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Role of Glycemic Control in Modulating Coronary Inflammation and Plaque Vulnerability in Low-Risk ACS: A Coronary CT-Based FAI Study

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ABSTRACT

Diabetes mellitus is a well-established risk factor for the development and progression of coronary artery disease.Coronary artery disease (CAD) remains a major contributor to cardiovascular morbidity and mortality. Therefore, early identification of low-grade vascular inflammation is essential for risk stratification and prevention of adverse events. Coronary computed tomography angiography (CCTA), when combined with pericoronary fat attenuation index (FAI) analysis, provides a non-invasive imaging modality to detect coronary inflammation and characterize high-risk atherosclerotic plaque features. alongside systemic inflammation assessed via C-reactive protein (CRP) levels. This investigation focuses on patients with low-risk acute coronary syndrome (ACS) who have been known to be diabetic.

KEYWORDS: Diabetes Mellitus (DM), Low-Risk ACS, Coronary Computed Tomography Angiography (CCTA), Pericoronary Fat Attenuation Index (FAI) ,C-Reactive Protein (CRP).

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INTRODUCTION

Coronary artery disease (CAD)

Coronary artery disease (CAD) is a leading cause of morbidity and mortality globally, impacting both developed and developing nations. It is a chronic atherosclerotic condition characterized by endothelial dysfunction and inflammation, leading to the development of lipid-laden plaques in the coronary arteries. Clinically, CAD manifests as stable angina, unstable angina, myocardial infarction, or sudden cardiac death [(1)]. Genome-wide association studies (GWAS) have identified several genetic variants strongly associated with CAD, and recent research suggests that global differences in CAD risk are largely shaped by demographic history [(2)]. In addition to genetic predisposition, environmental factors and individual lifestyle choices—such as smoking, diet, physical inactivity, and comorbid conditions—play critical roles in disease onset and progression. In India, CAD has become a major cause of death and disability, with mortality rates steadily increasing since 1985 and projections indicating a doubling by 2015 [(3, 4)]. Although advances in pharmacological interventions, including aspirin, statins, and beta-blockers, have improved outcomes, these therapies primarily slow disease progression and are effective in only a subset of patients (5). This underscores the continuing need for targeted prevention strategies and personalized treatment approaches.

Prevalence of Coronary Artery Disease

The prevalence of coronary artery disease (CAD), also referred to as coronary heart disease (CHD), varies significantly depending on geographic region, ethnicity, and gender. Epidemiological research on cardiovascular conditions has provided essential insights that can help shape effective prevention and control strategies at both individual and public health levels [(6)].

In the United States, data from 2010 indicated that CAD was most common among individuals aged over 65, with a prevalence rate of 19.8%. This was followed by those aged 45–64 years at 7.1%, and the 18–44 age group at 1.2%. In the United Kingdom, CAD accounted for 46% of all cardiovascular-related deaths in 2012 (7).

Risk Factors Associated with Coronary Artery Disease

Coronary artery disease (CAD) is a multifactorial condition influenced by both genetic predispositions and modifiable environmental and metabolic risk factors [(8)]. Among the most significant contributors is **cigarette smoking**, which accounts for approximately 30–40% of CAD-related deaths annually. Smokers exhibit a 70% higher CAD mortality rate compared to non-smokers, with a clear dose–response relationship observed between smoking intensity and disease risk. Mechanistically, smoking induces endothelial injury, promotes platelet adhesion, and stimulates vascular smooth muscle proliferation via platelet-derived growth factor (PDGF), all of which accelerate atherosclerosis [(9)]. **Type 2 diabetes mellitus** is another critical risk factor, often associated with atherogenic dyslipidemia characterized by elevated triglycerides, VLDL cholesterol, and reduced HDL cholesterol, contributing significantly to plaque formation [(10)]. **Hypertension** exacerbates CAD by increasing arterial wall stress and endothelial permeability, accelerating plaque development, and often coexisting with insulin resistance and dyslipidemia [(11)]. **Obesity**, particularly central adiposity, promotes CAD through dysregulated adipokine secretion and chronic inflammation, both of which enhance atherogenesis [(12)]. In addition to these common risk factors, rare metabolic disorders such as **homocystinuria** can elevate cardiovascular risk through hyperhomocysteinemia, which affects coagulation and endothelial function [(13)].

Hyperuricemia, while still under investigation for causality, is consistently linked to increased carotid intima-media thickness and may contribute to vascular smooth muscle proliferation, nitric oxide inhibition, and insulin resistance [14]. Finally, **psychosocial stress** is increasingly recognized as a modifiable contributor to CAD, influencing physiological pathways such as blood pressure regulation, insulin sensitivity, coagulation, and endothelial health [15] .

Diagnostic Tests and Procedures for Coronary Artery Disease (CAD)

A variety of diagnostic modalities are employed to assess coronary artery disease (CAD), each providing critical insights into cardiac function, perfusion, and anatomical integrity. These techniques range from non-invasive imaging to invasive procedures and molecular biomarker analysis [16].

Electrocardiogram (ECG or EKG)

An electrocardiogram records the heart's electrical activity, enabling the assessment of rhythm abnormalities and the detection of ischemic changes such as ST-segment depression or elevation, and T wave inversion. It is often the first-line diagnostic tool in suspected CAD cases [16].

Exercise Stress Testing

Stress tests evaluate the heart's performance under conditions of physical exertion, typically using a treadmill or stationary bicycle. During the test, ECG monitoring (and sometimes echocardiography or CT imaging) is performed to identify exercise-induced ischemic changes, including ST-segment deviations, T wave abnormalities, or arrhythmias, which are indicative of compromised myocardial perfusion [16] .

Cardiac Magnetic Resonance Imaging (MRI)

Cardiac MRI provides detailed visualization of myocardial tissue and blood flow patterns. It is especially useful in assessing structural heart diseases and differentiating cardiomyopathy subtypes using gadolinium-enhanced imaging. Cardiac MRI allows for precise evaluation of myocardial fibrosis, inflammation, and viability[16].

Positron Emission Tomography (PET)

Cardiac PET imaging is a nuclear diagnostic modality that quantifies myocardial blood flow and detects microvascular coronary disease. It is particularly valuable for evaluating coronary microcirculation and assessing myocardial viability and perfusion under resting or stress conditions [16].

Coronary Angiography

Invasive coronary angiography, often performed via cardiac catheterization, remains the gold standard for visualizing coronary artery lumen and identifying significant stenoses. It allows for real-time assessment of obstructive lesions and is typically used when non-invasive tests suggest high CAD probability. Advanced intravascular techniques such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) enhance lesion characterization by evaluating plaque composition (calcium vs. lipid-rich) and vessel wall morphology [16] .

Coronary Computed Tomographic Angiography (CTCA)

CTCA is a non-invasive imaging modality that provides high-resolution visualization of coronary arteries. It enables the quantitative evaluation of luminal narrowing, vessel wall remodeling, and plaque morphology—including total, calcified, and non-calcified plaque volumes—using advanced technologies such as dual-energy or spectral CT [17]. CTCA can also assess the remodeling index (RI), a parameter that indicates plaque direction of growth (inward vs. outward), which is not accessible via conventional X-ray angiography (XRA).

CTCA offers the advantage of simultaneously imaging the entire coronary tree with low contrast media usage, making it a promising tool for early detection and comprehensive risk stratification of CAD [17].

Myocardial Perfusion Imaging (MPI) via SPECT and PET

Nuclear imaging techniques, including single-photon emission computed tomography (SPECT) and PET, assess myocardial perfusion through the administration of radiotracers. These tests evaluate ischemia by quantifying blood flow and can also assess wall motion and myocardial thickening. Perfusion abnormalities during stress or rest are suggestive of flow-limiting coronary disease [18].

Cardiac PET is particularly sensitive for evaluating myocardial viability.

Therapeutic Approaches for CAD

Advancements in medical therapy have significantly improved the management of coronary artery disease (CAD), with pharmacologic interventions aimed at symptom control, prevention of ischemic events, and reduction of mortality [19].

Antiplatelet agents are central to CAD treatment. **Aspirin**, through irreversible inhibition of cyclooxygenase-1 (COX-1), prevents thromboxane A_2 formation and reduces platelet aggregation. A daily maintenance dose of 75–150 mg is effective in preventing cardiovascular events; however, its use is contraindicated in patients at high risk of bleeding [20]. **Thienopyridines**, such as clopidogrel, irreversibly inhibit P2Y12 receptors and block platelet aggregation via glycoprotein IIb/IIIa pathway inhibition. These are prodrugs requiring activation by hepatic CYP450 enzymes [21]. For high-risk or drug-resistant patients,

glycoprotein IIb/IIIa inhibitors like abciximab, tirofiban, and eptifibatide provide potent antiplatelet effects by directly blocking fibrinogen receptors on platelets [22].

β-blockers are essential in reducing myocardial oxygen demand by decreasing heart rate and contractility. Their use in angina and post-myocardial infarction patients has been shown to improve long-term survival, particularly in older adults [23]. **Nitrates**, especially sublingual nitroglycerin, provide rapid relief of angina symptoms by promoting vasodilation and enhancing oxygen supply, and are often used in conjunction with β-blockers when monotherapy is insufficient [24].

Calcium channel blockers are effective in managing coronary vasospasm and chronic stable angina by reducing vascular resistance and myocardial oxygen demand. In patients with refractory angina, **ranolazine**, a late sodium current inhibitor, has shown efficacy by decreasing intracellular calcium levels, thus reducing myocardial ischemia. It may also have beneficial effects on glycemic control and overall mortality [25].

Angioplasty (Percutaneous Coronary Intervention)

- Coronary angioplasty is also known as percutaneous coronary intervention. Balloon catheter is used to **open blocked coronary arteries** during acute MI.
- Reduces **chest pain** and **shortness of breath**. [20].
- **Stent Placement :** After angioplasty, a **stent** is placed to prevent re-narrowing [26]

Coronary Artery Bypass Grafting (CABG)

- **CABG** is a **surgical treatment** for severe CAD.
- Involves grafting a **healthy artery or vein** to bypass blocked coronary arteries.
- Preferred in:
    - Multi-vessel disease
    - Left main coronary artery disease
    - Diabetes with complex lesions

Chronic Coronary Syndrome (CCS) is a clinical entity within the spectrum of coronary artery disease (CAD), primarily resulting from atherosclerotic plaque accumulation in the epicardial coronary arteries. These plaques may be obstructive or non-obstructive and lead to recurrent or persistent myocardial ischemia. The progression of CCS can be modulated through lifestyle interventions, pharmacologic therapy, and revascularization procedures aimed at stabilizing or regressing the disease process [27].

Pathophysiology

The hallmark of CCS is **myocardial ischemia**, which arises from an imbalance between myocardial oxygen supply and demand. Increased heart rate and reduced stroke volume are key contributors to this imbalance. Sympathetic activation further exacerbates ischemia through α-adrenergic–mediated coronary vasoconstriction [28].

An important adaptive mechanism is the development of **coronary collateral circulation** (arteriogenesis), which involves the remodeling and enlargement of pre-existing microvascular channels (20–200 μm) in response to hemodynamic stress and hypoxia-induced signaling [29, 30]. Arteriogenesis proceeds in three stages:

1. **First 24 hours** – passive vessel dilation, endothelial activation, and matrix degradation;
2. **Day 1 to 3 weeks** – monocyte infiltration and cytokine-driven proliferation of vascular cells;
3. **3 weeks to 3 months** – structural maturation and wall thickening of collateral vessels, which may reach ~1 mm in diameter [31].

Etiology

While **atherosclerosis** remains the predominant cause of CCS [32], several **non-atheromatous** etiologies also contribute. These include:

- **Congenital anomalies** (e.g., anomalous origin of the LCA, myocardial bridging)
- **Coronary artery spasm** (e.g., Prinzmetal angina, stimulant-induced vasospasm)
- **Inflammatory vasculitides** (e.g., Kawasaki disease, Takayasu arteritis)
- **Embolic events** (e.g., from infective endocarditis or valvular disease)
- **Prothrombotic states** (e.g., polycythemia, hemoglobinopathies, oral contraceptives)
- **Traumatic injuries**, either iatrogenic or accidental [32].

Clinical Course

CCS is inherently **chronic and progressive**, often remaining stable over time but carrying the risk of **acute decompensation** due to **atherothrombotic events**, such as plaque rupture or erosion. Clinically, CAD presents as a continuum, with CCS representing the stable phase and **acute coronary syndrome (ACS)** denoting sudden-onset ischemia and infarction [32].

Acute Coronary Syndrome (ACS) refers to a group of urgent cardiac conditions caused by sudden reduction in coronary blood flow, including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). ACS is a major global cause of morbidity and mortality (33, 34).

The pathophysiology of ACS involves acute myocardial ischemia primarily triggered by coronary atherosclerosis and plaque disruption. The leading mechanisms include plaque rupture, the most common cause, and superficial plaque erosion. These processes promote platelet activation and thrombus formation, contributing to vessel occlusion. Complications of ACS include acute heart failure and increased short-term mortality, highlighting the condition's clinical severity (33, 34)

Diagnosis relies on clinical assessment, electrocardiography (ECG), and cardiac biomarkers, particularly high-sensitivity troponins, which facilitate rapid identification and rule-out of NSTEMI. Imaging tools like cardiac CT angiography and prehospital ECGs enhance early STEMI detection. Diagnosis can be challenging in women, older adults, and patients with comorbidities due to atypical presentations and confounding results (34, 35).

Management prioritizes immediate aspirin administration and prompt referral for emergency care. For STEMI, primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy, with fibrinolytic therapy as an alternative when PCI is unavailable (36). Pharmacologic treatment includes dual antiplatelet therapy, anticoagulants, beta-blockers, lipid-lowering agents, and neurohormonal antagonists. Secondary prevention focuses on intensive lipid management, lifestyle modification, and long-term pharmacotherapy to reduce recurrence risk.

Guidelines for ACS continue to evolve, emphasizing improved care approaches, especially for understudied populations, and refining risk stratification and treatment protocols (34, 35).

Low-risk Acute Coronary Syndrome (ACS) refers to patients presenting with chest pain or suspected ACS who, after initial clinical evaluation, are assessed to have a low likelihood of major adverse cardiac events (MACE). The goal in managing these patients is to optimize healthcare resource utilization by safely reducing unnecessary hospital admissions while ensuring patient safety (37).

Risk stratification commonly employs clinical decision tools such as the HEART and GRACE scores, which integrate clinical parameters including age, cardiovascular risk factors, ECG findings, and troponin levels to estimate the risk of MACE and guide decisions regarding safe discharge or further diagnostic testing (37). Low-risk patients typically demonstrate normal ECG findings, negative cardiac biomarkers, absence of ongoing chest pain, and low baseline demographic risk (37). Early coronary angiography identifies approximately 25% of ACS patients as very low risk, who may not require admission to a cardiac intensive care unit (CICU) (38).

Management protocols support safe discharge for up to 31% of emergency department chest pain patients classified as low risk, with clinical decision rules showing a 99.6% negative predictive value for 30-day adverse cardiac events (38). Coronary CT angiography (CCTA) serves as an effective non-invasive imaging modality in low-to-intermediate-risk patients, facilitating early discharge with no recorded myocardial infarction or cardiac death within 30 days following a negative scan (39). Additionally, virtual ward models involving remote monitoring for patients awaiting angiography reduce hospital length of stay and associated costs without increasing readmission rates or mortality (39).

Coronary computed tomography angiography (CCTA) has become an essential non-invasive imaging technique for the assessment of coronary artery disease (CAD), offering high diagnostic accuracy through detailed visualization of coronary anatomy and plaque morphology using advanced multi-detector CT scanners (40, 41). It is recommended as a first-line test in patients with suspected CAD, especially those presenting with chest pain and non-diagnostic ECG and normal cardiac biomarkers (42).

CCTA effectively rules out obstructive coronary stenosis with a high negative predictive value, reducing unnecessary invasive coronary angiography (ICA) procedures. While approximately one-third of patients undergoing ICA receive revascularization, most show either normal or non-obstructive CAD. The integration of CT-derived fractional flow reserve (FFR-CT) enhances the functional assessment of coronary lesions, improving patient selection for revascularization and allowing safe avoidance of ICA in many cases (43).

CCTA also plays a critical role in pre-procedural planning by providing comprehensive evaluation of vessel diameter, lesion length, and plaque composition, which assists in choosing appropriate intervention strategies such as PCI or coronary artery bypass grafting (CABG). Imaging quality is optimized using ECG-gating at specific cardiac cycle phases, enabling precise 3D reconstructions with measurements that correlate closely with invasive angiography (44).

Despite its advantages, CCTA has limitations including reduced image quality in patients with high heart rates, arrhythmias, or heavy calcification, and concerns related to radiation exposure and iodinated contrast use, especially in younger or renally impaired patients. Its primary output is anatomical data, necessitating complementary functional assessments for comprehensive ischemia evaluation (44).

CCTA's expanding applications include use in special populations such as transplant candidates and oncology patients, where non-invasive evaluation reduces procedural risks and informs clinical management (45).

Fat Attenuation Index (FAI) in Coronary Artery Disease Assessment via CCTA

Coronary artery disease (CAD) is a major contributor to global morbidity and mortality, with vascular inflammation recognized as a pivotal factor in its pathogenesis. Traditional imaging methods predominantly evaluate anatomical stenosis and calcification, but recent advances highlight the importance of assessing coronary inflammation (46-49).

The Fat Attenuation Index (FAI), derived from coronary computed tomography angiography (CCTA), is a novel non-invasive biomarker reflecting inflammatory activity in perivascular adipose tissue (PVAT) surrounding coronary arteries. Inflammation alters PVAT composition, increasing CT attenuation values (measured in Hounsfield Units, HU), which correspond to higher FAI scores. FAI is measured primarily in the proximal segments of major coronary arteries, including the right coronary artery (RCA), left anterior descending artery (LAD), and left circumflex artery (LCX), with reproducibility enhanced by AI-based algorithms (46-49).

Clinically, FAI serves as an in vivo indicator of coronary inflammation and is elevated in unstable plaques compared to stable ones, aiding in the identification of vulnerable plaques. Combining FAI with high-risk plaque characteristics (HRPC) improves prediction accuracy for major adverse cardiovascular events (MACE), underscoring its prognostic value beyond traditional imaging markers (46-49).

Clinical Applications of Fat Attenuation Index (FAI)

1. Risk Stratification for Prevention
    - FAI can aid in **both primary and secondary prevention**.
    - Useful in **asymptomatic individuals** and those with **known CAD** to better assess cardiovascular risk and tailor **preventive therapies**.
2. Chest Pain Evaluation
    - In patients with **new-onset chest pain** (excluding acute MI), combining FAI with **high-risk plaque characteristics (HRPC)** improves identification of individuals at higher risk for **major adverse cardiovascular events (MACE)**.
3. Prediction of Heart Failure
    - Elevated FAI, especially in the **left anterior descending (LAD)** artery, is predictive of **future heart failure hospitalization**, even in patients **without significant coronary stenosis**.
4. Surveillance in Cardiac Transplant Recipients
    - High baseline FAI levels may identify transplant patients at increased risk for **cardiac death** or **need for re-transplantation**.
5. Assessment in MINOCA and Tako-Tsubo Syndrome
    - FAI helps differentiate **inflammatory vs. non-inflammatory** coronary profiles in patients with:
        - **Myocardial infarction with non-obstructive coronary arteries (MINOCA)**
        - **Tako-Tsubo syndrome (TTS)** → Aiding in more accurate diagnosis and management (50).

Limitations & Future Directions

- While FAI holds significant promise, **further validation** is required through:
    - **Larger, multi-center studies**
    - Inclusion of **diverse patient populations**
- Key barriers to widespread clinical use include:
    - **Cost-effectiveness concerns**
    - Need for integration into **routine clinical workflows**
- **Emerging research** is focused on:
    - **Radiomics** and **radiotranscriptomics** to improve **perivascular fat phenotyping**
    - Enhancing risk prediction by identifying **molecular and structural imaging patterns**.

Assessment of Coronary Vulnerable Plaque Using CCTA

Evaluating vulnerable coronary plaques is essential for anticipating adverse cardiac events. Recent technological advancements, including **quantitative analysis**, **radiomics**, and **artificial intelligence (AI)**, have markedly enhanced the precision, efficiency, and prognostic usefulness of CCTA in detecting and characterizing these high-risk plaques.

Key Methods in Vulnerable Plaque Assessment

- **Quantitative Plaque Analysis:** CCTA allows for precise measurement of plaque burden and detailed assessment of plaque features such as:
    - **Low attenuation plaque**
    - **Positive remodeling**
    - **Spotty calcification** These features are known markers of plaque vulnerability (51-56).
- **Radiomics and Machine Learning:** By extracting a large number of imaging features from CCTA scans, radiomics-based models outperform traditional assessment methods in identifying vulnerable plaques. These models provide enhanced diagnostic accuracy and improve prediction of **major adverse cardiac events (MACE)**.

- **Deep Learning Systems:** Automated AI-driven deep learning algorithms quickly and accurately analyze plaque characteristics and stenosis severity. Their performance rivals expert human readers while dramatically reducing analysis time.
- **Perivascular Fat Attenuation Index (FAI):** FAI derived from CCTA quantifies coronary inflammation. Elevated FAI scores help pinpoint coronary arteries at higher risk for acute plaque rupture, supporting focused intervention strategies.

Type 2 Diabetes Mellitus (T2DM) and Cardiovascular Disease (CVD).

- T2DM significantly increases the risk of cardiovascular disease, with a 2- to 4-fold higher incidence of adverse cardiovascular events including myocardial infarction and stroke (57). This increased risk arises from accelerated atherosclerosis and both microvascular and macrovascular complications.
- **Endothelial Dysfunction in T2DM** Hyperglycemia disrupts endothelial homeostasis by inducing oxidative stress, enhancing platelet reactivity, and promoting chronic inflammation. Excess intracellular glucose metabolism via the polyol pathway alters the cellular redox state, activating protein kinase C (PKC), which decreases nitric oxide (NO) bioavailability and increases vascular permeability and tone (58). Advanced glycation end-products (AGEs) further impair endothelial function through receptor for AGE (RAGE)-mediated activation of NF-κB, upregulating pro-inflammatory and pro-thrombotic molecules such as VCAM-1, ICAM-1, and endothelin-1.
- **Chronic Inflammation and Atherosclerosis** T2DM is characterized by metaflammation, a persistent low-grade systemic inflammatory state marked by elevated cytokines (IL-1β, IL-6, IL-8, MCP-1) and oxidative stress. Hyperglycemia promotes NLRP3 inflammasome activation, increasing IL-1β and IL-18, which induce neutrophil extracellular traps (NETs) and sustain vascular inflammation (58).
- **Adipokine Dysregulation** T2DM-related adipose tissue dysfunction alters adipokine secretion, contributing to insulin resistance and vascular inflammation. Adiponectin, an insulin-sensitizing and anti-inflammatory adipokine, is decreased in T2DM and its deficiency correlates with endothelial dysfunction and accelerated atherosclerosis. Omentin and vaspin, other adipokines involved in glucose homeostasis and vascular protection, are also dysregulated, with reduced omentin and elevated vaspin levels associated with worsened cardiovascular outcomes (59).

CONCLUSION

This study establishes a significant correlation between glycemic control and coronary inflammation, as measured by the Pericoronary Fat Attenuation Index (FAI), along with plaque vulnerability assessed via Coronary Computed Tomography Angiography (CCTA), in patients with diabetes and low-risk Acute Coronary Syndrome (ACS). The data suggest that inadequate glycemic regulation is linked to elevated coronary inflammatory activity and increased plaque instability, which may play a pivotal role in the pathogenesis of adverse cardiovascular events.

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