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Association of Glycemic Gap with Short-Term Outcomes in Diabetic Patients Undergoing Elective Percutaneous Coronary Intervention

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Abstract

Diabetes mellitus represents a significant global health challenge, with ischemic heart disease being a leading cause of morbidity and mortality in this population. The relationship between hyperglycemia, cardiovascular outcomes, and percutaneous coronary intervention (PCI) outcomes is complex and multifaceted. This review examines the cardiovascular complications associated with diabetes mellitus, the pathophysiology underlying these complications, and the emerging role of glycemic gap as a novel predictor of adverse outcomes following PCI. We explore the mechanisms by which diabetes affects coronary artery disease progression, the challenges in managing diabetic patients undergoing PCI, and the potential of glycemic gap measurements to improve risk stratification and patient management strategies.

Keywords: Diabetes mellitus, percutaneous coronary intervention, glycemic gap, cardiovascular disease, risk stratification

Introduction

Cardiovascular disease remains the leading cause of death globally, with ischemic heart disease (IHD) accounting for approximately 126 million deaths worldwide and resulting in 9 million fatalities annually (1). The intersection of diabetes mellitus and cardiovascular disease represents one of the most significant challenges in contemporary medicine, as diabetic patients face substantially elevated risks of adverse cardiovascular outcomes.

Acute hyperglycemia is commonly observed in patients presenting to emergency departments with acute coronary syndrome (ACS), regardless of their diabetes status (2). The admission blood glucose level has emerged as an independent predictor of long-term mortality following acute myocardial infarction (AMI) in both diabetic and non-diabetic patients. While the prognostic value of hyperglycemia in non-diabetic individuals with ACS is well-established, its significance in diabetic patients continues to generate debate (3).

Stress hyperglycemia, characterized by transient increases in blood glucose levels during acute illness, can result from hormonal surges triggered by acute stress or may manifest in patients with undiagnosed diabetes or impaired glucose tolerance (4). This phenomenon involves

increased gluconeogenesis, enhanced glycogenolysis, elevated lipolysis, and tissue insulin resistance, all amplified by elevated levels of pro-inflammatory cytokines, cortisol, and glucagon (5).

The concept of glycemic gap has emerged as a potentially more accurate predictor of outcomes than absolute glucose values (6). The glycemic gap represents the difference between admission glucose levels and the A1C-derived average glucose (ADAG), calculated as [28.7 × HbA1c – 46.7] (7). This measure may better reflect acute stress-induced glycemic excursions beyond baseline glucose control, particularly in diabetic patients who may already have elevated baseline glucose levels.

Cardiovascular Complications of Diabetes Mellitus

Epidemiology and Risk Factors

Cardiovascular disease and diabetes mellitus demonstrate a profound correlation, with CVD accounting for the vast majority of deaths and complications in diabetic populations (8). Among adults with diabetes mellitus, the global death risk from CVD is 1.7 times greater than in those without diagnosed diabetes, primarily driven by increased risks of myocardial infarction and stroke.

The metabolic syndrome, defined by the World Health Organization and NCEP Adult Treatment Panel III as insulin resistance combined with additional CVD risk factors, affects 25-35% of the population in several Western nations (9). In the Middle East region, metabolic syndrome prevalence ranges from 15-60%, with central obesity representing a particularly high-risk factor for both sexes.

The National Health and Nutrition Examination Survey III (NHANES III) research demonstrated that approximately 85% of individuals with diabetes were classified as having metabolic syndrome, compared to only 12% of those with normal fasting glucose levels (10). Diabetes mellitus is considered a "risk equivalent" for coronary artery disease according to NCEP recommendations, meaning diabetic individuals have an absolute 10-year risk of major coronary events comparable to non-diabetics with established CAD.

Risk Factors Associated with Type II Diabetes Mellitus

Multiple interconnected risk factors contribute to cardiovascular disease in diabetic patients (11). Metabolic factors include hyperglycemia and hyperinsulinemia, obesity and dyslipidemia characterized by small, dense LDL particles, decreased HDL cholesterol and increased triglycerides, and hypertension.

Inflammatory and thrombotic markers play crucial roles, including elevated white blood cell count and microalbuminuria, increased C-reactive protein and pro-inflammatory cytokines, and enhanced monocyte chemotactic protein-1 (12). Additionally, altered coagulation profile with decreased antioxidant status, increased mean platelet volume and decreased antithrombin III, elevated von Willebrand factor, fibrinogen, and plasminogen activator inhibitor-1, and increased matrix metalloproteinase levels contribute to cardiovascular risk.

Vascular dysfunction manifests as endothelial dysfunction with decreased vascular reactivity, reduced prostacyclin release and increased nitric oxide degradation, and impaired flow-mediated dilation (13).

Pathophysiology of Cardiovascular Disease in Diabetes

Insulin resistance serves as a potential shared etiological factor in type 2 diabetes, with affected patients often exhibiting multiple independent cardiovascular risk factors (14). Individuals with insulin-resistant type II diabetes present a pro-atherogenic cardiovascular risk profile including microalbuminuria, inadequate glucose regulation, abdominal obesity, hypertension, and atherogenic dyslipidemia (15).

The metabolic syndrome strongly predicts type II diabetes mellitus development even in those with normal glucose tolerance. More importantly, metabolic syndrome increases CVD risk beyond any individual component, leading to a tripling of the risk for CAD, stroke, and CAD-related death (16). The presence of multiple metabolic syndrome components further amplifies cardiovascular and diabetes risk.

Cardiac Manifestations of Diabetes Mellitus

Coronary Artery Disease

Diabetic patients experience higher rates of myocardial infarction compared to non-diabetic individuals, with the underlying atherosclerotic process being similar between groups (17). However, diabetic patients demonstrate greater morbidity, mortality, and re-infarction rates following myocardial infarction, with mortality rates reaching approximately 50% after one year.

The enhanced coagulability observed in diabetic patients contributes to increased myocardial infarction incidence. Multiple studies have documented overexpression of glycoprotein IIB/IIIA receptors and von Willebrand factor in diabetics, leading to enhanced platelet activation (18). Elevated plasminogen activator inhibitor type 1 levels further contribute to thrombus formation, plaque development, and decreased fibrinolysis.

Diabetic neuropathy complications, including proteinuria and insufficient anti-coagulant levels such as protein C and antithrombin III, place diabetic patients in a prothrombotic and procoagulant state (12). Silent myocardial ischemia, typically asymptomatic and identified later, contributes to higher mortality and morbidity rates from myocardial infarction.

Mechanisms of Acute Coronary Syndrome in Diabetic Patients

Four primary pathophysiological abnormalities characterize ACS in diabetic patients. Insulin resistance leads to diminished glucose disposal, compensatory hyperinsulinemia, and increased free fatty acid utilization for energy. The myocardium uses free fatty acids instead of glucose due to impaired myocardial glucose uptake, which further reduces oxygen levels.

Endothelial dysfunction represents another critical mechanism. The endothelium, acting as an endocrine organ controlling arterial homeostasis, becomes severely compromised due to imbalanced vasodilatation and vasoconstriction in highly inflammatory, oxidative, and prothrombotic conditions (13). Hyperglycemia and free fatty acids activate protein kinase C,

inducing decreased activity of endothelial nitric oxide synthase and preventing endothelium-dependent vasodilation.

Plaque modifications occur as diabetes intensifies both atherosclerosis onset and progression through vascular smooth muscle cell proliferation, macrophage infiltration, and foam cell generation. Pro-inflammatory cytokines make atherosclerotic plaque less stable, with plaque rupture and thrombus development occurring when collagen synthesis slows and breakdown accelerates (19).

Platelet activation and coagulopathy represent the fourth mechanism. Diabetic patients exhibit larger, more aggressive, and glycated platelets with enhanced aggregation responses and increased glycoprotein IIb/IIIa surface receptors. Impaired fibrinolysis, a hallmark of type 2 diabetes, contributes to hypercoagulability through elevated PAI-1 and tissue factor levels (20).

Left Ventricular Dysfunction

Diastolic dysfunction can occur in asymptomatic individuals with intact ejection fraction, characterized by elevated filling pressures and increased LV stiffness (21). Approximately 21% of the general population experiences asymptomatic mild left ventricular diastolic dysfunction (LVDD), while 7% of diabetes patients develop moderate to severe diastolic dysfunction.

Multiple cardiovascular risk factors in metabolic syndrome induce complex metabolic cascades affecting cardiac function directly or indirectly. Notable alterations include insulin signaling changes, glyco- and lipotoxicity, elevated cytokine activity, and triacylglycerol and advanced glycation end product (AGE) deposition (22).

The initial stage of diabetic cardiomyopathy features left ventricular diastolic failure development, autonomic dysfunction, and myocardial hypertrophy, occurring before systolic dysfunction and potentially remaining undetected for extended periods. Endothelial dysfunction precipitated by multiple risk factors leads to atherosclerosis affecting coronary and systemic arteries, vascular remodeling, inflammation, and dysregulation of vascular permeability.

Heart Failure and Ejection Fraction

Tissue Doppler imaging and strain assessment have revealed subtle systolic function alterations in diabetic patients, potentially accompanied by impaired contractile reserve and cardiac sympathetic innervation (23). Interstitial fibrosis and increased collagen deposition may contribute to reduced heart function in diabetics.

Diabetic patients demonstrate higher heart failure prevalence (16-31% versus 4-6% in the general population), particularly heart failure with preserved ejection fraction (24). While conventional cardiovascular risk factors may partially explain this disparity, diabetes mellitus may influence cardiac form and function through fibrosis and hypertrophy promotion.

Right Ventricular and Atrial Involvement

Type 2 diabetes relates to left ventricular impairment that can progress to right ventricular dysfunction through various systemic changes. Right ventricular dysfunction and fibrosis associate with sudden cardiac arrest, ventricular arrhythmias, diminished cardiac output, and exercise limitation. Diabetic patients face elevated cardiac conduction problem risks, while

pulmonary microangiopathy can raise right ventricular afterload, leading to systolic dysfunction (25).

The Coronary Artery Risk Development in Young Adults (CARDIA) study demonstrated no correlation between diabetes and left atrial diameter over short-term follow-up. However, following a 20-year period, larger left atrial diameters were linked to diabetes, with most research confirming increased left atrial size in diabetic patients (26).

Diabetes Mellitus and Post-PCI Outcomes

Prevalence and Clinical Significance

Type 2 diabetes mellitus prevalence continues rising globally, with glucose irregularities serving as established coronary artery disease risk factors (27). These abnormalities occur more frequently in patients with acute and chronic coronary syndromes compared to the general population. Oral glucose tolerance tests can detect newly diagnosed diabetes or pre-diabetes in up to 70% of CAD patients, particularly those with obesity.

Hyperglycemic patients undergoing PCI face increased complication risks. Observational studies and randomized controlled trials have demonstrated doubled risks of in-hospital and short-term mortality in diabetic patients compared to non-diabetics following PCI (28). Newly diagnosed diabetes correlates with similarly poor long-term prognosis as individuals with pre-diabetes when admitted for ACS.

PCI Indications in Type 2 Diabetes

Symptomatic and prognostic indications for myocardial revascularization in diabetic patients mirror those in non-diabetic individuals. However, diabetic CAD anatomy affects revascularization success and prognosis, with left main and multivessel critical stenoses and diffuse disease involving minor arteries being more common.

Poor prognosis following coronary revascularization associates with frequent diabetic complications including peripheral vascular disease and renal impairment. Patient preferences and specific cardiac and non-cardiac factors determine optimal revascularization methods for diabetic individuals with CAD. The 2019 ESC guidelines provide specific recommendations for coronary revascularization based on disease complexity using SYNTAX scores (29).

Glycemic Status and PCI Complications

Abnormal pre-PCI glycemic readings correlate with procedural complications and long-term outcomes regardless of previous diabetes diagnosis, particularly in ACS settings. This correlation led to the "stress hyperglycemia" concept, describing acute blood sugar spikes responding to stressful situations like cardiac ischemia (30).

Higher glycemic variability appears more dangerous than long-term hyperglycemia regarding percutaneous revascularization complications in patients. The pathophysiological mechanisms underlying these complications involve multiple interconnected pathways affecting platelet function, endothelial integrity, and inflammatory responses.

No-Reflow Phenomenon

The no-reflow phenomenon, characterized by impaired myocardial perfusion without angiographic mechanical vascular blockage evidence, represents an uncommon but deadly PCI complication (31). Multiple studies have established significant correlations between initial glucose levels and no-reflow occurrence in AMI patients following successful percutaneous reperfusion.

Several mechanisms explain hyperglycemic conditions' increased no-reflow likelihood. Enhanced leukocyte entrapment occurs through increased pro-thrombotic adhesion molecule expression on coronary capillaries. Platelet activation, aggregation, and microthrombi formation in small coronary arteries result from elevated glucose levels (32). Acute hyperglycemia may alter ischemic preconditioning's protective effects and prevent vessel collateral development.

Preprocedural Myocardial Injury

Multiple studies demonstrate that pre-PCI glucose levels predict periprocedural myocardial damage, significantly linking to elevated cardiac adverse event incidence during long-term follow-up (33). High glycemic variability associates with increased troponin release following PCI. Individuals with impaired glucose metabolism demonstrate increased risk of myocardial infarction and cardiac mortality within 48 hours after PCI.

Both hyperglycemia and hypoglycemia prior to or during PCI increase periprocedural myocardial injury risk. The pathophysiological factors include oxidative stress, endothelial dysfunction, increased inflammation, and platelet hyperreactivity causing micro-embolization and coronary vasoconstriction.

Stent Thrombosis

Multiple clinical studies have found direct correlations between stent thrombosis and impaired glycemic status (34). Diabetic patients receiving PCI demonstrate higher stent thrombosis rates compared to non-diabetic individuals, particularly those using insulin, possibly due to disease progression, poorer glycemic control, and increased hypoglycemia likelihood.

The presence of diabetes mellitus represents a strong predictor of both definite and probable stent thrombosis. Inadequate glycemic management contributes to stent thrombosis recurrence, with patients experiencing recurrent events showing elevated blood glucose and HbA1c levels compared to those without recurrence (35).

In-Stent Restenosis and Neoatherosclerosis

Type 2 diabetes increases in-stent restenosis risk during coronary angioplasty by two-fold (36). Pre-clinical research demonstrates that type 1 diabetes mellitus, especially when untreated for extended periods, increases ISR development likelihood following endovascular stenting.

Enhanced macrophage infiltration, increased vasa vasorum neovascularization leading to intraplaque hemorrhage, and increased vascular smooth muscle cell proliferation contribute to ISR and neoatherosclerosis development in diabetic individuals (37). Endothelial dysfunction and resulting decreased nitric oxide generation due to impaired glycemic regulation and insulin resistance independently predict early restenosis following PCI.

Glycemic Gap

Definition and Calculation

The glycemic gap represents the difference between admission glucose levels and the A1C-derived average glucose (ADAG) (38). This measure provides more reliable blood glucose level variation monitoring compared to absolute glucose values, particularly in acute conditions. The glycemic gap serves as a marker of acute stress-induced hyperglycemia beyond baseline glycemic control.

The calculation involves subtracting the A1C-derived average glucose from admission glucose: ADAG = [28.7 × HbA1c] - 46.7 (7). This calculation determines mean glucose levels for the preceding 8-12 weeks, potentially serving as a more accurate outcome indicator than admission glucose alone. The glycemic gap accounts for individual baseline glycemic status while capturing acute stress responses.

Clinical Applications in Cardiac Disease

Association with Coronary Artery Disease

Multiple studies have demonstrated glycemic gap associations with unfavorable outcomes across various clinical settings, including intensive care outcomes, community-acquired pneumonia, acute heart failure, and ACS (39). However, most studies have not established specific glycemic gap cut-off values for risk stratification.

The stress response mechanism in severely disturbed physiological states triggers secondary complications including insulin resistance and sudden hyperglycemia. Stress hyperglycemia occurs through hypothalamic-pituitary axis and sympathetic nervous system activation, leading to increased cortisol and catecholamine levels driving gluconeogenesis, glycogenolysis, and lipolysis (40).

Research has consistently shown that both diabetic and non-diabetic patients with admission hyperglycemia face increased risks of in-hospital complications following ACS. Multiple studies, including those by Capes et al. and Foo et al., demonstrated that admission glycemia serves as a prognostic indicator, with increasing hyperglycemia correlating with higher rates of heart failure and cardiac arrest (41,42).

Association with Heart Failure

The relationship between admission glucose and mortality in hospitalized acute heart failure patients with diabetes has produced varied research findings. Some studies suggest stress-induced hyperglycemia associates with poor clinical outcomes across various serious diseases, while others show weak correlations between stress-induced hyperglycemia and disease severity in critically ill diabetic patients (43).

Hospital mortality in diabetic patients with acute heart failure appears better predicted by glycemic gap rather than admission glucose levels alone (44). Similar findings have emerged in patients with acute ischemic stroke, COPD exacerbations, community-acquired pneumonia, critical illness mortality, AMI, and liver abscesses. The glycemic gap analysis helps address

issues surrounding the link between admission hyperglycemia, chronic glycemic management, and adverse events.

Association with PCI Outcomes

Limited research has examined correlations between diabetic patients' HbA1c levels at PCI and clinical outcomes (45). The question of whether glycemic management after PCI can reduce cardiovascular events remains more significant than whether glycemic control before or during PCI correlates with post-PCI prognosis.

Studies suggest good glycemic control (HbA1c < 7.0%) links to better clinical outcomes following PCI, with major benefits including reduced major adverse cardiac events and decreased recurrent revascularization needs (46). However, the glycemic gap's specific role in PCI outcome prediction requires further investigation to establish standardized cut-off values and validate clinical applications.

Glucose Management Strategies During PCI

Aggressive Versus Conservative Approaches

The DIGAMI trial first demonstrated that patients with diabetes and ACS benefit from precise glycemic control, comparing conventional hyperglycemia treatment with aggressive insulin-based approaches (47). However, subsequent trials have produced mixed results regarding optimal glycemic management strategies (48).

Current evidence suggests that both hyperglycemia and hypoglycemia during acute periods correlate with poor outcomes (49). The deciding factor appears to be improved glycemic control benefits versus hypoglycemic episode risks from medication escalation (50).

Glucose-Lowering Agents During PCI

Insulin remains the preferred medication for acute hyperglycemia treatment due to its pharmacokinetic and pharmacodynamic properties enabling rapid blood glucose correction (51). However, careful consideration of oral glucose-lowering therapies is essential in both acute contexts and elective PCI planning (52).

Certain medications require withdrawal during admission, including sulfonylureas and thiazolidinediones (53). Metformin discontinuation may be necessary in patients with renal failure before elective PCI due to lactic acidosis concerns (54).

Novel Anti-Diabetic Agents

Glucagon-Like Peptide-1 Agonists

GLP-1 receptor agonists demonstrate multiple beneficial cardiovascular mechanisms beyond glycemic control, including vasodilation, improved endothelial function, and anti-atherogenic properties (55). Large-scale trials have shown 12% reductions in cardiovascular death, non-fatal stroke, and non-fatal MI risks (56).

Clinical trials suggest GLP1-RAs may benefit STEMI patients undergoing PCI by reducing infarct size and improving myocardial salvage (57). Experimental studies indicate these agents limit in-stent restenosis through reduced VSMC migration and proliferation (58).

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors enhance glycemic management while positively influencing endothelial function, oxidative stress, and inflammatory markers (59). These agents inhibit adhesion molecule production on endothelial cells, potentially slowing atherosclerotic plaque formation and stent-related complications (60).

Limited human data suggests chronic DPP-4 inhibitor use may reduce in-hospital complications and major adverse cardiac events in diabetic ACS patients, though additional research is needed (61).

Sodium-Glucose Cotransporter-2 Inhibitors

SGLT-2 inhibitors promote sodium and glucose excretion while potentially providing direct vascular benefits independent of glucose-lowering effects (62). These agents may reduce platelet aggregation through increased nitric oxide bioavailability and decreased ROS generation (63).

Preliminary studies suggest SGLT-2 inhibitors may reduce neointimal hyperplasia following DES implantation and decrease infarct size in experimental ischemia/reperfusion models (64).

Future Directions

The glycemic gap represents a promising tool for risk stratification in diabetic patients undergoing PCI. By accounting for baseline glycemic control while capturing acute stress-induced glucose excursions, this measure may provide more accurate outcome predictions than traditional glucose measurements alone.

Future research should focus on establishing standardized glycemic gap cut-off values for different clinical scenarios and validating these thresholds across diverse patient populations. Additionally, investigating whether glycemic gap-guided management strategies improve clinical outcomes represents an important research priority.

The integration of continuous glucose monitoring technology may facilitate real-time glycemic gap calculations and enable more precise glucose management during acute care settings. This approach could potentially reduce both hyperglycemic and hypoglycemic episodes while optimizing cardiovascular outcomes.

Conclusion

The glycemic gap emerges as a superior predictor of adverse outcomes in diabetic patients undergoing PCI compared to absolute glucose values alone. By capturing acute stress responses while accounting for baseline glycemic control, this measure addresses the "diabetes paradox" observed in cardiovascular studies. Optimal management requires multifaceted approaches combining acute glycemic control with long-term risk factor modification. Novel anti-diabetic agents show promise beyond glucose-lowering effects, demonstrating cardiovascular benefits and potential roles in preventing PCI complications. Future research should establish standardized glycemic gap cut-off values and validate management strategies to improve outcomes in the growing population of diabetic patients requiring cardiovascular interventions.

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