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Glycated hemoglobin correlates with inflammatory markers of cardiovascular risk in patients with type 2 diabetes mellitus

La hemoglobina glicada se correlaciona con marcadores inflamatorios de riesgo cardiovascular en pacientes con diabetes mellitus tipo 2

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ABSTRACT

Hyperglycemia promotes inflammation and increases cardiovascular risk. This study aimed to analyze the relationship between glycemic control and inflammatory and cardiovascular risk markers in patients with type 2 diabetes (T2DM). A cross-sectional, correlational study was conducted involving 300 adults (240 diabetics classified according to their HbA1c levels and 60 controls). Glucose, HbA1c, lipid profile, fibrinogen, high-sensitivity C-reactive protein (hs-CRP), atherogenix index of plasma (AIP), and erythrocyte sedimentation rate (ESR) were measured. Patients with T2DM had higher levels of fibrinogen, hs-CRP, AIP, and ESR compared to controls and among groups with poorer glycemic control ($p<0.001$). A significant positive correlation was observed between HbA1c and all biomarkers evaluated ($p<0.0001$). These findings support the use of HbA1c not only as an indicator of glycemic control but also as an indirect marker of cardiovascular risk in T2DM.

Keywords: cardiovascular risk, type 2 diabetes mellitus, HbA1c, inflammation.

RESUMEN

La hiperglucemia promueve la inflamación e incrementa el riesgo cardiovascular. El objetivo de este estudio fue analizar la relación entre el control glucémico y marcadores inflamatorios y de riesgo cardiovascular en pacientes con diabetes tipo 2 (DM2). Se realizó un estudio transversal y correlacional que incluyó 300 adultos (240 diabéticos clasificados según sus niveles de HbA1c y 60 controles). Se midieron glucemia, HbA1c, perfil lipídico, fibrinógeno, proteína C reactiva ultrasensible (PCR-us), índice aterogénico plasmático (IAP) y velocidad de sedimentación globular (VSG). Los pacientes con DM2 mostraron niveles más altos de fibrinógeno, PCR-us, IAP y VSG en comparación con los controles y entre los grupos con peor control glucémico ($p<0,001$). Se observó una correlación positiva significativa entre la HbA1c y todos los biomarcadores evaluados ($p<0,0001$). Estos hallazgos respaldan el uso de la HbA1c no solo como indicador del control glucémico, sino también como marcador indirecto de riesgo cardiovascular en la DM2.

Palabras clave: riesgo cardiovascular, diabetes tipo 2, HbA1c, inflamación.

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INTRODUCTION

Atherosclerotic cardiovascular disease (ACD) is the leading cause of morbidity and mortality in patients with diabetes mellitus. It is a chronic, progressive disease that affects the entire arterial body system and often presents as peripheral artery disease of atherosclerotic origin, cerebrovascular disease, and coronary artery disease (American Diabetes Association Professional Practice Committee, 2024). Type 2 diabetes mellitus (T2DM) is linked to early onset of ACD, with dyslipidemia and arterial hypertension being common risk factors in these patients (Liu et al., 2022).

Atherosclerosis is a complex chronic inflammatory process that combines alterations in endothelial function, thrombotic activation, increased oxidative stress, and dyslipidemia (Kong et al., 2022). In this context, T2DM represents a metabolic condition in which sustained hyperglycemia perpetuates low-grade systemic inflammation, evidenced by increased proinflammatory cytokines such as IL-6, TNF-α, and C-reactive protein (Rohm et al., 2022). This inflammatory response, together with oxidative stress induced by chronic hyperglycemia (Demir et al., 2021), favors a proatherogenic environment characterized by increased blood viscosity and plasma fibrinogen levels, both recognized risk factors for the development of atherosclerotic cardiovascular disease (Antonova et al., 2022).

On the other hand, the atherogenic index of plasma, calculated from the logarithmic ratio between triglycerides and HDL cholesterol, has been proposed as a useful biomarker of atherosclerosis and cardiovascular risk, showing an independent association with adverse cardiovascular events in patients with T2DM (Guo et al., 2025; Ma et al., 2020). At the same time, chronic hyperglycemia promotes the formation of glycosylated hemoglobin (HbA1c), the main indicator of long-term glycemic control and an independent predictor of coronary heart disease and stroke (Mitsios et al., 2018; Aguirre-Villegas & Pedreáñez, 2024).

Although several international studies have documented the relationship between hyperglycemia, inflammation, and atherogenic risk, evidence in Latin American populations remains limited. In Ecuador, and particularly in Riobamba, there is little information available that integrates classic inflammatory markers (high-sensitivity C-reactive protein, fibrinogen, and erythrocyte sedimentation rate) and metabolic markers (atherogenic index of plasma) according to

the degree of glycemic control. This gap limits the characterization of the inflammatory-atherogenic profile in local patients with T2DM and restricts the possibility of using these biomarkers as complementary tools for cardiovascular risk assessment.

In this context, the hypothesis was proposed that poor glycemic control, reflected by elevated HbA1c levels, is associated with an increase in inflammatory and atherogenic risk markers. Understanding this relationship could contribute to better cardiovascular risk stratification and optimization of clinical management of T2DM in our population. Therefore, this study aimed to analyze the relationship between glycemic control and inflammatory and cardiovascular risk markers in patients with T2DM.

METHODOLOGY

An observational, cross-sectional, correlational study was conducted between November 2023 and November 2024. The research included individuals of both sexes, aged between 35 and 65, who were treated at the internal medicine clinic of the Provincial General Teaching Hospital of Riobamba (Ecuador).

Intentional non-probabilistic sampling was used, based on patient availability and compliance with inclusion criteria. This type of selection was justified by the hospital nature of the study and the need for comparable groups in terms of glycemic control. However, it is recognized that this strategy limits the extrapolation of the results to the general population, so the findings should be interpreted within the clinical context of the sample studied.

People under 18 or over 75 years of age, with other types of diabetes, thyroid disease, acute infection, anemia, pregnancy, autoimmune diseases, or recent treatment with corticosteroids were excluded. No specific control was made of the use of lipid-lowering, antihypertensive, or anti-inflammatory medication, so these factors were not considered in the statistical analysis and are recognized as possible confounding variables in the interpretation of the results.

The sample size was estimated using Epi Info™ software, version 7.2.5.0, with a 95% confidence level, 80% power, an expected exposure proportion of 40%, and a minimum detectable relative risk of 1.8, expanded to compensate for possible losses.

The total sample included 300 participants, divided as follows: 240 people with a

confirmed diagnosis of T2DM with at least two years of evolution and 60 healthy controls with no history of metabolic, autoimmune, or inflammatory diseases. Patients with T2DM were classified into three subgroups according to their glycosylated hemoglobin (HbA1c) values: group 1 (HbA1c <7%, n=80), group 2 (HbA1c between 7–9%, n=80), and group 3 (HbA1c >9%, n=80).

Each participant underwent a medical history review, physical examination, and anthropometric measurements (weight and height) to calculate body mass index (BMI = weight/height²). Subsequently, venous blood samples were obtained after an 8–12-hour fast. Serum samples were centrifuged at 3000 rpm for 10 minutes and stored at −80°C until analysis.

Serum concentrations of glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and high-sensitivity C-reactive protein were determined using a Cobas C501 analyzer (Roche Diagnostics, USA), following standardized internal quality control procedures. Erythrocyte sedimentation rate was determined using the Wintrobe method. Plasma fibrinogen was quantified using the Von Clauss method from samples collected in sodium citrate tubes and centrifuged at 4°C. The reference values were: glucose (70–110 mg/dL), total cholesterol (<200 mg/dL), triglycerides (<150 mg/dL), HDL-C (>40 mg/dL in men, >50 mg/dL in women), LDL-C (<130 mg/dL), and CRP-us (<3 mg/L). Fibrinogen 200–400 mg/dL (2.0–4.0 g/L). Erythrocyte sedimentation rate ≤10 mm/h in men and ≤15 mm/h in adult women.

The atherogenic index of plasma was calculated using the formula AIP = log (TG/HDL-C), with concentrations expressed in mmol/L (Li et al., 2018). HbA1c was determined using a turbidimetric inhibition immunoassay (Tina-quant® HbA1c Gen. 3, Roche), certified by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the National Glycohemoglobin Standardization Program (NGSP).

The study complied with the ethical standards established in the Declaration of Helsinki (Shrestha and Dunn, 2019). All participants signed an informed consent form before inclusion. The protocol was approved by the Bioethics Committee of the Doctorate in Health Sciences at the University of Zulia, Venezuela.

Statistical analysis was performed using GraphPad Prism software version 8.0 (San Diego, California, USA). Data were expressed as mean ± standard deviation (SD). Before applying parametric tests, the assumptions of normality were verified using the Shapiro–Wilk test and the

homogeneity of variances using Levene's test. To compare variables between groups, a two-way analysis of variance (ANOVA) was used with Bonferroni's post hoc test for multiple comparisons. Associations between continuous variables were evaluated using Pearson's correlation. A p-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The baseline demographic and biochemical characteristics of the participants are shown in Table 1. Patients with T2DM had a significantly higher mean age than controls (p=0.007), with no significant differences in sex distribution between groups (p=0.702). Subjects with diabetes were classified according to their HbA1c levels into three groups: well controlled (<7%), moderately controlled (7–9%), and poorly controlled (>9%). Analysis of variance (ANOVA) revealed a progressive trend toward increased blood glucose, body mass index (BMI), and triglycerides as HbA1c values increased, with statistically significant differences for BMI (p=0.004), blood glucose (p<0.05), and triglycerides (p=0.032).

Table 1. Baseline and biochemical characteristics of the studied population

Parameters	Controls	Group 1 <7%	Group 2 7-9%	Group 3 >9%	*p* value
Number	60	80	80	80	–
Age (years)	41 ± 6	55 ± 10,9*	56 ± 11,3*	56 ± 12,8*	0.007
Male/female (%)	43/37	44/36	37/43	40/40	0.702 (NS)
Blood glucose (mg/dl)	97.4±3.2	120.3±11.2*	177.9±11.3*	264.4±47*[ab]	<0.05
BMI (kg/m^2)	25.6 ± 3.9	27.2 ± 2.1*	26.2 ± 4.3*	28.2 ± 3.3*	0.004
Hematocrit (%)	41.35 ± 3.8	42.03 ± 4.23	42.86 ± 4.24	42.33 ± 4.54	0.384 (NS)
Triglycerides (mg/dl)	109.74±35	141.6±62*	155.8±70*	170 ± 59*[ab]	0.032
Total cholesterol (mg/dl)	148.1 ± 38	150.8±40	152.4±35	156.9 ± 45	0.679(NS)
HDL-C (mg/dl)	44.46 ± 4.8	45.6±6.2	44.9±3.9	43.9 ± 3.2	0.184 (NS)
LDL-C (mg/dl)	91.8±4.3	92.48 ± 9.5	95.4±2.3	93.1±3.4	0.487 (NS)

Values are expressed as mean ± standard deviation (SD). One-way ANOVA followed by Bonferroni post hoc test. A value of $p < 0.05$ was considered statistically significant.
BMI: body mass index; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein.
*: significant versus control group.
[a]: significant versus group 1.
[b]: significant versus group 2.
NS: not significant.

Statistically significant differences were observed in the atherogenic index of plasma when controls were compared with subjects with T2DM. As well as between diabetic patients with different degrees of glycemic control (Figure 1). Control subjects presented a mean atherogenic index of plasma value of (0.34±0.12). The mean values for patients with T2DM were as follows: (group 1: 0.52±0.09; group 2: 0.56±0.11, and group 3: 0.57±0.09). Statistically significant differences were observed between controls and the three groups of subjects with T2DM ($p<0.0001$) and in diabetic patients between group 1 *vs.* group 3 ($p<0.007$). Figure 1.

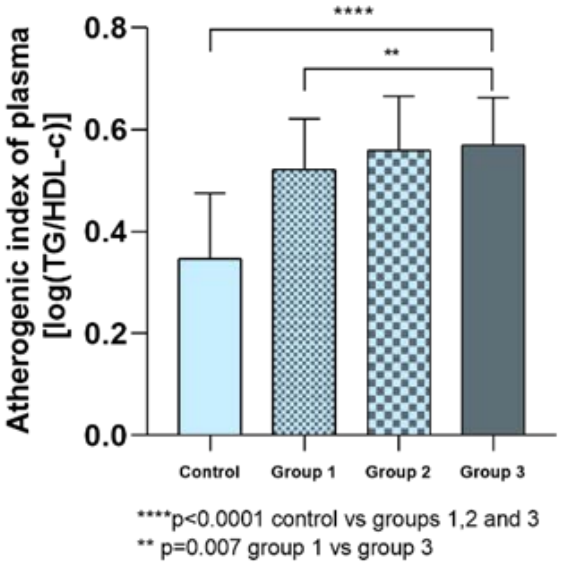
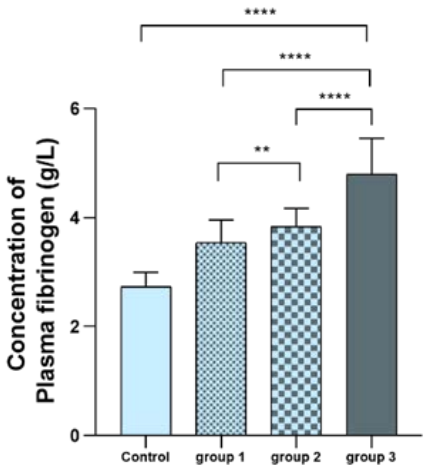


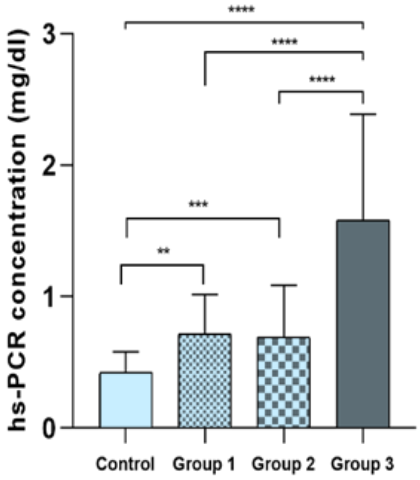
Figure 1. Atherogenic index of plasma in the study groups. Data expressed as mean ± SD; ANOVA with Bonferroni correction; n=60 (controls) and n=80 per T2DM group; $p<0.05$ was considered significant.

Statistical analysis revealed significant differences in fibrinogen, high-sensitivity C-reactive protein, and erythrocyte sedimentation rate concentrations between patients with T2DM and the control group ($p<0.001$). Likewise, relevant variations were observed between the different subgroups of diabetic patients, as shown in Figures 2, 3, and 4.



****p<0.0001 control vs groups 1,2 and 3
****p<0.0001 group 1 vs group 3 and group 2 vs group 3
**p=0.0002 group 1 vs group 2;

Figure 2. Plasma fibrinogen concentrations in the different groups studied. Data expressed as mean ± SD; ANOVA with Bonferroni correction; n=60 (controls) and n=80 per T2DM group.



**p= 0.004 control vs group 1; *** p=0.009 control vs group 2
****p<0.0001 control vs group 3; groups 1 and 2 vs group 3

Figure 3. Serum high-sensitivity C-reactive protein concentrations in the different groups studied. Data expressed as mean ± SD; ANOVA with Bonferroni correction; n=60 (controls) and n=80 per T2DM group.

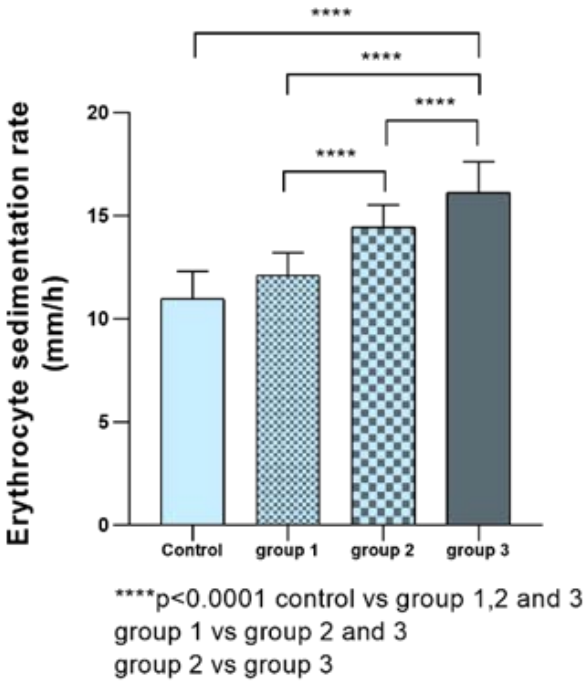


Figure 4. Values of erythrocyte sedimentation rate in the different groups studied. Data expressed as mean ± SD; ANOVA with Bonferroni correction; n=60 (controls) and n=80 per T2DM group.

Taking into account that a highly significant difference was found in the blood concentrations of the inflammatory markers studied, as well as in the atherogenic index of plasma in patients with T2DM. Correlations were performed to evaluate the association between the variables mentioned and HbA1c levels. Significant positive correlations were observed between the levels of the aforementioned variables with the HbA1c percentages in the subjects studied (high-sensitivity C-reactive protein: $r=0.3535$, $p<0.0001$; plasma atherogenic index: $r=0.5048$, $p<0.0001$; Fibrinogen: $r=0.8063$, $p<0.0001$; erythrocyte sedimentation rate: $r=0.8072$, $p<0.0001$) (Figure 5).

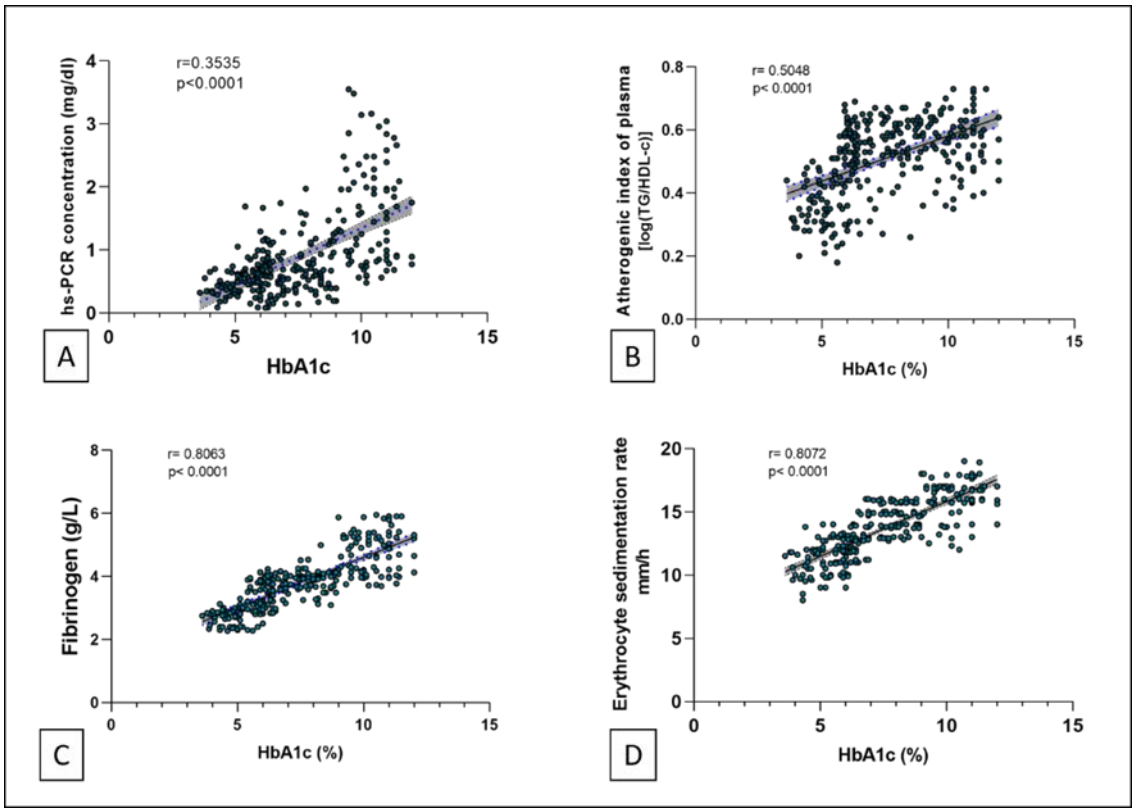


Figure 5. Correlations between HbA1c and inflammatory and cardiovascular risk biomarkers (Pearson analysis). Each point represents a subject with T2DM (n=240). A $p < 0.05$ (adjusted using Bonferroni correction for multiple comparisons) was considered significant. A) HbA1c vs hs-CRP; B) HbA1c vs AIP; C) HbA1c vs fibrinogen; D) HbA1c vs ESR. Pearson correlation. HbA1c: glycated hemoglobin; hs-CRP: high-sensitivity C-reactive protein.

Table 2 summarizes the average values of inflammatory biomarkers (fibrinogen, high-sensitivity C-reactive protein, erythrocyte sedimentation rate) and the atherogenic index of plasma in the different study groups, as well as their correlations with HbA1c levels in patients with T2DM. A progressive increase in all markers is observed as glycemic control worsens. Pearson's correlation shows significant positive associations between HbA1c and each of the biomarkers, indicating that higher levels of glycosylated hemoglobin are related to a more pronounced inflammatory state and a higher atherogenic risk. Statistical analysis was performed using ANOVA followed by Bonferroni correction for multiple comparisons; values of $p < 0.05$ were considered significant.

Table 2. Inflammatory biomarkers and correlation coefficients with HbA1c

Biomarker	Control	Group 1	Group 2	Group 3	r with HbA1c	p
Fibrinogen (mg/dL)	280±42	345±51	389±59	425±64	0.8063	<0.0001
hs-CRP (mg/L)	1.8±0.5	3.4±0.9	4.1±1.1	4.8±1.2	0.3535	<0.0001
ESR (mm/h)	8.5±2.4	13.7±3.1	16.9±3.8	19.4±4.2	0.8072	<0.0001
AIP (log TG/HDL-c)	0.34±0.12	0.52±0.09	0.56±0.11	0.57±0.09	0.5048	<0.0001

All analyses include the 240 patients with type 2 diabetes mellitus (n= 80 per group).
Values are expressed as mean ± standard deviation. The p-values indicate statistical significance when $p \leq 0.05$.
r: Pearson's correlation coefficient between HbA1c and inflammatory and cardiovascular risk biomarkers.
HbA1c: glycated hemoglobin; hs-CRP: high-sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; AIP: atherogenic index plasma.

This study evaluated plasma levels of fibrinogen, high-sensitivity C-reactive protein, erythrocyte sedimentation rate, and atherogenic index of plasma in subjects with T2DM who had different degrees of glycemic control. Patients with poor control (HbA1c > 9%) of these parameters showed significantly higher levels than well-controlled and healthy individuals. HbA1c correlated strongly and positively with all of these biomarkers, indicating a direct relationship between inadequate glycemic control and the intensity of inflammatory and atherogenic activity.

The increase in high-sensitivity C-reactive protein is consistent with previous studies, in which low-grade systemic inflammation is a central feature of T2DM (Yang et al., 2021; Zhou et al., 2024). This protein, synthesized by hepatocytes under the stimulation of IL-6 and IL-1β, is a sensitive marker of cardiovascular risk and mortality in diabetic patients (Tian et al., 2019; Reddy et al., 2024). Given that the subjects did not have active infections or inflammatory processes at the time of sampling, the elevated high-sensitivity C-reactive protein values can be attributed to metabolic inflammation induced by chronic hyperglycemia, reinforcing its usefulness as a complementary indicator of glycemic control and cardiovascular risk.

On the other hand, the mean fibrinogen concentration was significantly higher in patients with T2DM and was closely associated with HbA1c levels ($r = 0.8063$; $p < 0.0001$). This finding is consistent with studies linking increased fibrinogen to macrovascular and microvascular complications (Hamidullah et al., 2024; Khanam et al., 2024). Elevated fibrinogen reflects an increase in its hepatic production stimulated by proinflammatory cytokines (de Oliveira et al., 2021). In addition, glycosylated fibrinogen, which is more abundant in T2DM, forms more rigid clots that are resistant to fibrinolysis, increasing cardiovascular risk (Li et al., 2021; Pereira et al.,

2016; Perween et al., 2019; Nencini et al., 2024). Furthermore, the ability of glycosylated fibrinogen to interact with RAGE receptors activates proinflammatory pathways such as NF-κB, promoting the progression of atherosclerosis (Wieczór et al., 2019; de Vries et al., 2020; Sulimai et al., 2022; Wolberg, 2023; Nencini et al., 2024).

This study also detected a significant increase in triglyceride concentrations in patients with T2DM. Previous research has reported that dyslipidemia is a cardiovascular risk factor and a promoter of inflammatory responses that favor the formation of atherosclerotic lesions within the vascular wall (Viigimaa et al., 2020; Kane et al., 2021).

An increase in triglyceride concentration accompanied by a reduction in HDL-C levels, commonly defined as atherogenic dyslipidemia, has been observed in approximately 41% of patients with diabetes (Núñez-Cortés & Pedro-Botet, 2021). In this context, the plasma atherogenic index, calculated as the logarithm of the triglyceride/HDL-C ratio (in mmol/L), has been described as a key biomarker for assessing atherosclerosis and is closely related to the development of cardiovascular complications. It reflects the esterification degree of plasma ApoB lipoproteins, providing information on the balance between protective and atherogenic lipoproteins (Yin et al., 2023).

Hypertriglyceridemia and low HDL-C levels are easily measurable, low-cost markers that are independent of coronary heart disease. The plasma atherogenic index integrates these two parameters into a single biomarker. An increase in this parameter has been associated with adverse cardiovascular events in patients with T2DM (Ma et al., 2020) and may indicate a more severe metabolic form of the disease (Li et al., 2018). In addition, a recent systematic review and meta-analysis showed that people with high PAI values are more likely to develop atherosclerotic cardiovascular disease (Ulloque-Badaracco et al., 2022).

Erythrocyte sedimentation rate also increased significantly in patients with T2DM, correlating with HbA1c ($R = 0.8072$; $p < 0.0001$), in agreement with other authors (Li et al., 2015). Hyperglycemia promotes hemoglobin glycation and alters erythrocyte elasticity, reducing their deformability and affecting microcirculation (Lee et al., 2019; Obeagu, 2024). The erythrocytes of diabetic patients are less flexible and more fragile, contributing to the development of microangiopathy and coronary heart disease (Agrawal et al., 2016; Wang et al., 2021).

Limitations of the study included non-probabilistic sampling, moderate sample size, and lack of control over variables such as the use of lipid-lowering or anti-inflammatory drugs. However, the findings highlight the clinical utility of combining HbA1c with fibrinogen, high-sensitivity C-reactive protein, and plasma atherogenic index for better cardiovascular risk stratification. In the Ecuadorian context, where T2DM and cardiovascular diseases are leading causes of morbidity and mortality, the incorporation of these accessible biomarkers could strengthen comprehensive assessment and preventive strategies in clinical practice.

CONCLUSIONS

Poorer glycemic control was significantly associated with higher concentrations of these parameters, demonstrating a positive and direct correlation between HbA1c and systemic inflammation and atherogenic risk. These findings suggest that HbA1c, in addition to reflecting metabolic control, could be used as an indirect marker of inflammatory status and cardiovascular risk in T2DM. The joint evaluation of HbA1c with biomarkers such as fibrinogen, high-sensitivity C-reactive protein, and atherogenic index of plasma could improve risk stratification and guide more personalized therapeutic strategies aimed at reducing macro- and microvascular complications. Future research should expand on these results through multicenter longitudinal studies evaluating the predictive utility of these biomarkers and their response to therapeutic intervention. Furthermore, their integration into clinical metabolic monitoring programs could help optimize glycemic control and reduce cardiovascular burden in patients with T2DM.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Pablo Aguirre and Adriana Pedreáñez. **Data curation:** Pablo Aguirre and Adriana Pedreáñez. **Formal analysis:** Pablo Aguirre and Adriana Pedreáñez.

Investigation: Pablo Aguirre and Adriana Pedreáñez. **Methodology:** Pablo Aguirre and Adriana Pedreáñez. **Writing – original draft:** Pablo Aguirre and Adriana Pedreáñez. **Writing – review & editing:** Pablo Aguirre and Adriana Pedreáñez.

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