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Original Research Article

INSULIN RESISTANCE AND ITS CORRELATION WITH SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS WITHOUT DIABETES: A COMPARATIVE STUDY

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ABSTRACT

Background: Coronary artery disease (CAD) remains the leading cause of mortality globally. While diabetes mellitus is a well-established equivalent risk factor for CAD, the role of insulin resistance (IR) in patients with normoglycemia is less clearly defined. Subclinical metabolic dysregulation may drive atherogenesis before the onset of overt hyperglycemia. **Materials and Methods:** We conducted a cross-sectional comparative study involving 240 patients undergoing elective coronary angiography. Patients were divided into a CAD group (significant stenosis ≥50%) and a Control group (normal coronaries or insignificant stenosis). Patients with a known history of diabetes or HbA1c ≥6.5% were excluded. Fasting insulin and glucose were measured to calculate HOMA-IR. CAD severity was quantified using the Gensini score and the number of vessels affected. **Result:** The CAD group (n=140) exhibited significantly higher mean HOMA-IR levels compared to the Control group (n=100) (3.42±1.15 vs. 1.76±0.58, p<0.001). Patients with multi-vessel disease had higher HOMA-IR (4.1±1.2) compared to single-vessel disease (2.8±0.9). A strong positive linear correlation was observed between HOMA-IR and the Gensini score (r=0.68,p<0.001). Multivariate regression analysis identified HOMA-IR as an independent predictor of high CAD severity (Odds Ratio 2.85, 95% CI 1.65–4.92, p=0.002), independent of BMI and lipid profile. **Conclusion:** In non-diabetic individuals, insulin resistance is strongly associated with the presence and severity of coronary artery disease. HOMA-IR may serve as a valuable marker for early risk stratification in patients who do not meet the criteria for diabetes but possess metabolic vulnerability.

INTRODUCTION

Coronary artery disease (CAD) continues to be the predominant cause of morbidity and mortality worldwide, placing a substantial burden on healthcare systems.[1] While traditional risk factors such as hypertension, dyslipidemia, and smoking explain a significant proportion of cardiovascular risk, a residual risk remains unaccounted for, particularly in individuals who appear metabolically healthy by standard definitions.[2] Among the metabolic risk factors, Type 2 Diabetes Mellitus (T2DM) is widely recognized as a coronary risk equivalent. However, the pathological processes driving atherosclerosis often begin years, if not decades, before the clinical diagnosis of diabetes.[3]

Insulin resistance (IR) is defined as a sub-optimal biological response of peripheral tissues to insulin, leading to compensatory hyperinsulinemia to maintain euglycemia. It is the core pathophysiological defect in metabolic syndrome and a precursor to T2DM.[4] Recent evidence suggests that hyperinsulinemia itself exerts direct atherogenic effects. Insulin acts as a growth factor for vascular smooth muscle cells and promotes inflammation and endothelial dysfunction by impairing nitric oxide bioavailability.[5] Despite this, standard cardiovascular risk assessments often rely on fasting glucose or HbA1c, potentially missing a large cohort of patients with severe insulin resistance who maintain normal glucose levels through pancreatic compensation.[6]

The relationship between IR and cardiovascular events in diabetic populations is well-documented. However, data regarding the impact of IR on the severity and extent of coronary anatomical involvement in non-diabetic subjects remains conflicting.[7] Some studies suggest that IR is only relevant when accompanied by other components of metabolic syndrome, while others argue it is an independent predictor.[8] Furthermore, the use of specific angiographic scoring systems, such as the

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Gensini score, to correlate subclinical metabolic dysfunction with plaque burden in non-diabetics represents an area requiring further exploration.[9]
Therefore, the aim of this study was to investigate the correlation between insulin resistance, assessed via the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and the severity of coronary artery disease in a population of patients strictly defined as non-diabetic. We hypothesized that higher HOMA-IR levels would correlate with more complex and extensive coronary atherosclerosis, independent of traditional risk factors.

MATERIALS AND METHODS

Study Design and Population: This was a cross-sectional, observational, comparative study conducted at the cardiology care unit of tertiary care hospital.
Sample Size: Based on previous literature suggesting a correlation coefficient of 0.3 between HOMA-IR and CAD severity, with a power of 80% and an alpha error of 0.05, a minimum sample size of 190 patients was calculated. To account for potential dropouts or incomplete data, 240 patients were recruited.
Inclusion and Exclusion Criteria
Inclusion:
Adult patients (aged 30–75 years) undergoing elective coronary angiography (CAG) for suspected CAD (based on symptoms or positive stress tests) were eligible.
Exclusion:
Patients with a history of diabetes mellitus, those taking hypoglycemic agents, or those with a screening fasting plasma glucose ≥126 mg/dL or HbA1c ≥6.5% were excluded. Other exclusion criteria included acute coronary syndrome (STEMI/NSTEMI) within the last 4 weeks, severe heart failure (NYHA III-IV), chronic kidney disease (Creatinine >1.5 mg/dL), active infection, malignancy, or thyroid dysfunction.
Data Collection and Biochemical Analysis: Demographic data (age, sex, smoking status) and anthropometric measurements (BMI, waist circumference) were recorded. Venous blood samples were collected after an overnight fast (minimum 8 hours) prior to the angiogram.
Biochemical parameters included Total Cholesterol, Triglycerides, LDL, HDL, Fasting Plasma Glucose (FPG), and Fasting Serum Insulin (FSI). FSI was measured using chemiluminescent immunoassay.
Insulin resistance was calculated using the HOMA-IR formula: HOMA-IR = (fasting glucose x fasting insulin)/22.5.
A HOMA-IR value of >2.5 was considered indicative of insulin resistance.
Angiographic Assessment: Coronary angiography was performed via the radial or femoral approach. The angiograms were reviewed by two experienced interventional cardiologists blinded to the patients' biochemical profiles.

- Group Allocation: Patients were divided into two groups:
- CAD Group: Presence of ≥50% luminal stenosis in at least one major epicardial artery.
- Control Group: Normal coronaries or luminal stenosis <50%.
- Severity Assessment: In the CAD group, severity was quantified using the Gensini Score. This score assigns a severity point to each lesion based on the degree of stenosis (1 for 25%, 2 for 50%, 4 for 75%, 8 for 90%, 16 for 99%, and 32 for total occlusion) multiplied by a factor representing the functional significance of the myocardial area supplied by that segment. Patients were also classified by the number of vessels involved (Single, Double, or Triple Vessel Disease).

Statistical Analysis: Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) and compared using the Student's t-test or ANOVA. Categorical variables were presented as percentages and compared using the Chi-square test. Pearson's correlation coefficient (r) was used to assess the relationship between HOMA-IR and Gensini scores. Multivariate logistic regression analysis was performed to identify independent predictors of CAD. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics: A total of 240 patients met the inclusion criteria. Based on angiographic findings, 140 patients were assigned to the CAD Group and 100 to the Control Group. The mean age of the study population was 58.4±9.2 years.
As shown in Table 1, the CAD group had a higher proportion of males and smokers. While BMI was higher in the CAD group (28.1±3.4 vs. 26.5±3.1), the difference in Fasting Plasma Glucose was statistically significant but clinically narrow (94.2 vs. 89.5 mg/dL). However, Fasting Serum Insulin was markedly elevated in the CAD group (14.8 vs. 7.9 μU/mL), resulting in a significantly higher HOMA-IR.

Table 1: Baseline Demographic and Biochemical Characteristics

Parameter	CAD Group (n = 140)	Control Group (n = 100)	p-value
Age (years)	60.1 ± 8.5	56.2 ± 9.1	0.04
Male Gender, n (%)	88 (62.8%)	45 (45.0%)	0.01
BMI (kg/m²)	28.1 ± 3.4	26.5 ± 3.1	0.02
Total Cholesterol (mg/dL)	195.4 ± 32.1	178.2 ± 28.4	0.03
LDL Cholesterol (mg/dL)	122.5 ± 24.6	105.1 ± 21.3	<0.001

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HDL Cholesterol (mg/dL)	38.4 ± 8.2	46.5 ± 9.5	<0.001
Fasting Glucose (mg/dL)	94.2 ± 9.8	89.5 ± 8.4	0.02
Fasting Insulin (µU/mL)	14.8 ± 5.2	7.9 ± 3.1	<0.001
HOMA-IR	3.42 ± 1.15	1.76 ± 0.58	<0.001

Association Between HOMA-IR and Angiographic Severity: Within the CAD group, patients were stratified based on the number of vessels involved. There was a progressive, stepwise increase in HOMA-IR levels as the disease complexity increased. Patients with Triple Vessel Disease (TVD) had a mean HOMA-IR of 4.12±1.21, significantly higher than those with Single Vessel Disease (SVD) (2.85±0.94). The prevalence of insulin resistance (defined as HOMA-IR >2.5) was 82.6% in the TVD group compared to 54.3% in the SVD group. These findings are detailed in [Table 2].

Table 2: HOMA-IR Levels According to Number of Involved Vessels

Variable	Single Vessel (n=46)	Double Vessel (n=48)	Triple Vessel (n=46)	p-value*
Fasting Insulin (µU/mL)	11.8 ± 3.8	15.2 ± 4.5	17.5 ± 5.8	<0.001
HOMA-IR (Mean ± SD)	2.85 ± 0.94	3.28 ± 1.05	4.12 ± 1.21	<0.001
HOMA-IR > 2.5, n (%)	25 (54.3%)	36 (75.0%)	38 (82.6%)	0.008
Gensini Score	22.4 ± 8.5	44.1 ± 12.6	78.5 ± 21.4	<0.001

One-way ANOVA across the three subgroups.

Correlation and Regression Analysis: Pearson correlation analysis revealed a strong, positive linear relationship between HOMA-IR values and the Gensini score ($r=0.68, p<0.001$).

To determine if HOMA-IR was an independent predictor of high CAD severity (defined as Gensini score >40), a multivariate logistic regression was performed [Table 3]. After adjusting for potential confounders including age, gender, BMI, LDL, and smoking, HOMA-IR remained a significant independent predictor. For every 1-unit increase in HOMA-IR, the risk of having a high Gensini score increased by approximately 2.8 times.

Table 3: Multivariate Logistic Regression for Predictors of High CAD Severity (Gensini Score > 40)

Variable	Odds Ratio (OR)	95% Confidence Interval	p-value
Age	1.04	0.98 – 1.10	0.18
Male Gender	1.85	1.12 – 3.15	0.03
Smoking	2.10	1.25 – 3.65	0.01
BMI	1.08	0.99 – 1.18	0.09
LDL Cholesterol	1.02	1.01 – 1.04	0.04
HOMA-IR	2.85	1.65 – 4.92	0.002

DISCUSSION

The primary finding of this study is that insulin resistance, measured by HOMA-IR, is significantly elevated in non-diabetic patients with angiographically proven coronary artery disease compared to controls. Furthermore, we demonstrated a robust positive correlation between the degree of insulin resistance and the severity of atherosclerosis, as evidenced by the number of affected vessels and the Gensini score. Notably, HOMA-IR remained an independent predictor of severe CAD even after adjusting for traditional risk factors such as LDL cholesterol and BMI.

Our results align with the "common soil" hypothesis, which postulates that IR and atherosclerosis share common inflammatory and metabolic antecedents.[10] While previous studies have firmly established this link in diabetic populations, the non-diabetic cohort represents a critical "grey zone." Our finding that patients with Triple Vessel Disease had a mean HOMA-IR of 4.12—despite having normal fasting glucose—highlights that significant metabolic pathology can exist in the absence of hyperglycemia. This corroborates the findings of Adeva-Andany et al., who argued that insulin resistance is the universal cause of arterial disease, irrespective of glycemic status.[11]

The mechanism linking IR to CAD severity in non-diabetics is likely multifactorial. Under conditions of insulin resistance, the PI3K/Akt signaling pathway (which promotes nitric oxide production and vasodilation) is impaired, while the MAPK pathway (which promotes cellular proliferation and inflammation) remains active or becomes overstimulated.[12] This selective pathway dysfunction leads to endothelial dysfunction, the earliest stage of atherosclerosis. Additionally, hyperinsulinemia stimulates the migration of vascular smooth muscle cells into the intima and enhances the production of plasminogen activator inhibitor-1 (PAI-1), creating a pro-thrombotic state.[13]

Our study utilized the Gensini score for severity assessment, offering a more granular analysis than simply determining the presence or absence of disease. The strong correlation ($r=0.68$) observed here is consistent with the findings of Gayoso-Diz et al., who reported similar associations in a European cohort.[14] However, our odds ratio for HOMA-IR (2.85) was slightly higher than some previous reports, potentially due to the strict exclusion of pre-diabetics (HbA1c > 6.5%) in our control group, which

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sharpened the contrast between the metabolically healthy and unhealthy groups.

An interesting observation in our study was that BMI was not an independent predictor of CAD severity in the multivariate analysis, whereas HOMA-IR was. This supports the concept of the "metabolically obese normal-weight" phenotype.[15-18] It suggests that the metabolic activity of visceral adiposity (reflected by IR) is more atherogenic than the total body mass itself. This finding has significant clinical implications: reliance on BMI or glucose levels alone for risk stratification may provide a false sense of security in non-diabetic patients.[19-23]

Limitations: This study has several limitations. First, its cross-sectional design precludes the determination of causality. Second, HOMA-IR is a surrogate marker primarily reflecting hepatic insulin resistance; the gold standard hyperinsulinemic-euglycemic clamp was not feasible due to its complexity. Third, the study was single-centered, which may limit the generalizability of the results to different ethnic populations.

CONCLUSION

In conclusion, this study demonstrates that insulin resistance is a significant and independent marker for the severity of coronary artery disease in patients without diabetes. High HOMA-IR levels correlate strongly with extensive multi-vessel disease and higher plaque burden as quantified by the Gensini score.

These findings suggest that metabolic risk stratification in cardiology should extend beyond standard glucose and lipid profiles. The inclusion of fasting insulin and HOMA-IR calculation in routine cardiovascular assessments could identify a high-risk subset of "euglycemic" patients who may benefit from aggressive lifestyle interventions or insulin-sensitizing pharmacotherapy to halt the progression of atherosclerosis.

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