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Original Article

Biochemistry Section

# Serum Testosterone and Atherogenic Indices as an Independent Risk Factor for Predicting the Severity of Coronary Artery Disease: A Cross-sectional Study from North Eastern Region of India

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## ABSTRACT

**Introduction:** Coronary Artery Disease (CAD) is one of the primary causes of mortality worldwide. Dyslipidaemia is associated with the development of Atherosclerotic Cardiovascular Disease (ASCVD). Atherogenic indices are emerging lipid parameters related to atherosclerosis and CAD. There is a limited amount of data regarding the relationship between CAD severity, serum testosterone, and lipid indices, especially in the northeastern region of India.

**Aim:** To determine the relationship between serum testosterone and atherogenic indices as independent risk factors for the severity of CAD.

**Materials and Methods:** This cross-sectional study was conducted in the Department of Biochemistry in collaboration with the Department of Cardiology at the Regional Institute of Medical Sciences, Imphal, Manipur, India, from January 2021 to October 2022, consisting of 70 male patients with CAD who underwent coronary angiography and 70 male patients without CAD. Serum total and free Testosterone (TT and fT), Total Cholesterol (TC), Triglycerides (TG), High-density Lipoprotein (HDL), and Low-density Lipoprotein (LDL) were assessed. Atherogenic indices, including the Atherogenic Index of Plasma (AIP), Atherogenic Index (AI), and Castelli Risk Indices I and II (CRI-I and II), as well as the Triglyceride Glucose Index (TyG), were calculated using conventional lipid parameters and glucose, respectively. Binary logistic regression analysis was performed to examine the association of the atherogenic indices and testosterone with the severity of CAD.

**Results:** The mean age was found to be 63.4±11.8 years in cases and 60.8±9.1 years in controls. The median (interquartile range) of AI was 5.03 (4.2, 5.9) vs 3.04 (2.2, 3.6), p<0.001; AIP was 0.39 (0.36, 0.44) vs 0.14 (0.006, 0.24), p<0.001; CRI-I was 6.03 (5.22, 6.91) vs 4.04 (3.2, 4.61), p<0.001; CRI-II was 3.91 (3.3, 4.7) vs 2.31 (1.6, 2.78), p<0.001; and the TyG index was 4.84 (4.68, 4.96) vs 3.82 (3.7, 3.9), p<0.001. These values were significantly higher in the CAD group compared to the non CAD group. Total Testosterone (TT) was 2.05±1.1 ng/mL vs 4.93±0.65 ng/mL, p<0.001, and fT was (3.6±2.6 vs 15.7±4.7, p<0.001) were significantly lower in cases compared to controls. The Spearman's correlation analysis showed that AI (r=0.446, p<0.001), AIP (r=0.518, p<0.001), CRI-I (r=0.446, p<0.001), CRI-II (r=0.406, p=0.001), TGL/HDL-C (r=0.502, p<0.001), and the TyG index (r=0.305, p<0.010) were positively correlated with the Gensini score. The binary logistic regression analysis indicated that AI (OR: 3.08, 95% CI: 1.70-5.57, p<0.001), AIP (OR: 2.54, 95% CI: 1.84-3.78, p<0.001), CRI-I (OR: 3.07, 95% CI: 1.65-5.57, p<0.001), CRI-II (OR: 3.17, 95% CI: 1.64-6.10, p<0.001), and TyG (OR: 1.7, 95% CI: 1.01-1.98, p=0.009) were independent risk predictors of the severity of CAD after adjustment for confounders. Additionally, TT (OR: 1.417, CI: 1.24-1.70) and fT (OR: 1.67, CI: 1.12-1.98) were also found to be independent risk predictors of the severity of CAD.

**Conclusion:** The AI, AIP, CRI-I, CRI-II, TyG, TT, and fT were independent predictors of the severity of CAD and could serve as potential biomarkers for CAD risk assessment. To specifically explain the diagnostic use of these novel indices in the early diagnosis of ASCVDs and CAD incidence, long-term prospective cohort surveys must be designed.


**Keywords:** Atherogenic index of plasma, Castelli risk, Triglyceride glucose index

## INTRODUCTION

According to the World Health Federation (WHF) report of 2023, CVD mortality has risen worldwide from 12.1 million in 1990 to 20.5 million in 2021. Heart attacks and strokes account for more than four out of five CVD deaths, and one-third of these deaths occur prematurely in people under 70 years of age [1]. CAD is one of the most common cardiovascular disorders and poses a significant risk in both developed and developing nations. Atherosclerosis, the leading cause of CAD, is a complex, inflammatory, fibroproliferative response that develops due to the accumulation of atherogenic lipoproteins in the arterial intima. Atherogenic dyslipidaemia is also associated with the pathogenesis of endothelial dysfunction and microvascular coronary dysfunction [2]. High plasma levels of LDL, TC and TG, along with low levels of HDL, play a major role in the genesis of atherosclerosis [3-5]. Reducing LDL-C is the primary target in treating and preventing atherosclerotic CVD [6]. However, despite the reduction in LDL-C levels in the recommended targets, CVD risk persists. This necessitates the use of new CVD risk markers that utilise composite lipid indices to better reflect lipoprotein metabolism. Currently, AIP, CRI-I, CRI-II and TyG are used as better prognostic indicators of CAD risk, surpassing traditional single lipid parameters [7,8].

According to the Massachusetts Male Ageing Study, testosterone levels peak at the age of 30 years and thereafter decline by 1 to 2% annually [9]. It should be noted that a decline in Testosterone (T) concentration is associated with a heightened pro-inflammatory status after the fifth or sixth decade of life [10,11]. It has been demonstrated that androgens modulate the inflammatory response by inhibiting the production of pro-inflammatory leukotrienes, lowering pro-inflammatory mediators, and raising anti-inflammatory cytokines, resulting in a state of decreased inflammation [12-14]. This finding sparked curiosity about the relationship between low testosterone levels and cardiovascular risk. Additionally, evidence from various epidemiological studies indicates that men have a higher risk of CAD than women; hence, author assumed that sex hormones might play an important role in its development [15]. While the cardioprotective effects of oestrogen have been well established, the effect of testosterone is less documented [16]. However, to present knowledge, there is a scarcity of studies regarding the relationship between serum testosterone, lipid profile, and CAD in the northeastern region of India. Early identification of patients with atherosclerosis who are prone to develop CAD is of great importance for preventing its progression. The ratios of atherogenic indices can provide an extensive overview of an individual's balance between their atherogenic and anti-atherogenic potentials [17-19]. Hence, to fill this knowledge gap, the present cross-sectional study has been conducted to explore the association of atherogenic indices and testosterone with the severity of CAD.

## MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Biochemistry in collaboration with the Department of Cardiology at the Regional Institute of Medical Sciences, Imphal, from January 2021 to October 2022.

**Sample size calculation:** The sample size was calculated using the formula:

$$n=\frac{(u+v)^2\,(s_1^2+s_2^2)}{(m_1-m_2)^2},$$

Where: n=sample size, u=1.645 (with a power of 95%), v=2.58 (for a confidence level of 99%), $s_1$=Standard deviation of serum fT levels in normal subjects, $s_2$=Standard deviation of serum fT levels in CAD subjects, $m_1$=Mean of serum fT levels in normal subjects, m2=Mean of serum fT levels in CAD subjects.

Taking, $m_1$=10.44, $m_2$=7.22, $s_1$=2.75 and $s_2$=3.01 from a study conducted by Gururani K et al., [20]:

$$n=\frac{(1.645+2.58)^2(2.75^2+3.01^2)}{(10.44-7.12)^2}$$
$$\cong 70$$

The study consisted of 140 male patients aged 40 years and above, out of which 70 were without CAD and the remaining 70 were angiographically documented CAD patients. Ethical approval for the study was obtained from the Research Ethics Board, Institutional Ethics Committee (IEC), Regional Institute of Medical Sciences, Imphal (Ref no.- A/206/REB-Comm (SP)/RIMS/2015/676/17/2020). All patients signed informed consent forms.

**Inclusion criteria:** Only male CAD patients aged 40 years and above who had not yet received the lipid lowering medications were included in present study.

**Exclusion criteria:** Patients were excluded from the study if, they had a previous history of revascularisation procedures, malignancy, chronic illness, inflammatory diseases, if, they had used lipid-lowering drugs, or if, they were under hormone replacement therapy.

### Study Procedure

The CAD was defined as ≥50% stenosis of at least one epicardial major coronary artery (>2 mm in diameter), assessed by coronary angiography according to the 2012 American College of Dentistry (ACC)/American Heart Association (AHA) guidelines [21]. Diabetes mellitus was defined as a fasting blood glucose level ≥126 mg/dL or a known diagnosis of diabetes mellitus [22]. Smoking status was reported as positive for current smokers and for those who had quit smoking within the past year with a smoking history of >10 pack-years.

**Coronary angiography and gensini score group:** Coronary angiography was performed by an experienced interventional cardiovascular physician, and the results of the angiography were assessed using the Gensini score assessment system. The Gensini score is a comprehensive measure that determines the magnitude of coronary atherosclerotic disease burden. Each lesion score is multiplied by a factor that takes into account the importance of the lesion's position in the coronary circulation: 5 for the left main coronary artery, 2.5 for the proximal segment of the left anterior descending coronary artery, 2.5 for the proximal segment of the circumflex artery, 1.5 for the mid-segment of the left anterior descending coronary artery, 1.0 for the right coronary artery, the distal segment of the left anterior descending coronary artery, the posterolateral artery, and the obtuse marginal artery, and 0.5 for other segments. Luminal stenoses of 25%, 50%, 75%, 90%, 99%, and total occlusion are scored as 1, 2, 4, 8, 16, and 32, respectively. The Gensini score is calculated as the sum of the scores for all the coronary arteries. Finally, the Gensini score was calculated by summing the individual coronary segment scores [23,24]. In the present study, using a median Gensini score value of 31, patients were grouped as follows: Group I (Gensini score <31) and Group II (Gensini score ≥31).

**Blood sample collection and laboratory methods:** After an overnight fast of atleast 12 hours, venous blood samples were collected from the forearm of each participant. Serum was collected by centrifugation for five minutes and then stored at -80°C until measurement. Serum total and free testosterone were measured by competitive Enzyme-linked Immunosorbent Assay (ELISA) [25] using the testosterone Enzyme Immunoassay (EIA) kit for quantitative determination obtained from Calbiotech Inc., bearing Catalogue numbers: TE373S and FT178S, respectively. Serum lipids and fasting blood glucose were measured with an automatic biochemical analyser (Beckman Coulter AU700, USA). Serum lipids were measured by the enzymatic method, and fasting blood glucose was measured by the enzymatic UV (hexokinase method). As defined by the Indian Heart Association, serum lipids were classified as follows: (1) TC: normal: <200 mg/dL, high: >200 mg/dL; (2) TG: normal: <150 mg/dL, borderline: 150-200 mg/dL, high: >200 mg/dL; (3) LDL-C: normal: <100 mg/dL, near optimal: 100-129 mg/dL, borderline high: 130-159 mg/dL, high risk: >160 mg/dL; (4) HDL-C: normal: >40 mg/dL, low HDL-C: <40 mg/dL.

The AIP, AI, CRI-I, CRI-II and TyGI were expressed in mmol/L and calculated by the following formulas: Non HDL-C=TC-HDL-C, $AIP=\log(\frac{TG}{HDL\text{-}C})$, $AI=\frac{non\text{-}HDL\text{-}C}{HDL\text{-}C}$, $LCI=\frac{TC\times TG\times LDL}{HDL\text{-}C}$, Castelli risk index-I=$\frac{TC}{HDL\text{-}C}$, Castelli risk index-II=$\frac{LDL\text{-}C}{HDL\text{-}C}$ and $TyGI=\log(\frac{TG\times FBG}{2})$ [26,27].

## STATISTICAL ANALYSIS

The statistical analysis was conducted using IBM Statistical Packages for Social Sciences (SPSS) version 26.0 for Windows. Continuous variables were presented as mean±Standard Deviation (SD) (if, normally distributed) and were compared using Student's t-test. If, the variables were not normally distributed, they were expressed as median (interquartile ranges). Categorical variables were expressed as percentages and compared using the Chi-square test. Spearman's coefficient analysis was performed to evaluate the

correlation between biochemical parameters and the Gensini score. Binary logistic regression analysis was conducted using Gensini score as the dependent variable. The results were evaluated within a 95% Confidence Interval (CI) and at a significance level of a two-sided p-value less than 0.05.

## RESULTS

The study included a total of 140 male participants aged 40 years and above. The participants consisted of 70 CAD patients with a mean age of 63.4±11.8 years and 70 age-matched controls with a mean age of 60.8±9.1 years. The mean Gensini score of the CAD patients was 32.45±12.41. There was no significant difference observed in the age distribution between the CAD and control groups. The study showed that Body Mass Index (BMI), Fasting Blood Sugar (FBS), TC, TGL, AI, AIP, CRI-I, CRI-II, TGL/HDL-C, and the TyG index were significantly higher in the CAD group than non CAD group. Patients in the CAD group had significantly lower levels of HDL, TT, and fT [Table/Fig-1].

| Parameters | Non CAD group (n=70) | CAD group (n=70) | p-value |
|---|---|---|---|
| Age (years) | 60.8±9.1 | 63.4±11.8 | 0.149 |
| BMI (kg/m$^2$) | 21.4±3.4 | 29.3±3.4 | 0.001 |
| Smoking n (%) | 42 (60%) | 47 (67.1%) | 0.483 |
| Hypertension n (%) | 43 (61.4%) | 48 (68.6%) | 0.479 |
| Diabetes n (%) | 32 (45.7%) | 38 (54.3%) | 0.310 |
| FBS (mg/dL) | 99 (94.7, 110.0) | 104 (94.50, 126.0) | 0.04 |
| TC (mg/dL) | 164 (130, 182) | 200 (179, 209) | <0.001 |
| TGL (mg/dL) | 134 (110, 163) | 180 (150, 200) | <0.001 |
| LDL cholesterol (mg/dL) | 93.5 (64.5, 141.1) | 130 (115, 141) | <0.001 |
| HDL cholesterol (mg/dL) | 41 (38, 42) | 35 (30, 36) | <0.001 |
| AI | 3.04 (2.2, 3.6) | 5.03 (4.2, 5.9) | <0.001 |
| AIP | 0.14 (0.06, 0.24) | 0.39 (0.36, 0.44) | <0.001 |
| CRI-I | 4.04 (3.2, 4.61) | 6.03 (5.22, 6.91) | <0.001 |
| CRI-II | 2.31 (1.6, 2.78) | 3.91 (3.3, 4.7) | <0.001 |
| TGL/HDL-C | 3.27 (2.7, 4.1) | 5.56 (4.54, 6.31) | <0.001 |
| TyG index | 3.82 (3.7, 3.9) | 4.84 (4.68, 4.96) | <0.001 |
| TT (ng/mL) | 4.93±0.65 | 2.05±1.1 | <0.001 |
| fT (pg/mL) | 15.7±4.7 | 3.6±2.6 | <0.001 |

**[Table/Fig-1]:** Basic characteristics between non CAD and CAD groups (N=140).
**Student's t-test
TC: Total cholesterol (mg/dL); TGL: Triglyceride (mg/dL); HDL cholesterol (mg/dL): High density lipoprotein cholesterol; LDL cholesterol (mg/dL): Low density lipoprotein cholesterol; AI: Atherogenic index; AIP: Atherogenic index of plasma; CRI-I: Catelli risk index I; CRI-II: Catelli risk index II; TyG index: Triglyceride glucose index; TT: Total testosterone; fT: Free testosterone

The TC, LDL-C, and the Gensini score had a significant negative correlation with TT, while fT had a significant negative correlation with TC, TGL, LDL-C, AI, AIP, CRI-I, TGL/HDL, and the Gensini score. It further indicated that both fT and TT had a significant negative correlation with a higher Gensini score. It also demonstrated that fT had a significant positive correlation with HDL-C has been depicted in [Table/Fig-2].

As shown in [Table/Fig-3], TC, TGL, LDL-C, AI, AIP, CRI-I, CRI-II, TGL/HDL-C, and the TyG index were positively correlated with the Gensini score, whereas HDL, TT, and fT were negatively correlated with the severity of CAD. [Table/Fig-4] showed that AI, AIP, CRI-I, CRI-II, TGL/HDL-C, and the TyG index were positively associated with an increased risk of CAD severity (p<0.05). Furthermore, TT (OR: 1.41, CI: 1.24-1.70) and fT (OR: 1.67, CI: 1.12-1.98) were positively associated with CAD severity.

| Parameters | Total Testosterone (TT) | | Free Testosterone (fT) | |
|---|---|---|---|---|
| | Spearman's r | p-value | Spearman's r | p-value |
| TC (mg/dL) | -0.337 | 0.004 | -0.495 | <0.001 |
| TGL (mg/dL) | -0.252 | 0.035 | -0.447 | 0.003 |
| LDL-C (mg/dL) | -0.266 | 0.026 | -0.437 | <0.001 |
| HDL-C (mg/dL) | 0.060 | 0.623 | 0.345 | 0.003 |
| AI | -0.218 | 0.069 | -0.474 | <0.001 |
| AIP | -0.212 | 0.079 | -0.389 | <0.001 |
| CRI-I | -0.218 | 0.069 | -0.474 | <0.001 |
| CRI-II | -0.206 | 0.088 | -0.436 | <0.001 |
| TGL/HDL-C | -0.204 | 0.090 | -0.387 | <0.001 |
| TyG index | -0.114 | 0.347 | -0.077 | 0.527 |
| Gensini score | -0.500 | <0.001 | -0.675 | <0.001 |
| Group-I (Gensini score <31) | 0.087 | 0.626 | 0.230 | 0.19 |
| Group-II (Gensini score ≥31) | -0.584 | <0.001 | -0.504 | 0.002 |

**[Table/Fig-2]:** Correlation of total and free Testosterone (fT) with the clinical parameters.
**Spearman's correlation coefficient

| Parameters | Spearman's r | p-value |
|---|---|---|
| TC | 0.522 | <0.001 |
| TGL | 0.507 | <0.001 |
| LDL-C | 0.441 | <0.001 |
| HDL-C | -0.295 | 0.013 |
| AI | 0.446 | <0.001 |
| AIP | 0.518 | <0.001 |
| CRI-I | 0.446 | <0.001 |
| CRI-II | 0.406 | 0.001 |
| TGL/HDL-C | 0.502 | <0.001 |
| TyG index | 0.305 | 0.010 |
| TT | -0.500 | <0.001 |
| fT | -0.675 | <0.001 |

**[Table/Fig-3]:** Correlation of Gensini score with the risk factors of CAD.
**Spearman's correlation coefficient

| Parameters | OR (95% CI) | p-value |
|---|---|---|
| TC | 1.08 (1.04-1.12) | <0.001 |
| TGL | 1.05 (1.02-1.07) | <0.001 |
| LDL-C | 1.05 (1.02-1.09) | <0.001 |
| HDL-C | 0.85 (0.74-0.96) | 0.010 |
| AI | 3.08 (1.70-5.57) | <0.001 |
| AIP | 2.45 (1.84-3.78) | <0.001 |
| CRI-I | 3.07 (1.65-5.57) | <0.001 |
| CRI-II | 3.17 (1.64-6.10) | <0.001 |
| TGL/HDL-C | 1.21 (1.02-1.76) | 0.048 |
| TyG Index | 1.7 (1.01-1.98) | 0.009 |
| TT | 1.41 (1.24-1.70) | <0.001 |
| fT | 1.67 (1.12-1.98) | <0.001 |

**[Table/Fig-4]:** Binary logistic regression analysis with the severity of CAD.

## DISCUSSION

Atherosclerosis develops slowly over a lifetime, taking decades for the clinical consequences of ASCVD, such as peripheral, cerebral, or cardiac ischaemic syndrome, to manifest. Dyslipidaemia, a traditional cardiovascular risk factor, leads to lipid deposition on the arterial wall, which aggravates the process of atherosclerosis and worsens CAD [28]. TC, TGL LDL levels were significantly higher in the CAD group, while HDL was significantly lower when compared with the control group. These findings were consistent with the study conducted by Adissu B et al., which included 269 participants and showed that more than 75% of cardiac patients had at least one form of dyslipidaemia [29]. Low HDL cholesterol and high TG concentrations have been implicated as possible independent predictors of CVD [30]. The present study demonstrated that the AI,

AIP, CRI-I, CRI-II, TGL/HDL and TyG index were positively correlated with the severity of CAD. In a recent study by Wang L et al., which included 2,253 patients with CAD and 1,347 non CAD patients, it was revealed that AIP, as a biomarker, might assist in the prevention of CAD in the Chinese population [31]. Castelli WP et al., introduced CRI-I (TC/HDL-C) and CRI-II (LDL/HDL) as strong predictors of CAD [32]. In a 17-year follow-up cohort study, Calling S et al., reported a strong association between increasing TC/HDL-C and acute myocardial infarction, with the lowest Hazard Ratio (HR=1) in women with a ratio of ≤3.5 [33]. Sun T et al., reported that an increasing LDL/HDL ratio is associated with an increasing degree of coronary vascular stenosis and a higher Gensini score [34]. The TyG index is considered a dependable surrogate marker of insulin resistance [35,36]. Wang X et al., demonstrated that an increased TyG index was correlated with a higher risk of multi-vessel CAD [37]. Total and fT were negatively correlated with the severity of CAD, consistent with the findings of Gururani K et al., [20]. Sex hormones are shown to regulate lipoprotein metabolism and likely influence the development of CAD [38]. Low testosterone levels were responsible for low activity of lipoprotein lipase and a reduction in HDL cholesterol [39].

The present study demonstrated that AI, AIP, CRI-I, CRI-II, the TyG index, TT, and fT are independent risk predictors for the severity of CAD, which is consistent with the findings of Mahdavi-Roshan M et al., and Kato Y et al., [40,41]. LDL-C oxidation and structural modification increase the permeability of endothelial cells, which involves the expression of adhesion molecules, chemotactic proteins, and growth factors for monocyte-macrophages [42-44]. Previous studies have demonstrated that small dense LDL (sdLDL) is a subfraction of LDL particles that are easily oxidised and incorporated into the arterial wall, leading to atherosclerosis [45,46]. It has been reported that sdLDL can remain in circulation longer and has less affinity for LDL receptors [47]. As reported in previous studies of myocardial infarction and angiographically documented coronary disease, small dense LDL particles (specifically LDL-III) are associated with approximately a three-fold increased risk of CAD [48-51]. Nevertheless, due to the test's complexity and expense, measuring sdLDL is unlikely to be useful in everyday clinical practice. Hence, authors need to search for a simple method to indirectly measure LDL particle size.

In addition, HDL has anti-oxidative and anti-inflammatory properties by modulating endothelial homeostasis and anti-thrombus effects through diminishing platelet aggregation and adhesion responses. TG induces atherosclerosis via the production of pro-inflammatory cytokines, coagulation factors, and fibrinogen. It also increases the risk of CAD by increasing the LDL levels, decreasing HDL levels, disrupting the function of artery walls, and activating thrombogenic factors and plasminogen activators [27]. Considering the mechanisms and functions of TG and HDL-C in the pathogenesis of atherosclerosis, AIP has been considered to be associated with CAD. It is also regarded as an indirect indicator of sdLDL, as it is negatively correlated with LDL particle diameter [34].

### Limitation(s)

This study had several limitations. Firstly, it is a single-centre cross-sectional study with a limited number of participants, which hampered present ability to establish a firm causal relationship between lipid indices, testosterone, and CAD. Secondly, the study included only Northeast Indian males aged 40 years and above; hence, the present findings should be generalised to other populations with caution. Thirdly, the optimal diagnostic thresholds for the indices were not established, and further large-scale clinical studies are needed to establish these thresholds. Furthermore, authors agreed that the assessment of oxidised LDL and apolipoproteins, as well as the identification of anti-inflammatory markers, would support present findings.

## CONCLUSION(S)

Higher levels of AI, AIP, CRI-I, CRI-II, and TyG index, along with lower total and fT levels, were independently associated with the severity of CAD. These lipid indices, along with free and TT levels, might be superior to traditional lipid parameters. Additionally, these lipid indices can be easily calculated from routine lipid profiles and are readily available for use in clinical practice. Hence, they may provide additional support for managing CAD and offer a more accurate and comprehensive estimation of CAD risk compared to traditional lipid parameters. To specifically explain the diagnostic use of such novel indices in the early diagnosis of atherosclerotic CVDs and CAD incidence, long-term prospective cohort surveys must be designed.

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