



Original Research Article

Castelli risk index-1 and atherogenic coefficient are better predictors of cardiometabolic risk in patients with hypothyroidism

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ABSTRACT

Hypothyroidism resulting from a deficiency of thyroid hormones may be associated with dyslipidaemia. Since altered lipid profile is quite important in predicting CVD risk, therefore the present study aimed to investigate any possible association between the levels of certain lipid indices with thyroid profile and their diagnostic ability of cardiometabolic syndrome in patients with hypothyroidism.

Material and Methods: A cohort of 40 female patients diagnosed with hypothyroidism was included as cases and thirty age and gender matched healthy females were recruited as controls. Fasting blood samples were collected for analysis of thyroid hormones, cholesterol, triglycerides and high density lipoprotein cholesterol levels by Chemiluminescence immuno-assay, and enzymatic colorimetric methods respectively. Differences in all between groups were tested using parametric independent sample T test. Pearson's correlation or Spearman rank correlation analysis was done to study the correlations among the parameters as appropriate. Receiver operative characteristic (ROC) curve analysis was performed to study diagnostic utility of parameters.

Results: Lipid indices were found to be significantly increased in patients with hypothyroidism when compared to the controls. Castelli risk index-I (CRI-I), CRI-II, atherogenic coefficient (AC) and atherogenic index of plasma (AIP), were found to be significant positively correlated with low density lipoprotein cholesterol (LDL) ($r=0.923$, $p=0.0001$, $r=0.935$, $p=0.0001$, $r=0.970$, $p=0.0001$ and $r=0.382$, $p=0.0001$ respectively). The ROC curve analysis of lipid indices for cardiometabolic risk reveals that AUC for CRI-I and AC was high and statistically significant than other lipid parameters.

Conclusion: The present study suggests that in addition to routine lipid investigations the inclusion of lipid Indices especially CRI-I, AC, were better indices for screening of early detection of cardiometabolic risk in female patients with hypothyroidism.

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1. Introduction

Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones. It is more frequent with increasing age and in women. Cardiovascular, pulmonary, renal, neuromuscular, nervous and reproductive systems are mostly affected in this condition. Earlier study reported that even subclinical hypothyroidism independently doubled the relative risk of myocardial infarction in females.¹ Hypothyroidism is associated with many metabolic abnormalities such as elevated total cholesterol (TC), low density lipopro-

tein (LDL), triglyceride (TG) levels. Since dyslipidemia is implicated as cardiovascular risk factor, it might be relevant to find out possible correlation between lipid abnormality and the thyroid profile.² Evidence suggests that (Framingham study), comparison of certain lipid ratios are extensively more useful as predictors of cardiovascular diseases (CVD) than the individual levels of LDL or HDL cholesterol.² Furthermore, lipid ratio defined as Castelli's Risk Index-II (CRI-II) presented more prognostic value when compared with ordinary LDL or HDL fraction. In a related but different term, another lipid ratio, AIP defined as $\log(TG/HDL)$ was proposed as a marker of plasma atherogenicity (Helsinki et al.).³ Since then, various

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reports revealed that atherogenic index of plasma (AIP) is a useful diagnostic tool for possible replacement and highly important in predicting CVD risk, where TG and HDL were not alter significantly. However, there are scenarios where the usefulness of traditional risk factors is limited.⁴ Bhardwaj and co-workers (2013) reported that lipid ratios like AIP, CRI and Atherogenic coefficient could be used for identifying individuals at higher risk of cardiovascular disease in Indian population in the clinical setting especially when the absolute values of individual lipoproteins seem normal and in individuals with elevated TG concentrations. They suggest that application of lipid ratios provides further utility over ordinary individual lipid parameters. Furthermore, considering the running cost and lack of imaging techniques such as carotid doppler and operationalization for some significant CAD plasma markers such as apo-lipoproteins in resource-limited centers, these lipid ratios can add significant value to the assessment of CAD risk without problem.⁵ It was reported that calculating certain ratios using these parameters especially in situations where LDL levels are below target range may increase the identification of at-risk individuals.⁶ Limited studies were observed about lipid ratios in south Indian region. Hence the present study aimed to investigate the levels of lipid profile and ratios and their associations with thyroid profile in patients with hypothyroidism and to study the diagnostic ability of cardiometabolic risk in hypothyroid patients compared with healthy controls.

2. Materials and Methods

In the present study a total of 40 diagnosed patients with hypothyroidism female patients attending the Biochemistry outpatient department of Mahaveer Institute of Medical Sciences, Vikarabad were recruited into the study from the period of 13/12/2018 to 18/2/2019. Age and gender matched healthy individuals from among the patient's relatives and hospital staff recruited into the study as controls. The primary data was collected and recorded from the patients who were come for routine checkup and retrospectively data was collected and analyzed for lipid indices. Secondary data was utilized in the present study. Patients aged between 25-50 years who were not with no history osteoporosis, cardiovascular diseases, myocardial infarction, stroke and women with pregnancy were excluded from the study. Sample size calculation was done with relevant previous studies.

2.1. Sample collection

Three mL of venous blood was drawn from median cubital vein from subjects after an overnight fast of 8-10 hours. 3ml of blood of blood was transferred into additive free tube. Samples collected in additive free tubes were allowed to stand for 30 minutes to allow clotting and then centrifuged

at 2000 rotation per minute for 15 minutes to obtain serum for: lipid profile and thyroid profile. Samples were analysed immediately and values were recorded.

3. Methodology

Standardized questionnaire regarding medical history, current treatment, life style habits were collected from all the patients and recorded. Thyroid hormones were analyzed by Chemiluminescence immuno assay by Cobas e411 (Hitachi High Technologies corporation, Japan). Cholesterol analyzed by oxidase peroxidase method, Triglycerides by enzymatic colorimetric method, HDL by selective inhibition method; all the parameters analyzed by using ERBA Chem-7 semi-automated analyzer. VLDL was calculated by Friedwald's formula.

3.1. Calculations of risk indices

Castelli's Risk Index (CRI): CRI is calculated from TC, LDL and HDL and it is categorized into two; CRI-I and CRI-II.

CRI-I = TC/HDLc ratio.

CRI-II = LDLc/HDLc ratio.

Atherogenic Index of Plasma (AIP) is $\text{Log}_{10}(\text{TG}/\text{HDLc})$ ratio.

Atherogenic Coefficient (AC) is $[(\text{TC} - \text{HDL})/\text{HDL}]$ or $[(\text{Non-HDL})/\text{HDL}]$ ratio.

3.2. Statistical analysis

Data distribution was studied by using Kolmogorov Smirnov test. Data obtained was expressed as mean \pm SD or median inter quartile range as appropriate. Differences in all biochemical parameters studied among study and control groups were tested using parametric independent sample T test. Pearson's correlation or Spearman rank correlation analysis was done to study the correlations among the parameters as appropriate. Receiver operative characteristic curve (ROC) analysis was performed to study diagnostic utility of parameters. A 'p' value of < 0.05 was considered as statistically significant. Analyses were performed using Microsoft Excel spread sheets (Microsoft Redmond USA) and SPSS package (version 16.0 for windows) SPSS Inc., Chicago, USA.

4. Results

The study population characteristics are described in Table 1. The present study was designed to assess the use of specific ratios derived from routinely done basic lipid profile parameters in female patients with hypothyroidism used for identification of individuals for cardio metabolic risk. Case and control groups were age and gender matched. Total cholesterol and LDL cholesterol were found to be significantly higher in cases when compared to the

controls ($p < 0.001$, $p < 0.001$ respectively), HDL levels was significantly decreased in study group compared to control group ($p < 0.001$), T3, T4 and TSH found to be significantly higher in cases when compared to the control group ($p = 0.0001$, $p = 0.0001$, $p = 0.026$ respectively). CRI-I, CRI-II, AC and AIP were found to be significantly increased in cases when compared to the control group ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$ respectively).

Table 2 showed that correlation analysis of lipid parameters with lipid indices. Ratios CRI-I, CRI-II, AC and AIP, were found to be significantly positively correlated with Total cholesterol ($r = 0.865$, $p = 0.0001$, $r = 0.871$, $p = 0.0001$, $r = 1.000$, $p = 0.0001$ and $r = 0.489$, $p = 0.0001$ respectively). CRI-I, CRI-II, AC and AIP, were found to be significantly positively correlated with LDL ($r = 0.923$, $p = 0.0001$, $r = 0.935$, $p = 0.0001$, $r = 0.970$, $p = 0.0001$ and $r = 0.382$, $p = 0.0001$ respectively). AIP, were found to be significantly positively correlated with TGL cholesterol ($r = 0.879$, $p = 0.0001$). HDL significant negative correlation with CRI-I ($r = -0.827$, $p = 0.0001$), CRI-II ($r = -0.809$, $p = 0.0001$), AC ($r = -0.465$, $p = 0.001$), AIP ($r = -0.495$, $p = 0.0001$). CRI-I, CRI-II and AC were showed significant positive association with Thyroid profile (Table 3). AIP showed significant positive association with TSH ($r = 0.367$, $p = 0.011$) (Table 3). The present study found that significant positive associations were observed in between lipid ratios (Table 4).

Table 5 shows diagnostic utility of lipid indices for cardio metabolic risk in hypothyroidism patients compared with non cardio metabolic risk patients. CRI-I, CRI-II, AC, and AIP were found to have significant diagnostic ability to detect presence of cardiometabolic risk by ROC curve analysis. The AUC for CRI-I and AC was highest and statistically significant when compared to other lipid parameters (0.994, 0.994 respectively).

5. Discussion

Thyroid hormones have significant role to play in lipid metabolism. The present study observed that significant higher levels of TC and LDL and significant lower levels of HDL cholesterol in hypothyroid patients compared to controls. The present study observed that effect of hypothyroidism on lipid parameters is more marked in patients with higher serum TSH levels. As TSH levels goes on increasing dyslipidemia also increased. A south Indian study that was conducted in Andhra Pradesh on female patients, suggests that effect of hypothyroidism on the serum concentration of lipids is more marked in patients with higher serum TSH levels.⁷ The present study also accordance with this manner. Consequently lipid abnormalities exhibit enormous individual variability and there might be a potential link between hypothyroidism and atherosclerosis. According to Khan MAH et al., they

reported that significant increase in levels of TC were observed in hypothyroid patients compared to controls. Hypercholesterolemia is due to decreased activity of LDL receptors resulting in decreased receptor mediated catabolism of LDL and IDL in hypothyroidism.⁸ It was reported that in hypothyroidism number of LDL receptors in the liver decreases and causes delayed clearance of LDL as a result there is an increase in overall cholesterol and LDL-C (Jiskra et al.).⁹ The present study results were in consistent with Ravi Shekhar et al., who reports that total cholesterol and LDL levels were elevated in patients with hypothyroidism.¹⁰ The present study agreement with study done by Lakshmi LJ et al., showed that there is significant decrease in HDL levels in hypothyroid patients compared to controls. The present study found that the lipid indices such as CRI-I, CRI-II, AC and AIP, were found to be significantly positively correlated with Total cholesterol ($r = 0.865$, $p = 0.0001$, $r = 0.871$, $p = 0.0001$, $r = 1.000$, $p = 0.0001$ and $r = 0.489$, $p = 0.0001$ respectively), and LDL ($r = 0.923$, $p = 0.0001$, $r = 0.935$, $p = 0.0001$, $r = 0.970$, $p = 0.0001$ and $r = 0.382$, $p = 0.0001$ respectively), and showed significant negative correlation with HDL cholesterol ($r = -0.827$, $p = 0.0001$, $r = -0.809$, $p = 0.0001$, $r = -0.465$, $p = 0.001$, $r = -0.495$, $p = 0.0001$). AIP, were found to be significantly positively correlated with TGL cholesterol ($r = 0.879$, $p = 0.0001$). CRI-I, CRI-II and AC were showed significant positive association with Thyroid profile (TT3, TT4, TSH) (Table 3). AIP showed significant positive association only with TSH ($r = 0.367$, $p = 0.011$) (Table 3). The present study found that significant positive associations were observed in between lipid ratios (table 4). The present study could not observed significant changes in TG and associations with lipid indices in patients with hypothyroidism. This clearly suggests the relevance of the risk predictors over individual lipid parameters. The lipid ratio predicts cardiometabolic risk better than isolated lipoprotein sub fractions. The present study found that there was a significant increase lipid ratio of CRI-I and CRI-II, AC and AIP ($p < 0.001$) in patients with hypothyroidism compared to controls. Which is in accordance with study done by Khan FA et al.¹¹ The LDL/HDL or CRI-II is a better predictor for risk of heart disease than LDL alone. The several studies have found that the LDL/HDL ratio is an outstanding monitor for effectiveness of lipid lowering therapies. If the ratio of TC/HDL is increasing then risks is more. Previous studies also found that there was significant positive correlation between serum TSH values and lipid parameters.^{11,12} The present study found that significant positive associations between the lipid ratios (Table 4). It was stated that either the ratio of TC/HDL or LDL/HDL i.e CRI-I & II is the best lipid related predictive risk calculators of future cardiovascular events. By indication, index ratio perfectly reveals the presence of atherogenic small LDL particles, and therefore an accepted sensitive biomarker of atherosclerotic CVD

Table 1: Demographic and lipid ratios of patients with hypothyroidism compared with healthy controls

Parameter	Controls (n=30)	Patients with hypothyroidism	P value
	Mean ±SE	(n=40) Mean ±SE	
Age(years)	28.33±1.56	29.9 ±1.8	0.87
Total cholesterol (mg/dL)	167.8±4.6	244.7±9.3	0.000
High density lipoprotein cholesterol (mg/dL)	52.31±1.32	39.77±1.27	0.000
Tri glycerides (mg/dL)	109.8 ±6.8	129.7±14.5	0.17
Low density lipoprotein cholesterol (mg/dL)	93.46±4.99	179.0±8.66	0.000
Total Tri-iodothyronine (ng/dL)	103.0±7.48	150.7±5.14	0.000
Total Thyroxine (µg/dL)	7.08±0.18	9.39±0.37	0.00
Thyroid stimulating hormone (µIU/mL)	3.35±0.72	5.56±0.68	0.026
CRI-I	3.30±0.15	6.15±0.12	<0.001
CRI-II	1.87±0.14	4.49±0.16	<0.001
AC	166.8±4.6	243.7±9.3	<0.001
AIP	0.30±0.2	0.48±0.3	<0.001

Data presented as Mean ± Standard error. <0.05 considered as statistically significant. N: Number of samples, mg/dL: Milli gram per decilitre, µg/dL: Micro gram per deci litre, µIU/mL: Micro international unit permilli litre, CRI-I: Castellis risk index I, CRI-II: Castellis risk index II, AC: Atherogenic coefficient, AIP: Atherogenic index of plasma.

Table 2: Pearson correlation of Lipid indices with lipid parameters

Parameter	TGL		HDL		Total Cholesterol		LDL	
	r=value	p=value	r=value	p=value	r=value	p=value	r=value	p=value
CRI-I			-0.827**	0.000	0.865**	0.000	0.923**	0.000
CRI-II			-0.809**	0.000	0.875**	0.000	0.935**	0.000
AC			-0.465	0.001	1.000**	0.000	0.970**	0.000
AIP	0.879**	0.000	-0.495**	0.000	0.489**	0.000	0.382**	0.007

** : statistically significant, CRI-I: castellis risk index I, CRI-II: castellis risk index II, AC: Atherogenic coefficient, AIP: atherogenic index of plasma, TGL: Tri glycerides, HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol.

Table 3: Spearman Rank correlation of thyroid profile with lipid indices

Parameter	TT3		TT4		TSH	
	r=value	p=value	r=value	p=value	r=value	p=value
CRI-I	0.477**	0.000	0.588**	0.001	0.500**	0.000
CRI-II	0.488**	0.000	0.589**	0.000	0.521**	0.000
AC	0.453**	0.000	0.598**	0.001	0.506**	0.000
AIP					0.367**	0.011

** : statistically significant, NS: Not significant, TT3: Total Tri-iodothyronine, TT4: Total Thyroxine, TSH: Thyroid stimulating hormone, CRI-I: Castellis risk index I, CRI-II: Castellis risk index II, AC: Atherogenic coefficient, AIP: Atherogenic index of plasma

Table 4: Spearman rank correlation in between lipid indices

Parameter	Pearson Correlation	
	r=value	p=value*
CRI-I VS CRI-II	0.988	0.000
CRI-I VS AC	0.866	0.000
CRI-I VS AIP	0.550	0.000
CRI-II VS AC	0.867	0.000
CRI-II VS AIP	0.424	0.003
AC VS AIP	0.489	0.000

*: statistically significant, CRI-I: Castellis risk index I, CRI-II: Castellis risk index II, AC: Atherogenic coefficient, AIP: Atherogenic index of plasma

Table 5: Diagnostic utility of Indices of Cardiometabolic risk patients compared with non cardio metabolic risk patients

Test Result Variable(s)	Area Under the Curve			95% Confidence Interval	
	AUC	Std. Error	Asymptotic Sig*.	Lower Bound	Upper Bound
CRI-I	.994	.011	.000	.973	1.014
CRI-II	.896	.070	.001	.760	1.032
AC	.994	.011	.000	.973	1.014
AIP	.961	.034	.000	.894	1.028

*Statistically significant, AUC- area under the curve, CRI-I: castelli's risk index I, CRI-II: castellis risk index II, AC: Atherogenic coefficient, AIP: atherogenic index of plasma

risk. The present study observed diagnostic utility of lipid indices in hypothyroidism patients compared with healthy individuals. The present study was agreement with previous study, it was found that CRI-I and II are predictive of AIP as well as AC and therefore are likely to be related in their ability to pinpoint patients with risk of CVD (Adedokan et al.).¹³ The hypothyroid cases were divided into further groups depends on cardio metabolic risk and ROC curve analysis was done (Table 5). CRI-I, CRI-II, AC, and AIP were found to have significant diagnostic ability to detect presence of cardiometabolic risk by ROC curve analysis (Figure 1). The AUC for CRI-I and AC was highest and statistically significant when compared to other lipid indices (0.994, 0.994 respectively).

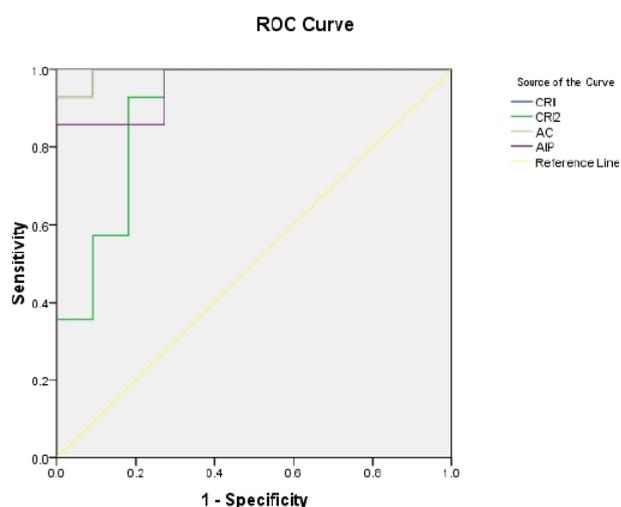


Fig. 1: Receiver operating characteristic curve analysis of lipid indices in patients Hypothyroidism for cardiometabolic risk compared with controls

ROC: Receiver operating characteristic curve, CRI-I: Castelli's risk index I, CRI-II: Castelli's risk index II, AC: Altherogenic coefficient, AIP: Atherogenic index of plasma

6. Conclusion

The present study concluded that lipid indices CRI-I and CRI-II, AC and AIP were considered to be better predictors

for cardio metabolic risk in patients with hypothyroidism and might be better than traditional lipid parameters. In addition to routine lipid investigations the inclusion of lipid indices especially CRI-I and AC might be better indices for screening of early detection of cardiometabolic risk in female patients with hypothyroidism. These lipid ratios can provide a significant value to the assessment of cardiometabolic risk in absence of blood biomarkers and imaging techniques in resource-limited centers.

7. Limitation

The study contains small sample size. Further studies will be required with large sample size and multicenter design to better validate of the conclusions.

8. Source of Funding

None.

9. Conflict of Interest

None.

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