

Association of Insulin Resistance, Systemic Inflammation, and Atherogenic Dyslipidemia With Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: A Prospective Cohort Study

Nasar Iqbal Ranjha¹, Faiqa Nasar², Madiha Shah³, Hira Laghari⁴, Umema Malik⁵, Noreen Atzaz⁶

¹ Consultant Physician, Department of Medicine, District Headquarters Hospital Sargodha / Sargodha Medical College, Sargodha, Pakistan.

² Final-Year MBBS Student, Niazi Medical and Dental College (NMDC), Sargodha, Pakistan.

³ Associate Professor of Medicine, Medical Unit 4, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan.

⁴ Senior Registrar, Department of Internal Medicine, Bilawal Medical College, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan.

⁵ Senior Lecturer, Department of Biochemistry, Islamabad Medical and Dental College, Islamabad, Pakistan.

⁶ Assistant Professor, Department of Chemical Pathology, Rawal Institute of Health Sciences, Islamabad, Pakistan.

Corresponding Author: Madiha Shah

Email: madihashah0092@gmail.com

Abstract

Background: Cardiovascular disease remains a major cause of morbidity and mortality in type 2 diabetes mellitus (T2DM), with residual risk persisting despite conventional risk-factor control. Insulin resistance, systemic inflammation, and atherogenic dyslipidemia may jointly contribute to this excess risk.

Objective: To evaluate the association of insulin resistance, systemic inflammation, and atherogenic dyslipidemia with major adverse cardiovascular events (MACE) in patients with T2DM.

Methods: This prospective multicenter cohort study included 200 adults with T2DM recruited from District Headquarters Hospital Sargodha/Sargodha Medical College and Bilawal Medical College, LUMHS, Jamshoro, from January 2025 to February 2026. Insulin resistance was assessed using HOMA-IR, systemic inflammation using high-sensitivity C-reactive protein (hs-CRP), and atherogenic dyslipidemia using triglyceride/HDL-C ratio and atherogenic index of plasma. The primary outcome was three-point MACE comprising cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke.

Results: During follow-up, 42 patients (21.0%) experienced MACE. Patients with MACE had significantly higher HOMA-IR, hs-CRP, triglycerides, triglyceride/HDL-C ratio, and atherogenic index of plasma. HOMA-IR (aHR 1.13, 95% CI 1.05–1.22), hs-CRP (aHR 1.09, 95% CI 1.03–1.15), and triglyceride/HDL-C ratio (aHR 1.11, 95% CI 1.03–1.20) independently predicted MACE. Patients with abnormalities in all three domains had a 3.27-fold greater adjusted hazard of MACE.

Conclusion: Insulin resistance, systemic inflammation, and atherogenic dyslipidemia independently predicted cardiovascular events in T2DM. Combined assessment may improve cardiovascular risk stratification.

Keywords: Type 2 diabetes mellitus; insulin resistance; HOMA-IR; hs-CRP; atherogenic dyslipidemia; cardiovascular disease; major adverse cardiovascular events

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Introduction

Type 2 diabetes mellitus (T2DM) is a huge global health issue and is strongly linked to premature cardiovascular morbidity and mortality. People with T2DM are much more likely to develop coronary artery disease, ischemic stroke, heart failure and cardiovascular mortality than people without diabetes [1]. While rates of events have been lowered with improvements in glycemic

management, lipid-lowering therapy, blood pressure (BP) control and use of glucose-lowering agents with cardiovascular benefit, a significant amount of cardiovascular risk remains [2]. This means that there are other factors than traditional cardiovascular risk factors responsible for the poor prognosis in patients with T2DM [3].

Central pathophysiological mechanism in the pathogenesis of T2DM and beyond impaired glucose metabolism, insulin resistance has important cardiovascular consequences. Insulin resistance results in endothelial dysfunction, oxidative stress, sympathetic activation, excessive glucose production in the liver, increased lipolysis and abnormalities in vascular signaling, all of which persist [4]. It also promotes a prothrombotic and proatherogenic metabolic state that could speed up the onset and growth of atherosclerotic cardiovascular disease [5]. Homeostatic model assessment of insulin resistance (HOMA-IR), calculated from fasting glucose and insulin levels, is a convenient surrogate marker of insulin resistance, and has been linked to poor cardiovascular outcomes in several clinical groups [6].

Another important mechanism in the link between T2DM and cardiovascular disease is chronic low-grade systemic inflammation. Hyperglycemia, visceral adiposity, oxidative stress, advanced glycation products, and endothelial injury could trigger innate immune mechanisms and lead to chronic release of pro-inflammatory mediators [7]. C-reactive protein (CRP) is a widely used marker of systemic inflammation and has been shown to be linked to the risk of cardiovascular events independent of conventional lipid parameters [8]. The increased persistence of inflammatory biomarkers despite current cardiovascular therapy has resulted in a growing appreciation of the residual inflammatory risk as a possible important part of cardiovascular disease in diabetes [9].

Atherogenic dyslipidemia is also common in patients with insulin-resistant T2DM and is generally characterized by high triglyceride levels, low high-density lipoprotein cholesterol (HDL-C), high triglyceride-rich remnant particles and small dense low-density lipoprotein particles [10]. The lipid phenotype could increase cardiovascular risk despite optimal low-density lipoprotein cholesterol control on statins [11]. Thus, simple indices based on lipids have been of interest as possible tools for measuring the remaining cardiometabolic risk [12].

Insulin resistance, systemic inflammation and atherogenic dyslipidemia are tightly linked and not isolated abnormalities. Insulin resistance contributes to increased hepatic triglyceride production, and abnormal lipoprotein metabolism, and an excess of free fatty acids (FFAs) and dysfunction of adipose tissue increases inflammatory signaling [13]. Chronic inflammation, in turn, can lead to further

deterioration of insulin action and endothelial function and can thus set up a vicious circle that drives atherosclerosis and cardiovascular events [14]. Combined assessment of these pathways may also offer a more thorough assessment of cardiometabolic risk than the assessment of any single biomarker alone [15].

Although there are more and more evidences on the individual prognostic value of insulin resistance, systemic inflammation, and atherogenic dyslipidemia, few prospective data have investigated a simultaneous association with MACE in T2DM patients. Patients in whom these metabolic abnormalities co-occur may be better risk-stratified for cardiovascular risk and a clinically relevant high-risk phenotype may be defined [17]. Hence, the current prospective cohort study was designed to explore the link between insulin resistance, systemic inflammation and atherogenic dyslipidemia with the occurrence of MACE in T2DM patients. We also wanted to find out if the presence of abnormalities in all three metabolic domains increased the risk for cardiovascular events more than the presence of any one abnormality alone.

Materials and Methods

Study Design and Setting

A prospective multicenter cohort study was performed at District Headquarters Hospital Sargodha/Sargodha Medical College, Sargodha, Pakistan, and Liaquat University of Medical and Health Sciences (LUMHS) Department of Internal Medicine, Bilawal Medical College, Jamshoro, Pakistan, from January 2025 to February 2026. A total of 200 adults with type 2 diabetes mellitus (T2DM) were recruited and then followed up prospectively for major adverse cardiovascular events (MACE).

Study Population

Eligible adults were those ≥ 35 years of age with known T2DM ≥ 6 months. Patients with type 1 diabetes, recent myocardial infarction or stroke within 3 months, active infection, inflammatory or autoimmune disease, a malignancy, end-stage kidney disease, severe liver disease, pregnancy or current corticosteroid or immunosuppressive therapy were excluded.

Clinical and Laboratory Assessment

Baseline information such as age, sex, diabetes duration, body mass index, blood pressure, smoking status, hypertension, previous atherosclerotic cardiovascular disease, and current medications were collected. Plasma glucose, insulin, HbA1c, serum creatinine, total cholesterol, LDL-C, HDL-C, triglycerides, and

high-sensitivity C-reactive protein (hs-CRP) were measured in the fasting blood samples.

Insulin resistance and inflammation assessment.

Insulin resistance was determined using the HOMA-IR which is defined as fasting insulin ($\mu\text{IU/mL}$) $\times$ fasting glucose (mg/dL) / 405. HOMA-IR was examined as a continuous variable, and also as a categorical variable with a cut point of ≥ 5.0 . Systemic inflammation was evaluated by the level of hs-CRP, which was defined as high inflammatory risk if $\geq 3 \text{ mg/L}$.

Assessment of Atherogenic Dyslipidemia

Fasting levels of triglycerides (TG), HDL-C, TG/HDL-C and the atherogenic index of plasma (AIP) were used to evaluate the atherogenic dyslipidemia. The AIP was determined as $\log_{10}$ (triglycerides in mmol/L / HDL-C in mmol/L). For combined-risk analysis, a triglyceride/HDL-C ratio ≥ 4.5 was used as a cut point for elevated.

Outcome Assessment

Three-point MACE (cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke) was the primary outcome. Follow-up of participants was performed by outpatient visits, telephone contacts and by reviewing hospital records. Suspected cardiovascular events were validated by pertinent clinical documentation, electrocardiography, cardiac biomarkers, imaging and discharge documentation.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range) and categorical variables were presented as frequencies and percentages. The independent-samples t test, Mann–Whitney U test, chi-square test, or Fisher exact test was used to compare participants with and without MACE, as appropriate. Independent predictors of MACE were identified by Cox proportional hazards regression, and reported as hazard ratios (HR) and adjusted hazard ratios (aHR) with 95% confidence intervals (CI). Kaplan–Meier analysis was used to compare MACE-free survival across cardiometabolic risk categories. Statistically significant differences were set at a 2 tailed p value of < 0.05 .

Ethical Considerations

The study was performed in compliance with the Declaration of Helsinki and institutional ethical guidelines. All participants gave written informed consent to participate in the study, which received ethical approval from the relevant institutional review committees of both centres.

RESULTS

Baseline Characteristics

A total of 200 patients with T2DM were included, with a mean age of 58.4 ± 9.2 years; 112 (56.0%) were male. In the median follow-up period of 10.1 months, 42 patients (21.0%) had an occurrence of MACE. Patients with MACE were older, had longer duration of diabetes, higher HbA1c and higher prevalence of previous atherosclerotic cardiovascular disease. They also had significantly elevated HOMA-IR, hs-CRP, triglyceride/HDL-C ratio, and atherogenic index of plasma, and significantly decreased HDL-C and eGFR (Table 1).

Table 1. Baseline Characteristics According to Major Adverse Cardiovascular Events

Variable	Over all (n=200)	No MACE (n=158)	MACE (n=42)	p-value
Age, years	58.4 $\pm$ 9.2	57.4 $\pm$ 8.9	62.1 $\pm$ 9.3	0.003
Male sex, n (%)	112 (56.0)	86 (54.4)	26 (61.9)	0.384
Diabetes duration, years	9.8 $\pm$ 5.3	9.1 $\pm$ 4.9	12.4 $\pm$ 5.8	<0.001
BMI, kg/m^2	29.1 $\pm$ 4.2	28.9 $\pm$ 4.1	29.8 $\pm$ 4.5	0.218
Hypertension, n (%)	137 (68.5)	103 (65.2)	34 (81.0)	0.049
Current smoking, n (%)	41 (20.5)	28 (17.7)	13 (31.0)	0.058
Previous ASCVD, n (%)	51 (25.5)	31 (19.6)	20 (47.6)	<0.001
HbA1c, %	8.3 $\pm$ 1.3	8.1 $\pm$ 1.2	8.9 $\pm$ 1.4	<0.001
eGFR, mL/min/1.73 m^2	81.6 $\pm$ 18.4	84.0 $\pm$ 17.5	72.7 $\pm$ 18.9	<0.001

HOMA-IR	4.8 (3.2–6.7)	4.2 (3.0–5.9)	6.5 (4.9–8.4)	<0.01
hs-CRP, mg/L	3.3 (1.9–5.4)	2.8 (1.6–4.5)	5.6 (3.7–7.9)	<0.01
Triglycerides, mg/dL	184 (146–236)	173 (141–220)	226 (181–282)	<0.01
HDL-C, mg/dL	39.8 ± 9.0	41.0 ± 8.7	35.4 ± 8.8	<0.01
TG/HDL-C ratio	4.8 (3.4–6.6)	4.3 (3.1–5.7)	6.4 (4.8–8.3)	<0.01
Atherogenic index of plasma	0.29 ± 0.19	0.25 ± 0.18	0.41 ± 0.18	<0.01

Incidence of Cardiovascular Events

Among the 42 patients who experienced MACE, nonfatal myocardial infarction was the most frequent first event, occurring in 19 patients (9.5%), followed by nonfatal ischemic stroke in 13 (6.5%) and cardiovascular death in 10 (5.0%). MACE occurred more frequently among patients with elevated HOMA-IR, hs-CRP, and triglyceride/HDL-C ratio. Event incidence progressively increased with accumulation of abnormal cardiometabolic domains, reaching 39.6% among patients with abnormalities in all three domains compared with 11.0% among those with zero or one abnormal domain (Table 2).

Table 2. Major Adverse Cardiovascular Events According to Cardiometabolic Risk Profile

Risk Profile/Outcome	Participants, n	MACE, n (%)	p-value
Nonfatal myocardial infarction	200	19 (9.5)	—
Nonfatal ischemic stroke	200	13 (6.5)	—

Cardiovascular death	200	10 (5.0)	—
HOMA-IR <5.0	108	13 (12.0)	<0.001
HOMA-IR ≥5.0	92	29 (31.5)	
hs-CRP <3 mg/L	95	12 (12.6)	0.006
hs-CRP ≥3 mg/L	105	30 (28.6)	
TG/HDL-C ratio <4.5	102	13 (12.7)	0.003
TG/HDL-C ratio ≥4.5	98	29 (29.6)	
0–1 elevated domains	91	10 (11.0)	<0.001
2 elevated domains	61	13 (21.3)	
3 elevated domains	48	19 (39.6)	

The three elevated domains were defined as HOMA-IR ≥5.0, hs-CRP ≥3 mg/L, and triglyceride/HDL-C ratio ≥4.5.

Predictors of Major Adverse Cardiovascular Events

On univariable Cox regression, HOMA-IR, hs-CRP, triglyceride/HDL-C ratio, previous ASCVD, HbA1c, and reduced eGFR were significantly associated with incident MACE. After multivariable adjustment, HOMA-IR remained independently associated with MACE (aHR 1.13, 95% CI 1.05–1.22; $p=0.002$), as did hs-CRP (aHR 1.09, 95% CI 1.03–1.15; $p=0.003$) and triglyceride/HDL-C ratio (aHR 1.11, 95% CI 1.03–1.20; $p=0.006$). Previous ASCVD was also independently associated with increased cardiovascular risk, whereas higher eGFR was associated with lower risk (Table 3).

Table 3. Cox Regression Analysis of Predictors of Major Adverse Cardiovascular Events

Predictor	Univariable HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
HOMA-IR, per 1-unit increase	1.19 (1.11–1.27)	<0.001	1.13 (1.05–1.22)	0.002
hs-CRP, per 1 mg/L increase	1.14 (1.08–1.20)	<0.001	1.09 (1.03–1.15)	0.003
TG/HDL-C ratio, per 1-unit increase	1.17 (1.09–1.26)	<0.001	1.11 (1.03–1.20)	0.006
Previous ASCVD	3.02 (1.65–5.53)	<0.001	2.18 (1.15–4.14)	0.017
HbA1c, per 1% increase	1.38 (1.14–1.68)	0.001	1.21 (1.00–1.47)	0.049
eGFR, per 10 mL/min/1.73 m ² increase	0.78 (0.68–0.90)	<0.001	0.84 (0.72–0.98)	0.027

Combined Cardiometabolic Risk

Kaplan–Meier analysis demonstrated progressively lower MACE-free survival with increasing numbers of abnormal cardiometabolic domains, with the lowest event-free survival observed among patients with abnormalities in all three domains (*log-rank* $p<0.001$). After adjustment for conventional cardiovascular risk factors, patients with all three abnormal domains had a 3.27-fold greater hazard of MACE compared with those with zero or one abnormal domain (aHR 3.27, 95% CI 1.55–6.90; $p=0.002$). Addition of HOMA-IR, hs-CRP, and triglyceride/HDL-C ratio to the conventional clinical model improved the C-statistic from 0.72 to 0.81, indicating enhanced discrimination for incident MACE (Figure 1).

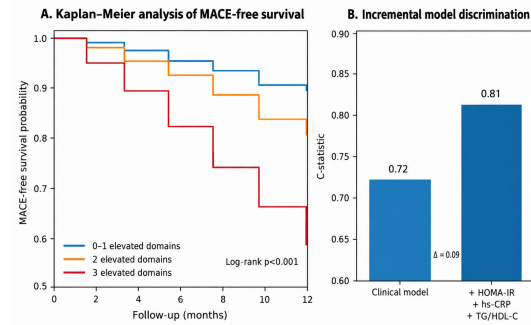


Figure 1. MACE-Free Survival According to Cardiometabolic Risk Burden and Incremental Predictive Performance of Biomarkers: (A) Kaplan–Meier curves showing MACE-free survival according to the number of elevated cardiometabolic domains. Participants with abnormalities in all three domains had the lowest event-free survival, whereas those with zero or one elevated domain had the highest survival probability. The difference between groups was statistically significant (*log-rank* $p<0.001$). Elevated domains were defined as HOMA-IR ≥ 5.0 , hs-CRP ≥ 3 mg/L, and triglyceride/HDL-C ratio ≥ 4.5 . **(B)** Incremental model discrimination showing improvement in the C-statistic from 0.72 for the conventional clinical model to 0.81 after addition of HOMA-IR, hs-CRP, and triglyceride/HDL-C ratio, corresponding to an absolute increase of 0.09.

Discussion

This prospective multicenter cohort study showed that insulin resistance, systemic inflammation, and atherogenic dyslipidemia were independently associated with major adverse cardiovascular events in type 2 diabetes mellitus patients. HOMA-IR, hs-CRP, triglyceride/HDL-C ratio and atherogenic index of plasma were significantly higher in patients who developed MACE compared with the event-free patients. Focusing on the results of the former, it is important to note that the presence of abnormalities for all three cardiometabolic domains was linked to the lowest rates of MACE-free survival and to a greater than threefold higher rate of adjusted cardiovascular risk. This research confirms the notion that there are multiple interlinked metabolic pathways that contribute to residual cardiovascular risk in T2DM in addition to hyperglycemia [1].

Even after controlling for standard cardiovascular risk factors, insulin resistance was found to be an independent predictor for MACE. Biologically, this finding is plausible since insulin resistance is associated with endothelial dysfunction, oxidative stress, sympathetic nervous system activation,

decreased nitric oxide bioavailability, increased production of triglyceride-rich lipoproteins in the liver and a prothrombotic state [2]. Insulin-resistance indices have also previously been shown to be associated with cardiovascular outcomes, and continuous insulin resistance could be a vascular risk factor, even for those on standard glucose lowering therapy [3]. In the current cohort, the independent association seen for HOMA-IR adds to the possible relevance of metabolic dysfunction, apart from glycemic control [4].

Systemic inflammation was also found to be a significant risk factor for cardiovascular disease. The hs-CRP levels were significantly elevated in patients with MACE, and hs-CRP was independently associated with cardiovascular risk after multivariate adjustment. Visceral adiposity, oxidative stress, advanced glycation products, endothelial injury, and activation of innate immune pathways are all factors that contribute to chronic inflammation in T2DM [4]. Residual inflammatory risk has been gained increasing attention in diabetes patients with proven cardiovascular disease, including those taking a proper lipid-lowering therapy [5]. Randomized evidence of reduction of cardiovascular events after targeted inhibition of inflammatory pathways further suggests that inflammation is not just a marker of risk, but an active participant in the progression of atherosclerotic disease [6].

Another major factor associated with MACE in this study was atherogenic dyslipidemia. Triglyceride levels were higher and HDL-C was lower, while AIP values and triglyceride/HDL-C ratios were higher in patients with cardiovascular events. This is typical of the insulin-resistant lipid phenotype that is found in T2DM, and is associated with elevated levels of triglyceride-rich lipoproteins, remnant cholesterol and small dense LDL particles [7]. Past research has found a correlation between AIP and cardiovascular outcomes via the triglyceride/HDL-C ratio, especially in patients with diabetes and known coronary disease [8]. These data suggest that there may be residual lipid-related risk even with conventional use of primarily LDL-C to assess risk [9-11].

The present study had several important findings, including that cardiovascular risk increased with the number of abnormal cardiometabolic domains. Those patients with all three abnormalities had a significantly lower MACE-free survival and a 3.27-fold higher adjusted hazard of cardiovascular events than those with zero or one abnormal domain [12]. The biological

coherence of this association is apparent as insulin resistance, inflammation and atherogenic dyslipidaemia share molecular and metabolic mechanisms. Insulin resistance leads to an increased free fatty acid flux and liver triglyceride production, while adipose tissue dysfunction leads to an increase in production of inflammatory cytokines. Inflammation can also disrupt the insulin signal and vascular function, leading to a vicious cycle of metabolic and vascular damage [13].

The increase in C-statistic to 0.81 after incorporating HOMA-IR, hs-CRP and triglyceride/HDL-C ratio implies that these biomarkers could offer additional prognostic value over traditional clinical parameters [14]. While this improvement is promising, caution should be exercised in interpreting these results as predictive models created in small cohorts can overestimate discrimination. However, combined metabolic, inflammatory and lipid abnormalities may be useful to identify a subset of T2DM patients at the highest cardiovascular risk despite traditional risk factor assessment [10,15].

The results also highlight the need for holistic cardiovascular risk reduction in patients with T2DM. Contemporary management involves glycemic control as well as parallel control of other factors (including blood pressure, lipids, body weight, smoking status, renal risk) and, if needed, use of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists [16-18]. Therefore, the measurement of HOMA-IR, hs-CRP, and triglyceride-derived lipid indices should be considered as potentially complementary to, but not a replacement for, existing methods of cardiovascular risk assessment and evidence-based therapy [19].

The multicenter prospective study design and the evaluation of three interconnected cardiometabolic pathways are important strengths of this study. However, some considerations need to be taken in mind. The sample size and the number of cardiovascular events were relatively small and the follow-up time was short (around one year). HOMA-IR is therefore a proxy for insulin sensitivity, and hs-CRP was determined at one time point only and might be subject to biological variation. The possibility of unmeasured residual confounding due to dietary factors, physical activity, adherence to medication, socioeconomic factors, and unmeasured biomarkers cannot be ruled out. Furthermore, the study was carried out at two centers in Pakistan and therefore might not be applicable to other populations. Thus, larger

multicenter studies with longer term follow-up and external validation are needed [20].

CONCLUSION

Insulin resistance, systemic inflammation and atherogenic dyslipidemia were independent risk factors for major cardiovascular events in T2DM. The levels of HOMA-IR, hs-CRP, and the triglyceride/HDL-C ratio identified increased cardiovascular risk, and the presence of abnormalities in all three domains was linked to significantly reduced MACE-free survival and a significantly higher adjusted risk of cardiovascular events. These cardiometabolic markers could be valuable for risk stratification of cardiovascular disease in T2DM, if added to traditional clinical assessment; larger prospective studies are required to confirm their incremental value and clinical utility.

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