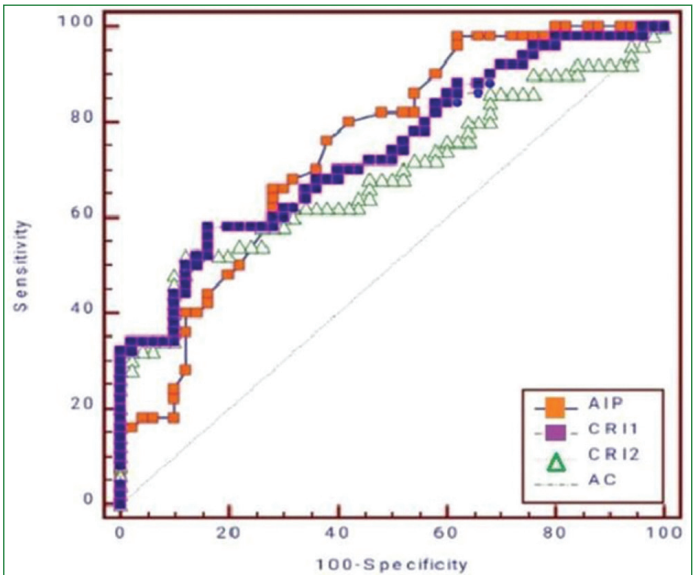
[Table/Fig-10,11] shows ROC analysis of AIs among overt hypothyroid patients. The AUC for AIP (0.747) was the highest, followed by AC (0.739), CRI-I (0.737), and CRI-II (0.690). This indicated that even in OH patients, AIP emerged as an important index compared to other AIs for predicting the risk of CVD.



[Table/Fig-9]: Receiver Operator Characteristic (ROC) curve of AIs in subclinical hypothyroid patients.
AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient

Atherogenic Indices (AI)	Area Under the Curve (AUC)	Standard Error (SE)	Confidence Interval (CI)
AIP	0.747	0.0488	0.650 to 0.828
CRI-I	0.737	0.0494	0.640 to 0.820
CRI-II	0.690	0.0538	0.590 to 0.779
AC	0.739	0.0493	0.641 to 0.822

[Table/Fig-10]: Area under the ROC curve of AIs among overt hypothyroid patients.
AIP: Atherogenic index of plasma; CRI-I: Castelli risk index-I; CRI-II: Castelli risk index-II; AC: Atherogenic coefficient



[Table/Fig-11]: Receiver operator characteristic curve of AIs in overt hypothyroid patients.

DISCUSSION

The present study aimed to evaluate dyslipidaemia and AIs as predictors of CVD risk by correlating individual lipid profile parameters and AIs with fT3, fT4, and TSH among SCH and OH patients compared to euthyroid controls.

Thyroid hormones play a major role in growth, development, sexual maturation, stimulation of adrenergic activity, myocardial contractility, carbohydrate and protein metabolism, and synthesis and degradation of cholesterol and TGs. All of these effects are increased in hyperthyroidism and decreased in hypothyroidism [17]. Hypothyroidism is a well-known cause of dyslipidaemia that leads to the formation of atherogenic plaque, which is a direct risk factor for CVD [13].

According to the present study, 68% of females and 32% of males had SCH, while OH was observed in 78% females and 22% males, indicating a higher prevalence of hypothyroidism among females. These findings were in accordance with the study conducted by Canaris GJ et al., where they also documented an increased concentration of TSH among women compared to men [21].

Both the SCH and OH groups showed increased BMI, SBP, and DBP compared to euthyroid controls, and this difference was statistically significant (p-value <0.001). Similar findings were observed in studies conducted by Shivaprakash G et al., and Talwalkar P et al., where it was observed that patients with a history of hypertension and diabetes mellitus had a higher prevalence of hypothyroidism [10,22].

Hypothyroidism is characterised by decreased cholesterol clearance and reduced LDL-c receptor activity, contributing to decreased receptor-mediated clearance of LDL-c particles. These are proposed mechanisms for elevated TC and LDL-c values in OH patients [14]. Additionally, decreased activity of lipoprotein lipase and decreased clearance of TG-rich lipoproteins result in hypertriglyceridaemia. Thyroid dysfunction also has a significant effect on HDL-c metabolism. Genes coding for proteins involved in intravascular metabolism of HDL-c are regulated by thyroid hormones. Therefore, significantly reduced serum HDL-c is considered a major risk factor for the development of CVD [13]. The results of the present study also revealed dyslipidaemic changes among OH group subjects, which is consistent with the study conducted by Prakash A and Lal AK, where they concluded that there was an evident effect of hypothyroidism on lipid metabolism in patients with increased TSH levels [23].

The current study documented a statistically significant correlation between TSH and fT3 with TC and LDL-c among OH patients, while SCH patients did not show a statistically significant correlation between thyroid and lipid profile parameters. These results align with the findings of the study conducted by Jayakumar A et al., where they also found that TSH showed a statistically significant positive correlation with TC, TG, and LDL cholesterol in the overt hypothyroid group [24].

According to the results obtained in the current study, it was observed that levels of AIs were significantly higher in SCH and OH group subjects compared to euthyroid subjects, and this difference was statistically significant. Correlation analysis between thyroid profile parameters and AIs revealed a statistically significant positive correlation. Among OH patients, TSH was positively correlated with CR-I, CRI-II, and AC, while a negative correlation was observed between fT3 and CRI-I, CRI-II, and AC. These findings are in line with the study conducted by Shivakrishna G et al., [10].

AIP is considered a surrogate marker for assessing CVD risk, and the ratio of TG to HDL cholesterol (HDL-c) is reported as a predictor of infarction. AIP is calculated using the formula log (TG/HDL-c). The present study showed a statistically significant increase in AIP values in both Subclinical Hypothyroid (SCH) and Overt Hypothyroid (OH) patients, contributing to the risk of CVD [25].

Castelli Risk Index (CRI) is also based on Total Cholesterol (TC), LDL cholesterol (LDL-c), and HDL-c. CRI-I is calculated using the ratio (TC/HDL-c), and CRI-II is calculated using the ratio (LDL-c/HDL-c). Many studies have shown that LDL-c/HDL-c values higher than 5 are associated with a sixfold increase in the rate of coronary events [26,27].

Atherogenic potential for the entire spectrum of lipoprotein fractions is reflected by AC, which is measured as (TC-HDL-c)/HDL-c [28]. The present study showed statistically significant higher values for CRI-I, CRI-II, and AC in both SCH and OH patients compared to euthyroid controls.

To assess the contribution of AIs in the evaluation of CVD risk among SCH and OH patients, ROC curve analysis was performed. It was observed that the AUC was higher for AIP compared to the other indices in both SCH (AUC=0.707) and OH patients (AUC=0.747). This suggested that AIP is a better predictor of CVD risk among the four indices. Additionally, several studies have shown that AIP is significantly associated with the dyslipidaemia state among hypothyroid patients compared to individual lipid profile parameters [11,15].

Limitation(s)

The limitations associated with the study are a small sample size and the lack of appropriate tools for detailed CVD risk assessment, such as echocardiography and 2-D echo. Follow-up of cases was not conducted to study the causal relationship between AIs and cardiovascular risk factors.

CONCLUSION(S)

The present study concluded that hypothyroidism is more common among women compared to men. Among the SCH and OH groups, OH patients showed significant lipid disturbances, such as elevated TC, TGs, LDL-c, and decreased HDL-c values. Comparison of AIs among SCH and OH subjects showed statistically significant increased values for AIP, CRI-I, CRI-II, and AC compared to euthyroid controls. Therefore, incorporation of AIs in the evaluation of lipid disturbances among hypothyroid patients helps in better risk stratification. According to the present study, AIP emerged as a better predictor of CVD risk compared to other indices. Hence, these indices should be implemented in routine evaluation for the early identification of high-risk individuals for CVD risk assessment at no extra cost, contributing to effective management of patients.

Acknowledgement

The study was conducted as part of a Short-Term Studentship (STS) project under Indian Council of Medical Research (ICMR).

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 14, 2023
- Manual Googling: Jun 14, 2023
- iThenticate Software: Jul 06, 2023 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Feb 10, 2023**
Date of Peer Review: **Apr 22, 2023**
Date of Acceptance: **Jul 07, 2023**
Date of Publishing: **Jan 01, 2024**