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RESEARCH

The relationship between atherogenic indices and type 1 diabetes mellitus

Aterojenik indeksler ile tip 1 diyabetes mellitus arasındaki ilişki

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Abstract

Purpose: The aim of this study was to analyze the relationship between atherogenic indices and type 1 diabetes mellitus (T1DM) and to evaluate their potential for predicting cardiovascular risk.

Materials and Methods: This retrospective cross-sectional analysis included a total of 405 participants, comprising 205 individuals with T1DM and 200 healthy controls. Several atherogenic indices—namely the Atherogenic Index of Plasma (AIP), Castelli Risk Indices I and II (CRI-I and CRI-II), the Atherogenic Coefficient (AC), and non–high-density lipoprotein cholesterol (NHC)—were calculated and compared between the study groups. Cardiovascular risk stratification was performed based on AIP, and the diagnostic performance of the indices was assessed using receiver operating characteristic (ROC) curve analysis.

Results: Patients with T1DM exhibited significantly higher AIP and NHC levels than controls, indicating a more atherogenic lipid profile (AIP: 0.25 ± 0.24 vs. 0.13 ± 0.19; NHC: 129.16 ± 40.32 vs. 116.91 ± 27.37 mg/dL). Among individuals at high AIP risk, triglyceride levels were markedly elevated and HDL-C levels were significantly reduced, accompanied by significant increases in CRI-I, CRI-II, AC, and NHC (TG: 140.36 ± 90.09 vs. 57.12 ± 13.23 mg/dL; HDL-C: 47.57 ± 10.76 vs. 59.70 ± 14.48 mg/dL). ROC analysis demonstrated moderate diagnostic accuracy for CRI-I and AC in the T1DM group (AUC = 0.774 for both).

Conclusion: AIP and NHC are robust and reliable indicators of cardiovascular risk in individuals with T1DM, whereas CRI-I, CRI-II, and AC provide complementary information. Their simplicity, affordability, and prognostic value support their integration into routine clinical practice for early identification of at-risk individuals and guidance of preventive strategies.

Keywords: Type 1 diabetes mellitus, atherogenic indices, cardiovascular risk, Castelli risk index.

Öz

Amaç: Bu çalışmanın amacı aterojenik indeksler ile tip 1 diyabetes mellitus (T1DM) arasındaki ilişkiyi analiz etmek ve bu indekslerin kardiyovasküler riski öngörme potansiyelini değerlendirmektir.

Gereç ve Yöntem: Retrospektif ve kesitsel tasarıma sahip bu çalışmaya, 205'i T1DM hastası ve 200'ü sağlıklı kontrol olmak üzere toplam 405 katılımcı dahil edildi. Plazma Aterojenik İndeksi (AIP), Castelli Risk İndeksleri I ve II (CRI-I ve CRI-II), Aterojenik Katsayı (AC) ve non–yüksek yoğunluklu lipoprotein kolesterol (NHC) hesaplanarak gruplar arasında karşılaştırıldı. Kardiyovasküler risk sınıflandırması AIP'ye göre yapıldı ve indekslerin tanısal performansı alıcı işletim karakteristiği (ROC) eğrisi analizi ile değerlendirildi.

Bulgular: T1DM hastalarında, kontrol grubuna kıyasla AIP ve NHC düzeyleri anlamlı olarak daha yüksek bulundu ve bu durum daha aterojenik bir lipid profilini yansıttı (AIP: 0,25 ± 0,24 vs, 0,13 ± 0,19; NHC: 129,16 ± 40,32 vs, 116,91 ± 27,37 mg/dL). Yüksek AIP risk grubundaki bireylerde trigliserid düzeyleri belirgin olarak artmış, HDL-C düzeyleri ise anlamlı şekilde azalmış olup; CRI-I, CRI-II, AC ve NHC değerlerinde de anlamlı artışlar saptanmıştır (TG: 140,36 ± 90,09 vs, 57,12 ± 13,23 mg/dL; HDL-C: 47,57 ± 10,76 vs 59,70 ± 14,48 mg/dL). ROC analizi, T1DM grubunda CRI-I ve AC için orta düzeyde tanısal doğruluk olduğunu göstermiştir (her ikisi için AUC = 0,774).

Sonuç: Plazma Aterojenik İndeksi ve non-HDL kolesterol, T1DM hastalarında kardiyovasküler riski öngörmede güçlü ve güvenilir göstergelerdir. CRI-I, CRI-II ve AC ise tamamlayıcı bilgiler sunmaktadır. Bu indekslerin kolay hesaplanabilir, düşük maliyetli ve prognostik açıdan değerli olması, yüksek riskli bireylerin erken tanımlanması ve önleyici stratejilerin yönlendirilmesi açısından klinik pratiğe entegrasyonunu desteklemektedir.

Anahtar kelimeler: Tip 1 diyabetes mellitus, aterojenik indeksler, kardiyovasküler risk, Castelli risk indeksi.

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) ranks among the most prevalent chronic autoimmune diseases, predominantly affecting children and adolescents, although it can occur at any age[1]. It results from autoimmune destruction of pancreatic β-cells in the islets of Langerhans, ultimately leading to absolute insulin deficiency and lifelong dependence on exogenous insulin therapy[2]. T1DM accounts for approximately 5–10% of all diabetes cases and affects around 8.4 million individuals worldwide[3]. In recent years, the global incidence of T1DM has risen markedly, placing a substantial burden on both public health and healthcare systems[3].

Recent observational studies have demonstrated a significantly increased risk of cardiovascular diseases (CVDs) including heart failure (HF), coronary artery disease (CAD), atrial fibrillation (AF), myocardial infarction (MI), atherosclerosis, and stroke among individuals with T1DM[4,9]. However, the causal relationship between T1DM and CVDs remains uncertain, largely due to residual confounding and reverse causality inherent in observational study designs. Clarifying these associations is essential for developing effective preventive strategies, identifying at-risk individuals at an early stage, and improving long-term disease management. Dyslipidemia is commonly observed in individuals with T1DM and is typically characterized by elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), along with reduced levels of high-density lipoprotein cholesterol (HDL-C)[10]. These lipid abnormalities contribute to the development of atherosclerosis, thereby increasing long-term cardiovascular (CV) risk[11]. Lipid parameters, together with various indices derived from them, may serve as valuable tools for identifying the risk of CVDs and CAD[12]. In this context, several lipid-based ratios collectively known as atherogenic indices have been proposed to enhance the predictive accuracy of conventional lipid profiles[13].

Atherogenic indices such as the Atherogenic Index of Plasma (AIP), Castelli Risk Index I and II (CRI-I and CRI-II), the Atherogenic Coefficient (AC), and non–high-density lipoprotein cholesterol (NHC) have gained attention as surrogate markers of CV risk[14]. CRI-I and CRI-II, derived from combinations of TC, LDL-C, and HDL-C, are particularly useful for assessing CV risk even when individual lipid levels fall within normal ranges[15]. AIP, calculated as the logarithmic ratio of TG to HDL-C, has been positively associated with CAD, while AC captures both atherogenic and anti-atherogenic lipoproteins, providing a more comprehensive assessment of atherosclerotic burden[16].

Beyond quantitative lipid abnormalities, qualitative alterations in HDL particles have gained increasing attention. Chronic hyperglycemia, oxidative stress, and low-grade inflammation in T1DM can impair HDL structure and function a phenomenon known as dysfunctional HDL[17]. Unlike physiologically protective HDL, dysfunctional HDL exhibits reduced cholesterol efflux capacity, diminished antioxidative and anti-inflammatory activity, and altered proteomic and lipidomic composition. These impairments may contribute to residual cardiovascular risk even when HDL-C levels appear normal or elevated. Understanding this dysfunctional HDL phenotype is crucial, as atherogenic indices (AIP, CRI-I, CRI-II, AC, and NHC) may reflect functional HDL impairment rather than HDL concentration alone[17].

Numerous investigations have examined the associations between atherogenic indices and chronic conditions such as metabolic syndrome, chronic kidney disease, and type 2 diabetes mellitus (T2DM)[18-20]. In contrast, evidence specifically focusing on the relationship between these indices and T1DM remains limited and inconclusive. This gap in the current literature highlights the need for further studies to evaluate the clinical relevance of atherogenic indices in T1DM populations. It is hypothesized that AIP and NHC may outperform conventional lipid markers in estimating CV risk among individuals with T1DM. Accordingly, this study was conducted to explore the relationship between atherogenic indices and T1DM. More specifically, the aim was to determine whether these indices exhibit statistically meaningful differences in individuals with T1DM and to examine their predictive relevance for CV risk within this population.

MATERIALS AND METHODS

Sample

This study included patients with type 1 diabetes mellitus (T1DM) aged 18–45 years, along with age-matched healthy controls without additional medical

conditions. The diagnosis of T1DM was confirmed according to the 2024 American Diabetes Association (ADA) criteria, including onset before the age of 35 years with classical symptoms (polyuria, polydipsia, polyphagia, and weight loss) and/or diabetic ketoacidosis; fasting plasma glucose (FPG) levels ≥126 mg/dL; plasma glucose ≥200 mg/dL measured two hours after an oral glucose tolerance test (OGTT); or a random plasma glucose concentration ≥200 mg/dL, in addition to the presence of pancreatic autoantibodies (e.g., glutamic acid decarboxylase, islet antigen-2, zinc transporter, or islet cell antibodies), C-peptide levels <0.6 ng/mL, and glycated hemoglobin A1c (HbA1c) ≥6.5%[21].

Inclusion criteria were as follows:

1. Individuals aged 18–45 years with a confirmed diagnosis of T1DM;
2. Healthy individuals aged 18–45 years without known chronic diseases.

Exclusion criteria included:

1. Type 2 diabetes mellitus (T2DM);
2. Gestational diabetes mellitus (GDM);
3. Systemic inflammatory or autoimmune diseases;
4. Active infections or acute inflammatory conditions;
5. Hematological disorders;
6. History of malignancy;
7. Use of medications that could affect lipid levels.

For comparative evaluation, participants were classified into two groups: the T1DM group (patients diagnosed with T1DM) and the control group (healthy individuals without T1DM or any other known chronic or systemic disease). Data from individuals with T1DM and healthy controls were included in the comparative analyses.

Given the retrospective cross-sectional design of the study, the sample size was determined by including all consecutive eligible individuals with complete data who met the inclusion and exclusion criteria during the study period. Initially, 618 individuals were assessed for eligibility (308 patients with T1DM and 310 healthy controls). Of these, 129 individuals were excluded because of incomplete clinical or laboratory data (62 with T1DM and 67 controls), leaving 489 individuals for further evaluation (246 with T1DM and 243 controls). Subsequently, 84 individuals were excluded based on the predefined exclusion criteria, including age below the specified study range (n = 4), T2DM (n = 2), GDM (n = 3), systemic inflammatory or autoimmune diseases (n = 13), active infections or acute inflammation (n = 41), hematological disorders (n = 3), history of malignancy (n = 2), and use of medications that could affect lipid levels (n = 16). After these exclusions, the final study population consisted of 405 participants, including 205 patients with T1DM and 200 healthy controls.

Procedure

Ethical approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Fethi Sekin City Hospital (meeting date: 8 May 2025; decision no.: 2025/9-16).

The study, designed using a retrospective cross-sectional methodology, was conducted at the Internal Medicine Outpatient Clinics of Elazığ Fethi Sekin City Hospital between April 2022 and April 2025. Patient records and laboratory results were retrospectively reviewed. All clinical evaluations and routine patient management procedures were performed in accordance with the institutional clinical practice standards of the hospital.

Clinical assessments and patient selection were carried out by internal medicine specialists based on electronic medical records and outpatient clinic files. Data extraction and verification were independently reviewed by the researchers prior to statistical analysis.

Laboratory measurements were obtained from the hospital's central biochemistry laboratory, where all analyses are routinely performed by certified laboratory technicians using standardized and regularly calibrated automated analyzers in accordance with institutional quality control procedures. Records with missing, inconsistent, or implausible values were excluded to ensure data reliability. All datasets were anonymized before analysis.

Laboratory analysis

As this was a retrospective study, data were obtained from patient records and the hospital information system. Demographic characteristics (age and sex) and laboratory parameters—including complete

blood count (CBC) and biochemical measurements—were retrieved for analysis.

NHC was calculated as TC minus HDL-C[22].

Atherogenic indices were computed based on lipid profile parameters as follows:

1) AIP = log (TG / HDL-C)[22-23];
2) CRI-I = TC / HDL-C[22-23];
3) CRI-II = LDL-C / HDL-C[22-23];
4) AC = NHC / HDL-C[22-23].

All indices were compared between groups. Cut-off values for CV risk were defined according to previous literature: AIP ≥ 0.1, CRI-I ≥ 4, CRI-II ≥ 3, AC ≥ 2, and NHC ≥ 130 mg/dL[23-24].

Statistical analysis

All statistical procedures were conducted using anonymized patient data. Statistical analyses and graphical visualizations were performed using both open-source and proprietary tools, specifically the Python programming language (version 3.11) and RStudio. The primary Python libraries used for data processing and analysis were as follows: pandas, for data frame creation and data cleaning (data management); numpy, for numerical computations and matrix-based calculations; scipy. stats, for normality testing and both parametric and non-parametric statistical tests (e.g., Mann–Whitney U test and Chi-square test); statsmodels, for advanced statistical modeling, including receiver operating characteristic (ROC) curve analysis, area under the curve (AUC) calculations, and regression modeling; matplotlib and seaborn, for data visualization and graphical presentation. All Python scripts were written manually without the use of graphical user interfaces or automated statistical wizards, thereby ensuring scientific reproducibility and transparency of the analytical workflow.

Descriptive statistics, including the arithmetic mean and standard deviation, were calculated for all continuous variables. The normality of data distributions was assessed using both the Kolmogorov–Smirnov and Shapiro–Wilk tests. When data deviated from a normal distribution, appropriate non-parametric methods were applied for statistical comparisons. Because several variables demonstrated non-normal distributions, non-parametric tests (Mann–Whitney U test and Chi-square test) were used to ensure robust comparisons. Minor differences in mean values may still achieve statistical significance owing to the rank-based sensitivity of non-parametric methods.

Group comparisons for non-normally distributed variables were performed using the Mann–Whitney U test to evaluate differences in central tendencies. This test was applied to compare atherogenic indices (e.g., CRI-I, CRI-II, and AC) between patients with T1DM and healthy controls, as well as between subgroups stratified according to AIP-defined cardiovascular risk (low vs. high). To determine whether associations between atherogenic indices and T1DM status were independent of demographic factors, age- and sex-adjusted logistic regression models were fitted for predefined high-risk classifications (AIP ≥ 0.1; CRI-I ≥ 4; CRI-II ≥ 3; AC ≥ 2; NHC ≥ 130 mg/dL; sensitivity analysis: NHC ≥ 100 mg/dL). Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Multiple comparisons were controlled using the Holm correction.

Age- and sex-adjusted logistic regression models were constructed to evaluate the association between T1DM status and predefined high-risk classifications of atherogenic indices. Age and sex were included a priori in all models based on their well-established effects on lipid metabolism and cardiovascular risk, as well as their statistically significant differences between the study groups, thereby fulfilling their role as potential confounding variables. No additional covariates were included to avoid model overfitting, given the predefined nature of the risk classifications and the study's cross-sectional design. ORs were reported with 95% CIs. To control for multiple testing across risk classifications, p-values were adjusted using the Holm method.

Associations between categorical variables across study groups were examined using the Chi-square (χ^2) test. For subgroup analyses involving low cell counts, Fisher's exact test was applied when appropriate. Results with p values < 0.05 were considered statistically significant.

ROC curve analysis was conducted to evaluate the ability of CRI-I, CRI-II, and AC to discriminate individuals at high cardiovascular risk, as defined by AIP. Estimates of AUC values and corresponding 95% confidence intervals (CIs) were calculated for each parameter. AUC values > 0.70 and confidence intervals not including 0.50 were considered indicative of meaningful discriminatory performance.

In a secondary analysis, age- and sex-adjusted ROC curves were generated for CRI-II, NHC, AC, and AIP against independent clinical outcomes (HbA1c ≥ 6.5% and C-reactive protein [CRP] ≥ 3 mg/L). The primary threshold for CRP was set at ≥3 mg/L, in accordance with established cardiovascular risk literature, and the threshold for HbA1c was defined as ≥6.5%.

RESULTS

The study included 405 participants, comprising 205 patients with T1DM and 200 non-diabetic controls. As shown in Table 1, the mean age was lower in the T1DM group (26.42 ± 6.76 years) than in the control group (27.71 ± 5.86 years; $p < 0.01$). Sex distribution also differed significantly between the groups ($p < 0.01$), with a slightly higher proportion of males in the T1DM group.

Glycemic and lipid profiles revealed marked differences between groups. Patients with T1DM exhibited significantly higher HbA1c levels compared with controls (9.18 ± 2.06 vs. 5.17 ± 0.30, $p < 0.001$). Levels of TC, LDL-C, HDL-C, and C-reactive protein (CRP) were all significantly higher in individuals with T1DM, with all comparisons yielding p values < 0.001 (Table 1).

Table 1. Comparison of demographic and clinical features between T1DM and control groups

Variable	T1DM Mean ± SD	Control Mean ± SD	P
Age (years)	26.42 ± 6.76	27.71 ± 5.86	**< 0.01a**
Gender (Male %)	53.4%	50.5%	**< 0.01a**
HBA1C (%)	9.18 ± 2.06	5.17 ± 0.30	**< 0.001a**
TG (mg/dL)	129.88 ± 100.10	114.42 ± 70.55	0.253a
LDL (mg/dL)	105.47 ± 34.35	94.02 ± 23.99	**< 0.001a**
HDL (mg/dL)	51.89 ± 14.28	48.50 ± 10.58	**< 0.001a**
TC (mg/dL)	181.05 ± 43.52	165.41 ± 29.63	**< 0.001a**
CRP (mg/L)	4.01 ± 2.95	2.62 ± 1.97	**< 0.001a**
AIP	0.25 ± 0.24	0.13 ± 0.19	**<0.001a**
CRI-I	3.39 ± 0.90	3.20 ± 0.80	0.308a
CRI-II	1.95 ± 0.64	1.87 ± 0.73	0.090a
NHC	129.16 ± 40.32	116.91 ± 27.37	**< 0.001a**
AC	2.39 ± 0.90	2.20 ± 0.80	0.116a

HbA1C = Glycated Hemoglobin A1c, CRP = C-reactive protein, TC = Total Cholesterol, TG = Triglyceride, LDL = Low-Density Lipoprotein, HDL = High-Density Lipoprotein, AIP = Atherogenic Index of Plasma, CRI = Castelli Risk Index, NHC = Non-HDL cholesterol, AC = Atherogenic Coefficient. Group comparisons were carried out with the Mann–Whitney U (MWU) test for numerical variables and the Chi-square test (χ^2) for nominal data (a: MWU; b: χ^2), based on data type and distribution.

Analysis of lipid-related indices demonstrated a pronounced increase in AIP values in the T1DM cohort, with a mean of 0.25 ± 0.24 compared with 0.13 ± 0.19 in controls ($p < 0.001$), indicating a shift toward a more atherogenic lipid profile in patients with T1DM (Table 1). Although mean values of CRI-I and CRI-II were numerically higher in the T1DM group (3.39 ± 0.90 vs. 3.20 ± 0.80 and 1.95 ± 0.64 vs. 1.87 ± 0.73, respectively), these differences did not reach statistical significance ($p > 0.05$ for both comparisons). A similar pattern was observed for AC, which showed slightly higher values in the T1DM group (2.39 ± 0.90 vs. 2.20 ± 0.80) without statistical significance ($p > 0.05$). In contrast, NHC levels were significantly higher in participants with T1DM, with a mean value of 129.16 ± 40.32 mg/dL compared with 116.91 ± 27.37 mg/dL in the control group ($p < 0.001$), supporting its potential utility as a surrogate indicator of CV risk in this population.

Age- and sex-adjusted logistic regression analyses were performed to evaluate predefined high-risk classifications (AIP ≥ 0.1; CRI-I ≥ 4; CRI-II ≥ 3; AC ≥ 2; NHC ≥ 130 mg/dL; sensitivity analysis at NHC ≥ 100 mg/dL). Odds ratios (ORs) with 95% confidence intervals (CIs) were reported, and multiple testing was controlled using the Holm

adjustment. Adjusted ORs are summarized in Table 2.

In the adjusted analyses, only NHC ≥ 130 mg/dL was significantly associated with T1DM status (OR = 2.359, 95% CI: 1.545–3.602; p < 0.001), whereas AIP, CRI-I, CRI-II, and AC did not show statistically significant associations (Table 2).

Table 2. Age and sex adjusted logistic regression

Outcome (n=405)	OR (T1DM vs Control)	95% CI (lower)	95% CI (upper)	P
AIP ≥ 0.1	0.827	0.51	1.339	0.440
CRI-I ≥ 4	1.354	0.85	2.158	0.202
CRI-II ≥ 3	1.685	0.868	3.273	0.123
AC ≥ 2	1.407	0.903	2.191	0.131
NHC ≥ 130 mg/dL	2.359	1.545	3.602	**<0.001**
NHC ≥ 100 mg/dL	1.349	0.854	2.129	0.199

Note: This table presents age- and sex-adjusted logistic regression results evaluating predefined high-risk classifications for atherogenic indices. Outcomes were coded as binary risk categories (AIP ≥0.1; CRI-I ≥4; CRI-II ≥3; AC ≥2; NHC ≥130 mg/dL; sensitivity: NHC ≥100 mg/dL). Odds ratios (ORs) compare T1DM vs. control groups. AIP = Atherogenic Index of Plasma, CRI = Castelli Risk Index, NHC = Non-HDL cholesterol, AC = Atherogenic Coefficient.

Patients were stratified into low-risk (AIP < 0.1) and high-risk (AIP ≥ 0.1) categories. As shown in Table 3, individuals in the high-risk group exhibited significantly higher TG levels (140.36 ± 90.09 vs. 57.12 ± 13.23, p < 0.001) and lower HDL levels (47.57 ± 10.76 vs. 59.70 ± 14.48, p < 0.001). The high-risk group also demonstrated significantly elevated levels of CRI-I, CRI-II, AC, and NHC, with all comparisons reaching statistical significance (p < 0.001). In contrast, LDL levels did not differ significantly between the AIP-based risk groups (p > 0.05).

Within the T1DM group (Table 4), patients classified as high AIP risk exhibited significantly higher TG, TC, CRI-I, CRI-II, AC, and NHC values (p ≤ 0.001), along with significantly lower HDL levels (p < 0.001), compared with their low-risk counterparts. No statistically significant differences in LDL levels were observed between the groups stratified by AIP risk.

The associations between elevated atherogenic indices—specifically CRI-I ≥ 4, CRI-II ≥ 3, and AC ≥ 2—and AIP-based risk categories were examined separately in the T1DM and control cohorts. Chi-square (χ^2) analysis, as detailed in Table 5, demonstrated that CRI-I ≥ 4 and AC ≥ 2 were strongly associated with high AIP risk in both groups (p < 0.001 for each). In contrast, CRI-II ≥ 3 showed a statistically significant association only within the T1DM group (p < 0.01), whereas no such association was observed in the control group (p > 0.05).

Table 3. Comparison of lipid parameters and atherogenic indices by aip-based risk classification (all patients)

Variable	Low Risk (Mean ± SD)	High Risk (Mean ± SD)	P
TG (mg/dL)	57.12 ± 13.23	140.36 ± 90.09	**< 0.001**
HDL (mg/dL)	59.70 ± 14.48	47.57 ± 10.76	**< 0.001**
LDL (mg/dL)	98.81 ± 27.53	100.08 ± 30.93	0.904
CRI-I	2.90 ± 0.52	3.77 ± 0.90	**< 0.001**
AIP	-0.02 ± 0.10	0.42 ± 0.24	**< 0.001**
CRI-II	1.71 ± 0.49	2.17 ± 0.72	**< 0.001**
AC	1.90 ± 0.52	2.77 ± 0.90	**< 0.001**
NHC	109.58 ± 30.37	126.86 ± 35.34	**< 0.001**

This table presents the comparative evaluation of cardiovascular risk-related lipid parameters and derived atherogenic indices between patients categorized based on AIP: low risk (AIP < 0.1) and high risk (AIP ≥ 0.1). TG = Triglyceride, HDL = High-Density Lipoprotein, LDL = Low-Density Lipoprotein, AIP = Atherogenic Index of Plasma, CRI = Castelli Risk Index, AC = Atherogenic Coefficient, NHC = Non-HDL cholesterol. Statistical comparisons were conducted using MWU test based on data distribution.

Table 4. Subgroup analysis within T1DM group based on AIP risk score

Variable	Low Risk (Mean ± SD)	High Risk (Mean ± SD)	P
TG (mg/dL)	57.62 ± 13.44	151.51 ± 104.61	**< 0.001**
LDL (mg/dL)	99.49 ± 28.03	107.26 ± 35.91	0.071
HDL (mg/dL)	59.77 ± 17.77	49.54 ± 12.17	**< 0.001**
TC (mg/dL)	169.53 ± 30.64	184.50 ± 46.21	**< 0.05**
AIP	-0.01 ± 0.11	0.43 ± 0.25	**< 0.001**
CRI-I	2.95 ± 0.60	3.84 ± 0.99	**< 0.001**
CRI-II	1.76 ± 0.56	2.24 ± 0.80	**< 0.001**
NHC	109.77 ± 31.94	134.97 ± 40.84	**< 0.001**
AC	1.95 ± 0.60	2.84 ± 0.99	**< 0.001**

This table shows the comparison of lipid markers and atherogenic indices within T1DM patients grouped by AIP-based cardiovascular risk level. TC = Total Cholesterol, TG = Triglyceride, LDL = Low-Density Lipoprotein, HDL = High-Density Lipoprotein, AIP = Atherogenic Index of Plasma, CRI = Castelli Risk Index, NHC = Non-HDL cholesterol, AC = Atherogenic Coefficient. Given the deviation from normality in the data distribution, the MWU test was selected for statistical comparisons.

Table 5. Chi-square results for categorical risk classifications by group

Index	Chi² (T1DM)	p (T1DM)	Chi² (Control)	p (Control)
CRI-I ≥ 4	23.638	**< 0.001**	15.111	**< 0.001**
CRI-II ≥ 3	7.493	**< 0.01**	3.222	0.073
AC ≥ 2	16.462	**< 0.001**	28.100	**< 0.001**

CRI = Castelli Risk Index AC = Atherogenic Coefficient. χ^2 test was used for comparison.

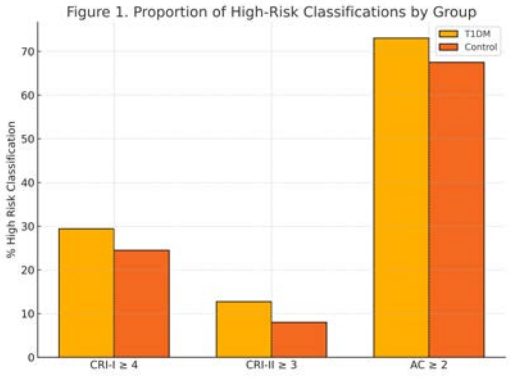


Figure 1. Proportion of high-risk classifications according to CRI-I, CRI-II, and AC thresholds in T1DM and control groups.

This bar chart illustrates the percentage of individuals classified as high-risk (CRI-I ≥ 4, CRI-II ≥ 3, and AC ≥ 2) based on AIP-defined cardiovascular risk categories. Orange bars denote the T1DM group, and red bars denote the control group. Error bars represent the 95% confidence intervals for the percentage of high-risk participants within each group. A higher proportion of individuals met high-risk criteria in the T1DM group—particularly for CRI-I and AC—indicating a more atherogenic lipid profile compared with controls. Data are expressed as percentages with 95% CIs. CRI = Castelli Risk Index; AC = Atherogenic Coefficient; AIP = Atherogenic Index of Plasma; T1DM = Type 1 Diabetes Mellitus.

Figure 1 illustrates the distribution of participants classified in the high-risk category across both groups. Notably, a greater concentration of individuals with elevated CRI-I and AC values was observed in the T1DM cohort compared with the control group.To evaluate the ability of selected atherogenic indices to predict high AIP risk, receiver operating characteristic (ROC) analysis was performed (Table 6).

AIP demonstrated perfect discrimination in both the T1DM and control groups (AUC = 1.000). In the T1DM cohort, CRI-I and AC exhibited moderate diagnostic accuracy (AUC = 0.774 for both), whereas CRI-II and NHC showed lower but acceptable performance (AUC = 0.679 and 0.677, respectively; Figure 2). Among the evaluated indices, CRI-I and AC demonstrated the strongest predictive performance, particularly in the control group (AUC = 0.906 for both).

In these secondary ROC analyses conducted using predefined clinical thresholds (HbA1c ≥ 6.5% and CRP ≥ 3 mg/L), the discriminative performance of AIP and NHC was preserved. NHC demonstrated the highest discriminative ability for identifying poor glycemic control (HbA1c ≥ 6.5%; AUC = 0.594),

whereas AIP showed the strongest performance among all indices for detecting elevated inflammatory status (CRP ≥ 3 mg/L; AUC = 0.623). Notably, AIP yielded the highest single AUC value across both analyses, while NHC remained the most consistent predictor, demonstrating statistically significant discrimination across both glycemic and inflammatory thresholds. Detailed results are presented in Table 7, Figure 3 (CRP ≥ 3 mg/L), and Figure 4 (HbA1c ≥ 6.5%).

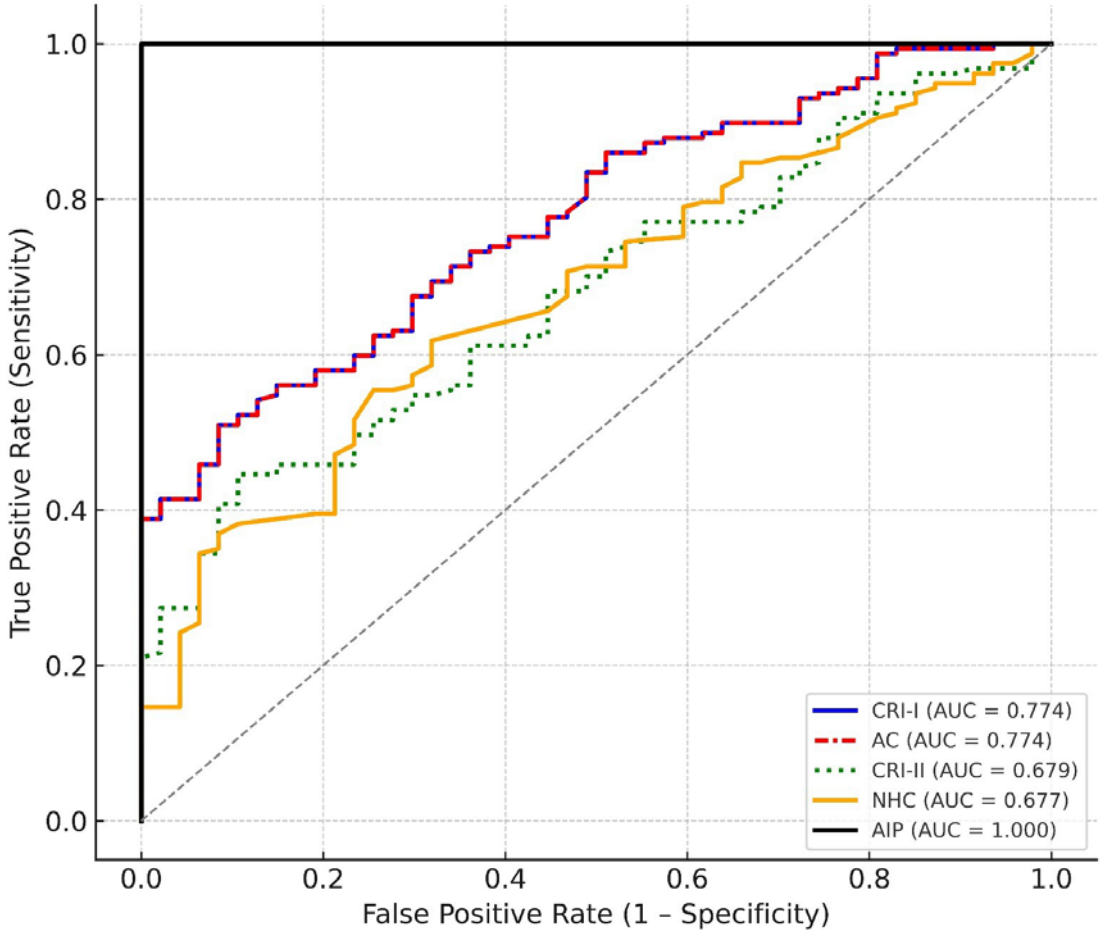


Figure 2. Receiver operating characteristic (ROC) curves of atherogenic indices for predicting high AIP-defined cardiovascular risk in T1DM patients.

This ROC analysis compares the diagnostic performance of five lipid-derived indices in distinguishing individuals with high AIP risk (AIP ≥ 0.1). AIP (black solid line) achieved perfect discrimination (AUC = 1.000), reflecting its use as the reference variable for defining risk categories. CRI-I (blue solid line) and AC (red dashed line) demonstrated moderate diagnostic accuracy (AUC = 0.774 each; 95% CI: 0.698–0.837), whereas CRI-II (green dotted line) and NHC (orange solid line) showed lower yet acceptable performance (AUC = 0.679 and 0.677, respectively). The gray diagonal dashed line represents the line of no discrimination (AUC = 0.5). Clinically, the greater AUCs of CRI-I and AC suggest their potential as auxiliary lipid ratios for cardiovascular risk estimation in T1DM. Abbreviations: AIP = Atherogenic Index of Plasma; CRI = Castelli Risk Index; AC = Atherogenic Coefficient; NHC = Non-HDL cholesterol; T1DM = Type 1 Diabetes Mellitus. Note: Because AIP itself was used to define the cardiovascular risk categories, its ROC analysis against the same classification mathematically yields a perfect AUC of 1.000; this represents a deterministic outcome rather than model overfitting or superior predictive ability.

Table 6. Diagnostic performance of atherogenic indices in predicting high AIP risk

Group	Predictor	AUC (95% CI)	p
T1DM	AIP	1.000 (1.000–1.000)	
	CRI-I	0.774 (0.698–0.837)	**<0.01**
	AC	0.774 (0.698–0.837)	**<0.01**
	CRI-II	0.679 (0.594–0.752)	**<0.01**
	NHC	0.677 (0.596–0.753)	**<0.01**
Control	AIP	1.000 (1.000–1.000)	
	CRI-I	0.906 (0.832–0.961)	**<0.01**
	AC	0.906 (0.837–0.962)	**<0.01**
	CRI-II	0.826 (0.739–0.897)	**<0.01**
	NHC	0.845 (0.767–0.908)	**<0.05**

Separate ROC analyses were applied within the T1DM and control groups to assess how well the atherogenic indices discriminated between high and low AIP risk categories. AIP showed perfect discrimination in both groups. Among the other indices, CRI-I and AC demonstrated higher diagnostic performance, particularly in the Control group. AIP = Atherogenic Index of Plasma, CRI = Castelli Risk Index, NHC = Non-HDL cholesterol, AC = Atherogenic Coefficient. Note: Because AIP itself was used to define the cardiovascular risk categories, its ROC analysis against the same classification mathematically yielded a perfect AUC of 1.000; this should not be interpreted as model overfitting.

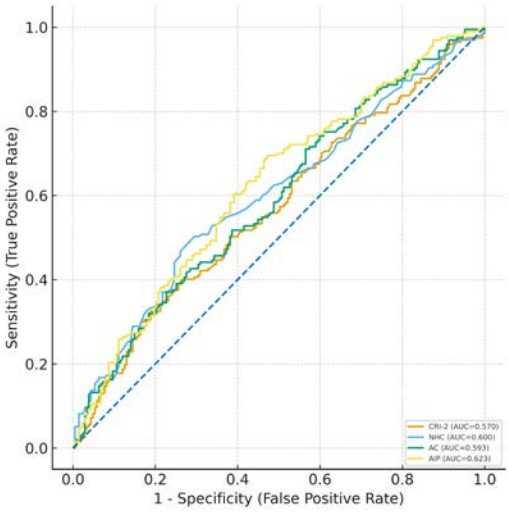


Figure 3. ROC curves of CRI-II, NHC, AC, AIP for CRP≥3 mg/L.

This figure illustrates the ROC performance of four atherogenic indices CRI-II (orange line), NHC (green-teal line), AC (light-blue line), and AIP (yellow line) in identifying participants with elevated inflammatory status defined as CRP ≥ 3 mg/L. The diagonal navy dashed line represents the reference line indicating no discriminative ability (AUC = 0.50). Among the evaluated indices, AIP and NHC demonstrated comparatively higher discriminatory performance. Corresponding AUC values with DeLong 95% confidence intervals are presented in Table 7. AIP = Atherogenic Index of Plasma; CRI = Castelli Risk Index; AC = Atherogenic Coefficient; NHC = Non-HDL cholesterol.

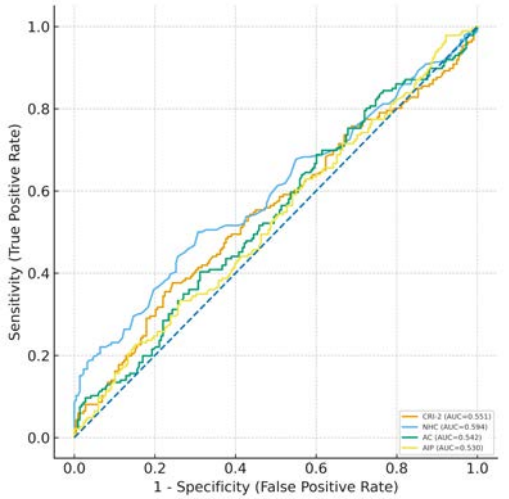


Figure 4. ROC curves of CRI-II, NHC, AC, AIP for HbA1c≥6.5%.

This figure presents the ROC curves evaluating the discriminative ability of four atherogenic indices CRI-II (orange line), NHC (green line), AC (light-blue line), and AIP (yellow line) to identify participants with poor glycemic control, defined as HbA1c ≥ 6.5%. The navy dashed diagonal line represents the reference line indicating no discriminative capacity (AUC = 0.50). Consistent with the CRP-based analysis, NHC and AC showed comparatively better discrimination at this glycemic threshold. Corresponding area under the curve (AUC) values with DeLong 95% confidence intervals are provided in Table 7. AIP = Atherogenic Index of Plasma; CRI = Castelli Risk Index; AC = Atherogenic Coefficient; NHC = Non-HDL cholesterol.

Table 7. ROC AUCs (DeLong 95% CIs) of CRI-II, NHC, AC, and AIP against independent outcomes (HbA1c≥6.5% and CRP≥3 mg/L).

Outcome	Predictor	AUC	95% CI (lower)	95% CI (upper)	p
HbA1c ≥ 6.5%	CRI-II	0.551	0.494	0.608	0.080
	NHC	0.594	0.538	0.650	<0.01
	AC	0.542	0.485	0.598	0.148
	AIP	0.530	0.473	0.586	0.300
CRP ≥ 3 mg/L	CRI-II	0.570	0.514	0.626	<0.05
	NHC	0.600	0.545	0.656	<0.001
	AC	0.593	0.538	0.648	<0.001
	AIP	0.623	0.569	0.678	<0.001

This table summarizes the discriminative performance of CRI-II, NHC, AC, and AIP for identifying participants with elevated HbA1c (≥6.5%) or elevated CRP (≥3 mg/L). Secondary ROC analyses were performed using independent clinical thresholds to avoid circularity inherent to AIP-defined categories. AUC values are presented with 95% confidence intervals and p-values. CRI = Castelli Risk Index; NHC = Non-HDL cholesterol; AC = Atherogenic Coefficient; AIP = Atherogenic Index of Plasma.

DISCUSSION

This study investigated the status of atherogenic indices (AIP, CRI-I, CRI-II, AC, and NHC) in patients with T1DM, compared these indices with those of healthy individuals, and evaluated their discriminative performance according to AIP-defined CV risk. Our findings demonstrated that, in individuals with T1DM, both AIP and NHC were markedly elevated, whereas CRI-I, CRI-II, and AC showed upward trends that did not reach statistical significance. Among individuals in the high AIP risk group, elevated TG levels, reduced HDL levels, and significant increases in other atherogenic indices were observed. ROC analyses further indicated that CRI-I and AC exhibited moderate discriminative performance, whereas AIP emerged as the strongest marker. Collectively, these results suggest that dyslipidemia and atherogenic indices play an important role in CV risk assessment in patients with T1DM and may inform future research in this field.

T1DM is frequently diagnosed during adolescence or early adulthood. Prior investigations by Rawshani et al. and Livingstone et al. emphasized that younger adults are disproportionately affected by T1DM and may experience a heightened cumulative burden of CV risk over time[25-26]. In the current study, the T1DM group exhibited a significantly younger mean age compared with the control group, which is consistent with the earlier clinical onset of the disease. Additionally, as anticipated, HbA1c values were substantially higher in the T1DM cohort ($p < 0.001$; Table 1). The markedly elevated HbA1c levels in the T1DM group indicate that poor glycemic control contributes to increased CV risk. Similarly, Lin et al. reported a positive association between HbA1c levels and CV mortality[27].

Additionally, a modest but statistically significant difference in sex distribution was observed between the groups ($p < 0.01$); however, this difference is unlikely to have influenced our lipid-related findings, as age- and sex-adjusted models yielded comparable results.

Because both age and sex differed significantly between the study groups variables known to influence lipid metabolism and atherogenic indices we performed age- and sex-adjusted analyses to ensure that the observed associations were not driven by demographic imbalance. In age- and sex-adjusted logistic regression models, only NHC ≥130 mg/dL remained independently associated with T1DM status, whereas AIP, CRI-I, CRI-II, and AC showed no significant adjusted associations, highlighting the superior robustness of NHC as a demographic-independent lipid marker (Table 2). Taken together, these findings suggest that AIP primarily reflects underlying dyslipidemic and inflammatory disturbances rather than serving as an independent determinant of T1DM status, whereas NHC captures a broader atherogenic burden that remains significant even after adjustment for age and sex.

In the T1DM cohort, serum levels of TC, LDL-C, and HDL-C were all significantly elevated ($p < 0.001$; Table 1). Given the well-recognized tendency toward dyslipidemia in individuals with T1DM, the observed elevations in TC and LDL-C relative to the control group are consistent with patterns previously documented in the literature[28]. However, findings regarding HDL-C elevation have been inconsistent across studies. Chapman et al. suggested that

improved glycemic control and insulin therapy in T1DM may enhance lipoprotein lipase activity and promote HDL synthesis, thereby contributing to increased HDL-C levels[29]. Nevertheless, as demonstrated by Heier et al., despite higher HDL-C concentrations, its functional properties such as cholesterol efflux capacity and antioxidative functions may be impaired in individuals diagnosed with T1DM during childhood or early adulthood[30]. This observation indicates that structural and compositional alterations in HDL particles, associated with chronic hyperglycemia and inflammation, may attenuate their atheroprotective effects.

Importantly, HDL's cardioprotective properties cannot be inferred from concentration alone. In T1DM, alterations in the HDL proteome and lipidome together with oxidative stress and glycation can impair cholesterol efflux capacity (CEC) and anti-inflammatory or antioxidant activity, resulting in a "dysfunctional HDL" phenotype despite normal or elevated HDL-C levels[31-32]. Consistent with this concept, studies in younger T1DM populations have demonstrated reduced CEC and attenuated anti-inflammatory function despite preserved HDL-C levels. Moreover, large cohort studies have shown that functional HDL metrics, such as CEC, correlate more strongly with CV events than HDL-C concentration alone[32-33]. Accordingly, the observed elevation in HDL-C in our study should be interpreted with caution, as concentration alone does not guarantee cardioprotection. Future studies incorporating HDL functional assays (e.g., CEC) are warranted to clarify the relationship between HDL-C levels and clinical risk in T1DM.

In addition, the significantly elevated CRP levels observed in our cohort ($p < 0.001$) underscore the contribution of chronic inflammation to T1DM-related CV risk[34]. Taken together, these findings align with existing literature and support the concept that qualitative defects in HDL functionality rather than HDL-C quantity alone may contribute to the persistent elevation of CVD risk in individuals with T1DM.

A unique strength and original contribution of this study lies in the simultaneous evaluation of multiple atherogenic indices (AIP, CRI-I, CRI-II, AC, and NHC) within the same cohort of young adults with T1DM. Previous studies have typically examined these indices in isolation or focused predominantly on AIP alone, whereas integrated assessment of several lipid-derived ratios in a relatively young T1DM population remains limited in the literature. By analyzing these indices collectively, our study provides a more comprehensive characterization of atherogenic burden and demonstrates differential behavior among these markers most notably, the pronounced elevation of AIP and NHC in contrast to the non-significant changes observed in CRI-I, CRI-II, and AC. This multidimensional lipid evaluation offers novel insights into early cardiometabolic alterations in young individuals with T1DM and underscores the need for age-specific and disease-specific risk stratification approaches.

Recent literature has consistently demonstrated an increased burden of CVD in T1DM, including MI, CAD, cerebrovascular disease (CVD), peripheral arterial disease (PAD), HF, and AF[35-39]. In light of this evidence, accurate assessment of CVD risk in individuals with T1DM has become increasingly important.

Atherogenic indices, particularly the AIP, have been widely used to assess CV risk across diverse clinical settings. Zhang et al. reported that elevated AIP was associated with an increased risk of MI in the general population, Jin et al. demonstrated that AIP was a strong predictor of CAD independent of traditional risk factors, and Qin et al. identified AIP as a significant predictor of CV mortality[35-37]. Moreover, Mullins et al. emphasized that excess CV risk is driven not only by dyslipidemia but also by chronic inflammation and endothelial dysfunction[38].

In the present study, AIP values were markedly elevated in the T1DM cohort compared with controls ($p < 0.001$; Table 1), supporting the role of AIP as a clinically relevant marker of cardiometabolic risk. These findings are consistent with previous studies linking AIP to carotid intima–media thickness, arterial stiffness, and coronary artery calcification, thereby reinforcing its validity as a surrogate marker of vascular health[39,40]. Importantly, the ability of AIP to integrate lipid abnormalities with inflammation-related risk pathways renders it a versatile and informative predictor across different populations. Emerging evidence further suggests that longitudinal monitoring of AIP may reflect the progression of vascular damage and therapeutic response, highlighting its potential as a dynamic and actionable risk marker.

T1DM patients were categorized into low-risk (AIP < 0.1) and high-risk (AIP ≥ 0.1) groups according to

AIP levels. In the high-risk group (AIP ≥ 0.1), TG levels were significantly elevated ($p < 0.001$), whereas HDL levels were significantly reduced ($p < 0.001$; Table 3). In addition, CRI-I, CRI-II, AC, and NHC were all significantly higher in this group ($p < 0.001$; Table 3). Similar associations between high AIP, elevated TG, reduced HDL, and increased atherogenic ratios have been reported by previous studies[41,42].

In the present study, although LDL-C concentrations were significantly higher in individuals with T1DM compared with healthy controls ($p < 0.001$; Table 1), stratification by AIP risk within the T1DM group did not reveal a significant difference in LDL-C levels ($p = 0.904$; Table 3). This distinction is clinically important, as it indicates that while absolute LDL-C levels are elevated in T1DM relative to controls, LDL-C does not vary according to AIP-defined risk among T1DM patients. This observation is consistent with accumulating evidence suggesting that LDL-C alone may be insufficient for CV risk stratification in certain populations. Individuals with LDL-C levels within recommended targets but elevated AIP or other atherogenic markers may still carry substantial residual risk, driven by increased small dense LDL particles, remnant lipoproteins, or lipoprotein particle number factors not fully captured by LDL-C measurements. Indeed, discordance analyses have demonstrated that elevated non-HDL-C or apoB predicts CV events and mortality even when LDL-C is within target ranges in statin-treated patients[43].

Furthermore, within the T1DM subgroup, individuals with high AIP exhibited significantly higher TC, CRI-I, CRI-II, AC, and NHC values ($p < 0.001$; Table 4), supporting the robustness of AIP as a composite lipid index that integrates multiple dimensions of dyslipidemia more comprehensively than LDL-C alone. Consistent with this interpretation, Tien et al. demonstrated that AIP has superior predictive performance compared with individual lipid indices and may be particularly informative in younger adult populations[44].

In our study, although CRI-I and CRI-II values were numerically higher in the T1DM group than in controls (Table 1), these differences did not reach statistical significance, which partially contrasts with findings reported in other disease contexts[45,46]. This discrepancy may be attributable to several factors specific to our study population. The relatively young age, shorter disease duration, and better metabolic control of patients with T1DM may have limited the extent of subclinical atherosclerosis that these indices are designed to capture, thereby reducing their discriminatory power. Moreover, well-managed T1DM patients often maintain LDL-C and HDL-C levels within near-normal ranges, which may blunt the predictive capacity of CRI-based ratios, particularly in the early stages of disease. In addition, population-specific cultural and dietary patterns may have influenced lipid profiles, further contributing to the lack of statistical significance. Another important explanation is the relatively short duration of diabetes and the absence of advanced micro- or macrovascular complications in most participants. Such clinical stability may have prevented the lipid remodeling and lipoprotein glycation typically observed in long-standing T1DM. In older or complication-burdened populations, prolonged exposure to hyperglycemia, oxidative stress, and endothelial dysfunction markedly elevates these indices. In contrast, in younger cohorts with preserved metabolic control, compensatory mechanisms such as increased lipoprotein lipase activity and partial normalization of lipid transport may attenuate these alterations. Consistent with this interpretation, Lui and Tan and Denimal et al. reported that young adults with well-controlled T1DM exhibited near-normal CRI and AC levels despite an increased CV risk[31,32]. Notably, in our AIP-based risk stratification analysis, CRI-I ≥4 and AC ≥2 were significantly associated with high AIP risk in both the T1DM and control groups ($p < 0.001$; Table 5), underscoring their potential role in CV risk assessment. By contrast, CRI-II ≥3 was significantly associated with high AIP risk only in the T1DM group ($p < 0.001$; Table 5), suggesting that CRI-II may capture disease-specific lipid alterations that are more pronounced in T1DM. Taken together, the absence of group-level statistical significance for CRI indices likely reflects the early and metabolically stable disease stage of our cohort rather than a true lack of atherogenic risk. Longitudinal studies incorporating a broader age range and longer disease duration are warranted to clarify the temporal evolution of these indices as T1DM progresses.

Likewise, our analyses showed that AC values were higher in the T1DM group; however, the difference between group means did not reach statistical significance (Table 1). This finding contrasts with evidence reported by Lumu et al. and Wang, who observed significant associations between AC and CV risk, particularly in individuals with T2DM or

obesity[47-48]. Notably, in our AIP-based risk stratification, AC ≥2 was significantly associated with high AIP risk in both the T1DM and control groups ($p < 0.001$; Table 5), suggesting that AC may still reflect elevated CV risk when evaluated within risk categories rather than by simple comparisons of group means. In our study, the relatively young and metabolically stable cohort may not yet exhibit the degree of atherogenic burden that AC captures in mean-based analyses. Moreover, lifestyle and genetic factors, along with the absence of certain comorbidities prevalent in other populations, may have contributed to the observed differences. Integrating AC with inflammatory markers or additional indices may enhance its predictive utility and represents a potential direction for future research[47-48]. Longitudinal analyses particularly in patients with T1DM transitioning from adolescence to adulthood could further elucidate age-related changes in AC and its association with vascular complications.

The increase in NHC observed in this study is consistent with prior evidence indicating that NHC may outperform LDL-C in predicting CV risk, particularly in women and in individuals with poor metabolic regulation[49,50]. Our findings suggest that NHC may serve as a valuable complementary marker to LDL-C, especially in cases where LDL-C levels fall within recommended targets yet residual CV risk persists. This is clinically relevant, as traditional LDL-C measurements reflect only the cholesterol content of LDL particles, whereas NHC captures the total cholesterol burden carried by all atherogenic lipoproteins, including very-low-density lipoprotein, intermediate-density lipoprotein, and lipoprotein(a). Consequently, NHC may reveal a hidden atherogenic burden that LDL-C alone can overlook, particularly in patients with elevated triglycerides or small dense LDL particles features commonly observed in T1DM. Moreover, NHC has been positively associated with plaque burden and adverse CV outcomes, even among statin-treated patients, further supporting its potential role in guiding therapeutic strategies within more nuanced risk profiles[49,50]. Given its broader lipid coverage and stronger predictive capacity, NHC provides a more comprehensive approach to lipid risk assessment. Its incorporation into clinical practice guidelines and risk prediction models may facilitate individualized treatment planning and improve outcomes, particularly in populations at increased CV risk, such as patients with T1DM.

The marked elevation of AIP and its association with increased levels of other atherogenic indices in the high AIP risk group further reinforce its role as a robust marker of CV risk[51]. Previous studies have demonstrated the independent predictive value of AIP and its association with insulin resistance[52]. Owing to its simplicity, low cost, and strong prognostic performance, AIP represents an attractive tool for routine clinical use, particularly in resource-limited settings. Incorporating AIP into screening programs may enable earlier identification of high-risk individuals, facilitate timely interventions, and optimize healthcare resource utilization[51-52]. Furthermore, AIP may assist clinicians in intensifying therapeutic strategies for patients with elevated predicted risk and in monitoring responses to interventions, thereby improving both short- and long-term outcomes. It may also function as an effective communication tool when discussing CV risk with patients, potentially enhancing adherence to lifestyle modifications and prescribed therapies.

In our ROC analysis, AIP exhibited perfect discrimination (AUC = 1.000) in both groups. This finding is expected, as AIP served as the reference variable used to define the risk classification itself; therefore, its AUC reflects a deterministic relationship with the outcome rather than an independent predictive value. Because the primary endpoint of this study was defined as AIP ≥ 0.1, evaluating AIP against the same endpoint is inherently circular and, as anticipated, yields a perfect AUC of 1.000. Accordingly, ROC/AUC results for AIP are not clinically interpretable, and performance comparisons were therefore limited to CRI-I, CRI-II, AC, and NHC. This analytical approach is consistent with TRIPOD recommendations, which emphasize maintaining independence between predictors and outcomes[53].

CRI-I and AC demonstrated high diagnostic accuracy in controls and moderate accuracy in patients with T1DM for predicting CVD risk (Table 6), in line with previous reports[54-55]. Among the evaluated indices, CRI-I and AC emerged as the strongest predictors after AIP, showing moderate diagnostic performance in the T1DM group (AUC = 0.774 for both) and high performance in controls (AUC = 0.906 for both). These findings support earlier evidence suggesting that CRI-I and AC represent accessible and clinically useful indicators of CV risk in individuals with diabetes. As noted by Kubalová and Çelik, variability in AUC values across different indices may reflect

differences in participant age, disease duration, or population-specific characteristics[54,55].

In addition, the 95% confidence intervals reported for each AUC provide important insight into statistical uncertainty, with wider intervals indicating greater variability and reduced precision in diagnostic performance estimates. Despite these considerations, ROC analysis remains a valuable clinical tool, facilitating the identification of optimal cut-off values and supporting evidence-based decision-making, even in resource-limited settings. Furthermore, the application of ROC-derived metrics for patient risk stratification may enable more targeted preventive strategies while minimizing overtreatment in lower-risk individuals. Identifying optimal cut-off values across distinct T1DM subpopulations, such as adolescents versus adults, may further refine screening strategies and improve personalized risk assessment.

Given that ROC analysis of AIP against AIP-defined CV risk categories inevitably yields a deterministic AUC of 1.000, secondary ROC analyses were performed using outcome-independent clinical thresholds (HbA1c ≥ 6.5% and CRP ≥ 3 mg/L) to avoid circularity. In these analyses, NHC demonstrated the strongest discriminative ability for identifying poor glycemic control (Table 7, Figure 4; AUC = 0.594), whereas AIP showed the highest performance for detecting elevated inflammatory status (Table 7, Figure 3; AUC = 0.623). Notably, AIP yielded the highest single AUC value overall, while NHC emerged as the most consistent predictor across both glycemic and inflammatory thresholds, supporting the robustness and external validity of these indices.

Collectively, these findings indicate that atherogenic indices particularly AIP and NHC provide clinically meaningful insights into CV risk among patients with T1DM. Their application may facilitate the early identification of high-risk individuals, enabling more personalized therapeutic strategies and potentially reducing long-term complications and healthcare costs. Further research may support the development of T1DM-specific risk models integrating these indices with clinical, genetic, and lifestyle factors, thereby enhancing risk stratification and improving outcomes. Incorporation of these indices into electronic health records and risk calculators could further streamline their clinical use and promote adherence to guideline-recommended care. In the future, combining atherogenic indices with imaging modalities and biomarker panels may enable more comprehensive, multidimensional CV risk assessment in T1DM.

This study has several limitations that warrant acknowledgment. First, its retrospective, single-center, and cross-sectional design precludes the establishment of temporality in exposure–outcome relationships; therefore, causal inference cannot be made and generalizability is inherently limited. The findings reflect contemporaneous associations, and residual confounding, as well as potential selection or measurement bias, cannot be fully excluded. Accordingly, external validation in prospective, preferably multicenter and longitudinal cohorts is required before consideration of clinical implementation.

Second, the relatively modest sample size may have limited the ability to detect subtle associations. In addition, no formal a priori or post hoc power analysis was performed. Consequently, although statistically significant associations were observed for the primary outcomes, the adequacy of statistical power particularly for secondary or subgroup analyses cannot be definitively established, and the results should be interpreted with appropriate caution.

Third, several clinically important variables were unavailable in the present dataset, including diabetes duration, age at disease onset, daily insulin dose, glycemic variability, and the presence or severity of diabetic complications (e.g., retinopathy, nephropathy, neuropathy, or macrovascular disease). These factors are known to substantially influence lipid metabolism, atherogenic remodeling, and long-term cardiovascular risk in individuals with T1DM. Their absence limits the ability to fully interpret the observed associations between atherogenic indices and cardiometabolic risk and may partially account for residual heterogeneity in the findings. Future prospective studies should systematically incorporate these parameters to enable more comprehensive risk stratification and assessment of effect modification related to disease burden.

Fourth, long-term clinical outcomes were not evaluated, and risk estimates were derived exclusively from cross-sectional data. In addition, unmeasured confounders such as dietary habits, physical activity, and genetic predisposition may have influenced the results. Given the regionally restricted study population, the findings may not be fully

generalizable to broader national or international populations and should be interpreted cautiously across different geographic, ethnic, and sociocultural contexts.

Finally, functional assessments of HDL such as cholesterol efflux capacity, anti-inflammatory activity, and apolipoprotein profiling (apoA1 and apoB) were not performed. Consequently, HDL-C concentrations may not accurately reflect HDL quality or functional capacity. The absence of these functional and structural measures limits interpretation of HDL-related findings and should be addressed in future prospective investigations.

In conclusion, this study demonstrates that AIP and NHC are robust indicators of atherogenic risk in patients with T1DM, whereas CRI-I, CRI-II, and AC provide complementary but comparatively less sensitive information. The practicality, low cost, and reproducibility of these indices support their integration into routine clinical workflows. In outpatient settings, AIP and NHC can be readily calculated from standard lipid parameters, enabling early CV risk stratification even before the development of overt complications. These indices may help identify individuals with concealed or residual dyslipidemia despite apparently optimal LDL-C levels, thereby prompting timely adjustments in therapy or lifestyle interventions.

From a longitudinal perspective, serial assessment of AIP and NHC during follow-up visits may offer a simple yet informative means of monitoring lipid dynamics, therapeutic response, and treatment adherence. In high-risk or poorly controlled patients, rising AIP values could alert clinicians to intensify lipid-lowering therapy, initiate combination regimens, or implement targeted nutritional counseling. Conversely, stabilization or improvement of AIP and NHC over time may reflect enhanced metabolic stability and more favorable glycemic–lipid control.

In resource-limited or high-volume outpatient clinics, incorporating these indices alongside conventional lipid profiles may optimize preventive care by supporting individualized, risk-based monitoring strategies. Their complementary use with established markers such as LDL-C, HbA1c, and BMI may provide a more nuanced and comprehensive assessment of cardiometabolic risk in T1DM. Collectively, these findings highlight the translational potential of AIP and NHC as practical, clinically meaningful tools for early CV risk detection and personalized management. Nevertheless, given the retrospective and cross-sectional design of this study, these observations should not be interpreted as causal and require confirmation in prospective longitudinal investigations.

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