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Hyperglycemia and Diabetes in Myocardial Infarction

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1. Introduction

The proposal of this chapter is explain the importance and relevance of the understanding of the role that play the level in the serum glucose during the acute myocardial infarction (AMI). Since many years the investigation in this area has showed that the hyperglycemia is a strong predictor of mortality in acute myocardial infarction, as representation of the response of the myocardial cell to the ischemic injury, related mainly to acute catecholamine release.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with diabetes, for which 65% of deaths are attributable to heart disease or stroke. Hyperglycemia is encountered in up to 50% of all ST elevation myocardial infarcted (STEMI) patients, whereas previously diagnosed DM is present in only 20% to 25% of STEMI patients.¹ When admission glucose level exceeds 200 mg/dL, mortality is similar in non-DM and DM subjects with MI. Admission glucose has been identified as a major independent predictor of both in-hospital congestive heart failure and mortality in STEMI.²

In the HEART2D Study treating diabetic survivors of AMI with prandial versus basal strategies achieved differences in fasting blood glucose, less-than-expected differences in postprandial blood glucose, similar levels of A1C, and no difference in risk for future cardiovascular event.³

Recently the glucose variability has been highlighted. In the results in a re analysis of HEART2D study results, the intraday glucose variability as target compared with the basal glucose, in diabetic type 2 patients after myocardial infarction, showed similar overall glycemic control but did not result in a reduction in cardiovascular outcomes⁴. Treating diabetic survivors of AMI with prandial versus basal strategies achieved differences in fasting blood glucose, less-than-expected differences in postprandial blood glucose, similar levels of A1C, and no difference in risk for future cardiovascular event.

2. Diabetes mellitus and risk for myocardial infarction

The main cause of death in the industrialized countries is the coronary artery disease (CAD). The risk of myocardial infarction is high in patients with diabetes mellitus. In United States, diabetes is the most prevalent risk factor for cardiovascular events⁵ The patient with diabetes mellitus have increased risk for cardiovascular disease, a risk that contributes to a significant decrease in life expectancy. The patients with diabetes have a risk for myocardial infarction (MI) comparable to that of the risk of recurrent myocardial infarction in a patient without diabetes. The association between diabetes and cardiovascular disease has been well identified, and the increased of risk for acute coronary syndromes and the poor outcome linked to raised blood glucose levels has been studied in many trials.

A Finnish population-based study has shown that patients with diabetes without a previous MI have as great a risk for infarction as individuals without diabetes with a previous myocardial infarction (Figure 1).¹¹ The 7-year incidence rates of MI (fatal and nonfatal) in subjects without diabetes were 18.8% in those with a previous MI and 3.5% in those without a history of infarction; the corresponding rates in individuals with diabetes were 45.0% and 20.2%, respectively⁶

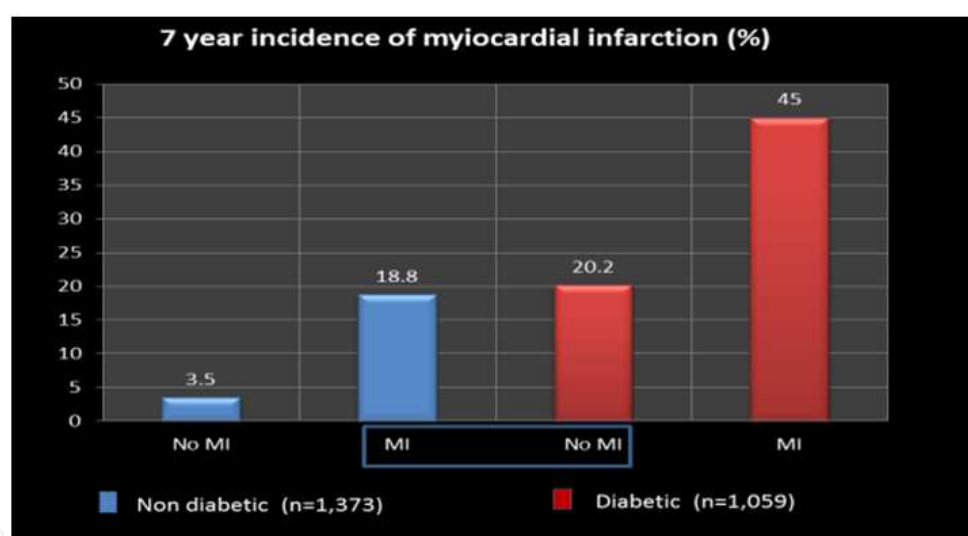


Figure 1. Diabetes mellitus as a risk equivalent of coronary artery disease.

(Adapted from Hafner S M, N Engl J Med. 1998;339:229-342)

Diabetes mellitus is associated with a 2 to 4 fold increase of the risk for cardiovascular disease.^{7,8} 75 to 80% of the deaths in patients with diabetes mellitus are conditioned by a thrombotic event⁵ This increased risk is the main factor underlying the excess mortality and reduced life expectancy of people with type 2 diabetes; the life expectancy of people with type 2 diabetes at the age of 40 is reduced by an estimated 8 years in comparison with individuals without diabetes⁹

The prognosis is poorer in patients with diabetes mellitus type 2 that suffers a myocardial infarction compared with people without diabetes mellitus. In patients with acute myocardial infarction the underlying mechanism in the increase of mortality associated to

glucose levels are poorly understood. In a study by Nicolau JC and cols, with 52 patients with acute myocardial infarction with ST segment elevation and hyperglycemia, in the first 24 hours compared radionuclide ventriculography at day 4 and six months, finding that basal glucose level like independent and powerful predictor of left ventricular growth after an acute myocardial infarction¹⁰

Hyperglycemia increases the morbidity and mortality in hospitalized patients in Intensive Care Units with acute myocardial infarction, stroke and those with aortocoronary bypass. The treatment with infusion of insulin has showed a better outcome in these patients¹¹

A1c hemoglobin (A1cHb) or glycosylated hemoglobin is a marker of the glucose level in two previous months, and that is affected in minimal mode by the levels of glucose associated to acute coronary syndromes. In the OPTIMAAL study, in Danish population with acute myocardial infarction complicated with heart failure, was concluded that A1cHb levels showed to be a predictor of mortality in patients without diabetes previously known.¹²

In a Japanese study was evaluated the impact of elevated level of glucose in patients with acute myocardial infarction with percutaneous coronary intervention, concluding that the hyperglycemia at time of admission was associated with an increased mortality a short term (30 days), and that the presence of diabetes mellitus was associated a poor outcome at long term (3 years), considering that both, the acute hyperglycemia in myocardial infarction and diabetes mellitus must be treated as two different problems¹³

3. Mechanisms induced by hyperglycemia than increased risk in acute myocardial infarction

Acute phase hyperglycaemia and diabetes are both associated with adverse outcomes in acute myocardial infarction, with higher reported incidences of congestive heart failure, cardiogenic shock, and death. However, the association between hyperglycaemia and adverse outcomes is not confined to patients with diabetes. The mechanism is not clear, but it is commonly regarded as a response to stress resulting from catecholamine induced glycogenolysis. Hyperglycemia, therefore, is seen as an epiphenomenon that is associated with poor outcomes only because adrenergic stress is closely related to the extent of myocardial injury.

The possible mechanisms that influence the increased risk in diabetes for cardiovascular events include, insulin resistance, changes in endothelial function, dyslipidemia, chronic inflammation and release of mediators of inflammation, procoagulability and impaired fibrinolysis.

3.1. Insulin resistance

Insulin resistance is a hallmark in diabetes mellitus type 2 and obesity, the resistance to action of insulin in skeletal muscle, leads to a decrease in the glucose disposal and the use of fatty acids and compensatory hyperinsulinemia.¹⁴ With relative insulinopenia, however, the

ischemic myocardium is forced to use free fatty acids instead of glucose as an energy source because myocardial glucose uptake is acutely impaired. Thus, a metabolic crisis may ensue as the hypoxic myocardium becomes less energy efficient in the setting of hyperglycemia and insulin resistance.

The SMART study group published a prospective cohort study in 2611 patients with manifest arterial disease without known diabetes. Homeostasis model of insulin resistance (HOMA-IR) was used to quantify insulin resistance. The relation of HOMA-IR with cardiovascular events (vascular death, myocardial infarction or stroke) and all causes of mortality were assessed. In patients with manifest arterial disease without known diabetes, the results of this trials concludes than insulin resistance increases with the number of metabolic syndrome components, and elevated insulin resistance increases the risk of new cardiovascular events¹⁵

Diabetes mellitus type 2 is result of two developments, a chronic overnutrition with resultant insulin resistance and least a relative failure of pancreatic β -cells to release sufficient insulin to maintain glucose homeostasis. Insulin resistance is the basic mechanism, but its diagnosis is not straightforward. Commonly, attempts are made using the homeostasis model of insulin resistance¹⁶

Intact pro insulin is a precursor molecule of the insulin that is released into circulation. Proinsulin is associated with increased resistance to insulin, and have a similar adipogenetic activity than insulin, but only the 10% to 20% of the glucose-lowering effect. Recently, determination of proinsulin has been used as a diagnostic tool because an increasing proinsulin to insulin ratio predicts insulin resistance and deterioration of glucose tolerance.¹⁷ Hyperglycemia is a reflection of relative insulinopenia, which is associated with increased lipolysis and free fatty acid generation, as well as diminished myocardial glucose uptake and a decrease in glycolytic substrate for myocardial energy needs in STEMI. Myocardial ischemia results in an increased rate of glycogenolysis and glucose uptake via translocation of GLUT-4 receptors to the sarcolemma.¹⁸

Finally, in the setting of acute MI and revascularization, blood glucose control in patients with diabetes should routinely involve fasting and post meal glucose measurements (such as hyperglycemic peaks with the associated sequelae of hyperinsulinemia, reactive oxygen species generation, and endothelial dysfunction) because only the latter reflects the amount and type of ingested carbohydrates.¹⁹⁻²⁰

3.2. Endothelial dysfunction

A single layer of endothelial cells lines the inner surface of all blood vessels, providing a metabolically active interface between blood and tissue that modulates blood flow, nutrient delivery, coagulation and thrombosis, and leukocyte diapedesis. It synthesizes important bioactive substances, including nitric oxide and other reactive oxygen species, prostaglandins, endothelin, and angiotensin II, that regulate blood vessel function and structure. Nitric oxide potently dilates vessels and mediates much of the endothelium's

control of vascular relaxation. A number of fundamental mechanisms contribute to the decreased bioavailability of endothelium-derived nitric oxide in diabetes:

1. Hyperglycemia inhibits production of nitric oxide by blocking eNOS synthase activation and increasing the production of reactive oxygen species, especially superoxide anion (O_2^-), in endothelial and vascular smooth muscle cells. Superoxide anion directly quenches nitric oxide by forming the toxic peroxynitrite ion, which uncouples eNOS by oxidizing its cofactor, tetrahydrobiopterin, and causes eNOS to produce O_2
2. Insulin resistance leads to excess liberation of free fatty acids from adipose tissue, which activate the signaling enzyme protein kinase C, inhibit phosphatidylinositol-3 (PI-3) kinase (an eNOS agonist pathway), and increase the production of reactive oxygen species—mechanisms that directly impair nitric oxide production or decrease its bioavailability once produced.
3. Production of peroxynitrite decreases synthesis of the vasodilatory and antiplatelet prostanoid prostacyclin.

In addition to reducing ambient concentrations of nitric oxide, diabetes increases the production of vasoconstrictors, most important, endothelin-1, which activates endothelin-A receptors on vascular smooth muscle cell to induce vasoconstriction.

Acute coronary syndromes are associated to unstable atheromatous plaques in which inflammation and endothelial dysfunction play key roles, as well as in subsequent occlusive coronary thrombosis a global flow abnormality affecting the entire coronary tree is associated with adverse clinical outcomes in patients with ACS and might be caused by a combination of global inflammation and vasoconstriction.²¹⁻²²

Endothelial dysfunction is caused by acute hyperglycemia. Williams et al assessed endothelium-dependent vasodilation through brachial artery infusion of methacholine chloride in non-diabetic subjects. They showed that hyperglycemia significantly attenuated the forearm blood flow response to methacholine, but did not reduce endothelium-independent vasodilation to verapamil.²³

3.3. Dyslipidemia

Characteristic abnormalities in the lipid profile in type 2 diabetes include elevated triglyceride levels, decreased atheroprotective high-density lipoprotein (HDL) levels, and increased levels of small dense LDL. Increased efflux of free fatty acids from adipose tissue and impaired insulin-mediated skeletal muscle uptake of free fatty acids increase hepatic free fatty acid concentrations.²⁴ In response, the liver increases VLDL production and cholesteryl ester synthesis.²⁵

Free fatty acids combine with a cholesterol molecule to form a cholesteryl ester. Cholesteryl ester concentrations may regulate VLDL production, with increased concentrations resulting in elevated VLDL synthesis. Overproduction of triglyceride-rich lipoproteins and impaired clearance by lipoprotein lipase lead to the hypertriglyceridemia common in

diabetes. Low levels of HDL represent the second common abnormality in type 2 diabetes. Elevated levels of triglyceride rich lipoproteins lower HDL levels by promoting exchanges of cholesterol from HDL to VLDL via cholesteryl ester transfer protein. Diabetic patients with CAD more commonly have the combination of elevated triglycerides and low HDL than elevated total and LDL cholesterol levels.

Strongly related to insulin resistance, obesity is a known risk factor for heart failure. Animal studies suggest that the underlying mechanisms are overstorage of lipids and lipotoxic injury to myocytes associated with high serum levels of free fatty acid and triglycerides that involve increased free fatty acid uptake, diminished mitochondrial oxidative capacity, generation of ROS, and increased apoptosis.

3.4. Inflammation

In a study Esposito et al²⁶ measured circulating levels of cytokines, including interleukin (IL)-6, IL-18 and tumor necrosis factor- α in subjects with normal or IGT during 3 consecutive pulses of intravenous glucose separated by a 2-h interval. The plasma cytokine levels increased as the blood glucose level increased but immediately returned to normal as glucose returned to normal levels. Interestingly, when the first elevation in the blood glucose level was maintained by subsequent continuous intravenous glucose infusion, plasma cytokine concentrations gradually returned to normal levels.

The exact mechanism by which glucose stimulates pro inflammatory events is not clear, although indirect evidence suggests that it does so possibly by stimulating production of tumor necrosis factor (TNF)- α (a pro inflammatory cytokine). A diet with a high glycemic load and hyperglycemia induced production of acute-phase reactants. Similar to glucose, TNF- α also enhances free radical generation by augmenting polymorphonuclear leukocyte NADPH oxidase activity, activates NF- κ B, and increases intercellular adhesion molecule-1 expression in endothelial cells. This similarity in the actions of glucose and TNF- α , and the ability of former to enhance acute phase reactants suggests, but does not prove, that glucose may enhance TNF- α production and brings about its pro inflammatory actions.

TNF- α is secreted by adipose tissue, macrophages and cardiac tissue, and plays roles in the pathogenesis of insulin resistance, type 2 diabetes mellitus, inflammation, and septic shock. Release of TNF- α occurs early in the course of AMI and reduces myocardial contractility in a dose dependent manner.²⁷⁻²⁸

It has been suggested that four key biochemical changes induced by hyperglycemia: increased flux through the polyol pathway (in which glucose is reduced to sorbitol, reducing levels of both NADPH and reduced glutathione), increased formation of advanced glycation end products, activation of protein kinase C (with effects ranging from vascular occlusion to expression of pro-inflammatory genes), and increased shunting of excess glucose through the hexosamine pathway (mediating increased transcription of genes for inflammatory cytokines and plasminogen activator inhibitor-1 [PAI-1]) – are all activated by a common mechanism: overproduction of superoxide radicals. Excess plasma glucose drives

excess production of electron donors (mainly NADH/H⁺) from the tricarboxylic acid cycle; in turn, this surfeit results in the transfer of single electrons (instead of the usual electron pairs) to oxygen, producing superoxide radicals and other reactive oxygen species (instead of the usual end product, H₂O). The superoxide anion itself inhibits the key glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GADPH), and in consequence, glucose and glycolytic intermediates spill into the polyol and hexosamine pathways, as well as additional pathways that culminate in protein kinase C activation and intracellular AGE formation.²⁹ (Figure 2)

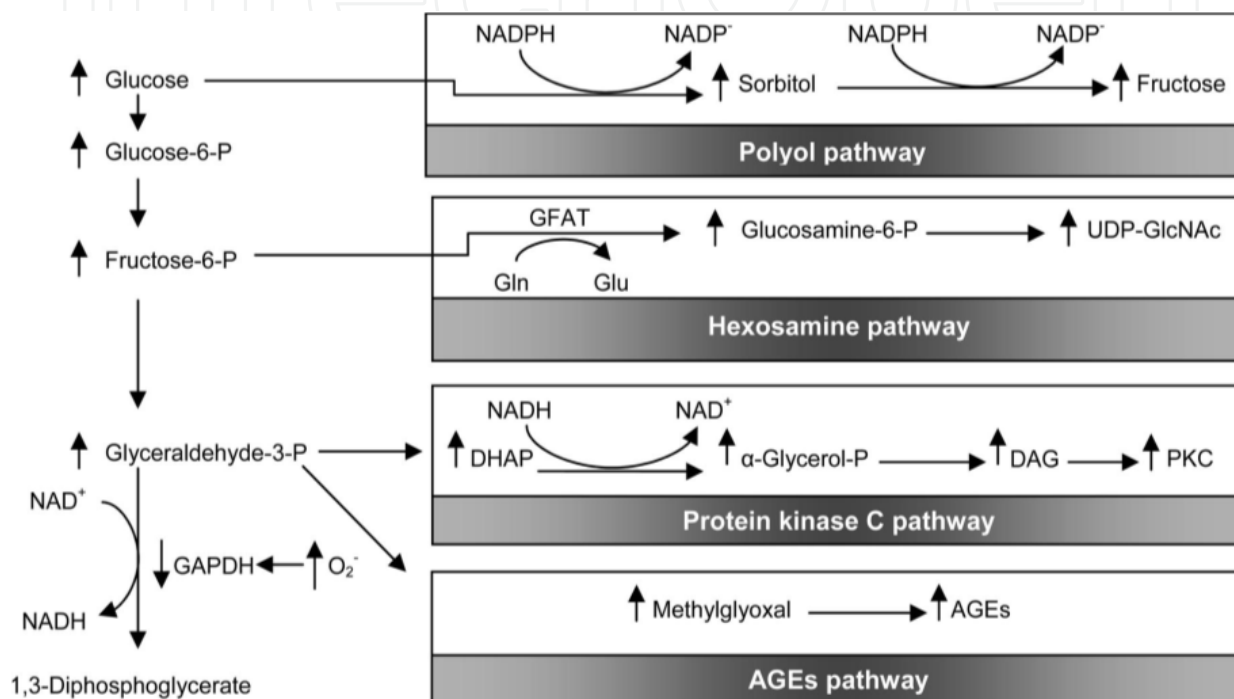


Figure 2. Potential mechanism by which hyperglycemia-induced mitochondrial superoxide overproduction activates four pathways of hyperglycemic damage. Excess superoxide partially inhibits the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thereby diverting upstream metabolites from glycolysis into pathways of glucose overutilization. This results in increased flux of dihydroxyacetone phosphate (DHAP) to diacylglycerol (DAG), an activator of protein kinase C (PKC), and of triose phosphates to methylglyoxal, the main intracellular AGE precursor. Increased flux of fructose-6-phosphate (Fructose-6-P) to UDP-N-acetylglucosamine increases modification of proteins by O-linked N-acetylglucosamine (GlcNAc), and increased glucose flux through the polyol pathway consumes NADPH and depletes glutathione. GFAT, glutamine: fructose-6-phosphate aminotransferase; Gln, glutamine; Glu, glutamate; NAD, nicotinamide dinucleotide; UDP, uridine diphosphate. Adapted from Ceriello A. Diabetes care 2009 Nov;32 Suppl 2:S232-6

3.5. Procoagulability

Hyperglycemia also stimulates coagulation and platelet aggregation. It has been reported that hyperglycemia elevates coagulant activation markers, including thrombin antithrombin complexes and soluble tissue factor, whereas hyperinsulinemia inhibits fibrinolysis.

Platelets can modulate vascular function and participate significantly in thrombus formation. Abnormalities in platelet function may exacerbate the progression of

atherosclerosis and the consequences of plaque rupture. Intraplatelet glucose concentration mirrors the extracellular concentration, since glucose entry into the platelet does not depend on insulin. In the platelet, as in endothelial cells, elevated glucose levels lead to activation of protein kinase C, decreased production of platelet-derived nitric oxide, and increased formation of O₂–

Patients with diabetes have increased platelet-surface expression of glycoprotein Ib (GpIb), which mediates binding to von Willebrand factor, and GpIIb/IIIa, which mediates platelet fibrin interaction. These abnormalities may result from decreased endothelial production of the anti aggregants nitric oxide and prostacyclin, increased production of fibrinogen, and increased production of platelet activators, such as thrombin and von Willebrand factor. Thus, diabetic abnormalities increase intrinsic platelet activation and decrease endogenous inhibitors of platelet activity

3.6. Impaired fibrinolysis

Patients with type 2 diabetes have impaired fibrinolytic capacity because of elevated levels of plasminogen activator inhibitor type 1 in atherosclerotic lesions and in non atheromatous arteries.³⁰ Diabetes increases the expression of tissue factor, a potent procoagulant, and plasma coagulation factors such as factor VII and decreases levels of endogenous anticoagulants such antithrombin III and protein C.³¹⁻³²

Impaired fibrinolysis, due to elevated levels of plasminogen activator inhibitor type 1 (PAI-1), further contributes to a hypercoagulable state in patients with diabetes. PAI-1 inhibits the conversion of plasminogen into plasmin and consequently reduces fibrinolytic activity. An in vivo study in healthy volunteers using a hyperinsulinemic euglycemic clamp, demonstrated a 2.5-fold increase in levels of PAI-1 relative to baseline. This study suggested that impaired fibrinolysis in patients with diabetes is mediated by hyperinsulinemia rather than hyperglycemia.³³

Hyperinsulinemia increases PAI-1 levels by stabilization of the PAI-1 messenger RNA transcript through the actions of insulin and insulin-like growth factor type 1. Adipocytes have been found to be a major source of PAI-1, providing a direct link between obesity and a suppressed fibrinolytic system. Finally, inflammatory cytokines such as transforming growth factor-beta and tumor necrosis factor-alpha both of which are believed to have important roles in the metabolic syndrome increase the release of PAI-1 from adipose tissue

4. The hyperglycemic effect in the outcomes in acute coronary syndromes

Acute hyperglycemia is associated with multiple biological effects that contribute to a poor outcome of the acute coronary syndromes,³⁴ this effects are listed in the table number 1 Admission hyperglycemia is associated with long-term risk for ACS mortality³⁵, but this association is not homogeneous in different ACS presentations,³⁶ unstable angina, NSTEMI, or STEMI. Besides, mortality up to 1 year can be predicted both by admission glucose and fasting blood glucose, but the better predictor of mortality for longer periods is fasting glucose.³⁷

In the OASIS registry, a 6-nation study of unstable angina and non-Q-wave MI, diabetes independently increased the risk of death by 57%.³⁸ Elevated plasma glucose and glycated hemoglobin levels on admission are independent prognosticators of both in-hospital and long-term outcome regardless of diabetic status.³⁹⁻⁴⁰ For every 18 mg/dL increase in glucose level, there is a 4% increase in mortality in nondiabetic subjects.⁴¹

Hyperglycemia also interferes with ischemic preconditioning. Ischemic preconditioning is a potent endogenous cardioprotective mechanism that is promoted by the brief transient ischemia proceeding subsequent prolonged ischemia and reperfusion. In the clinical setting, it has been demonstrated that prodromal angina occurring shortly before the onset of AMI is associated with smaller infarct size, preserved LV function and lower mortality after reperfusion therapy.⁴²

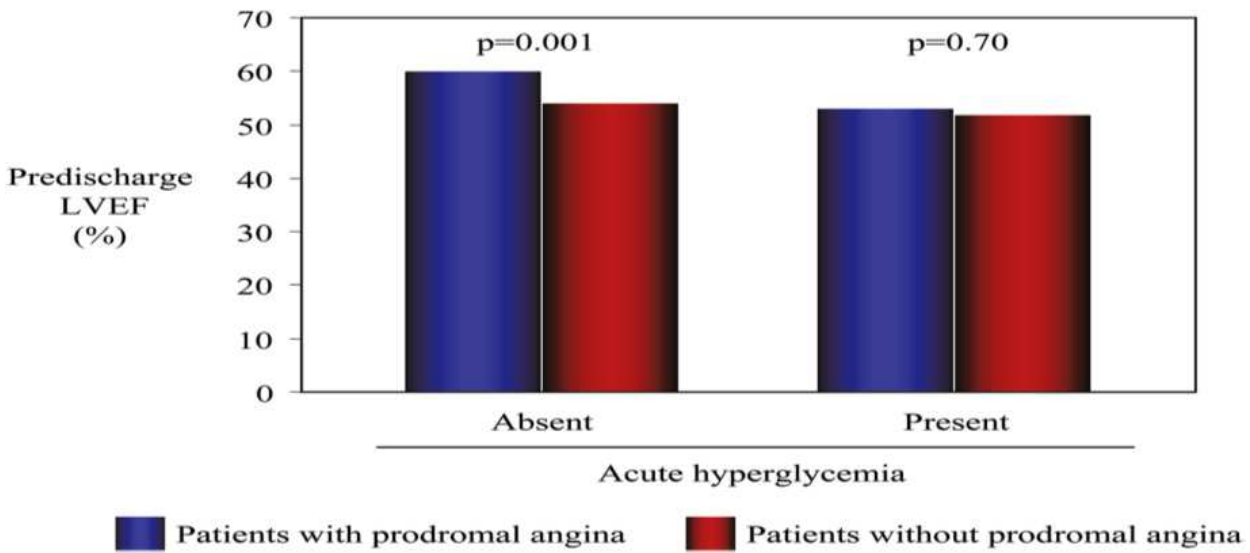


Figure 3. In the absence of acute hyperglycemia, prodromal angina was associated with preserved predischarge in left ventricular ejection fraction (LVEF). Among patients with acute hyperglycemia, there was no significant difference in predischarge LVEF between patients with (blue bars) and without prodromal angina (red bars). Adapted from Ishihara et al Ischemic preconditioning delays infarct progression during the early hours after the onset of AMI and extends the window of time for reperfusion therapy⁴³

Endothelial dysfunction
Platelet hyperreactivity
Increased cytokine activation
Increased lipolysis and free fatty acid levels
Reduced glycolysis and glucose oxidation
Increased oxidative stress (Increased myocardial apoptosis)
Impaired microcirculatory function (“no-reflow” phenomenon)
Impaired ischemic preconditioning
Impaired insulin secretion and insulin stimulated glucose uptake

Table 1. Acute Cardiovascular Effects of Hyperglycemia

5. Importance of glucose levels in diabetic and nondiabetic patients in acute myocardial infarction.

Elevation of blood glucose on admission is a common feature during the early phase after acute myocardial infarction, even in the absence of a history of diabetes mellitus.⁴⁴ However the optimal plasma glucose level may be different between diabetic and nondiabetic patients. Many studies have shown that an elevated plasma glucose level on admission is a major independent predictor of in-hospital and long-term outcome in patients with acute myocardial infarction, regardless of diabetes status.

Acute hyperglycemia is common in patients with STEMI even in the absence of a history of diabetes. Hyperglycemia is encountered in up to 50% of all STEMI patients, whereas previously diagnosed diabetes mellitus is present in only 20% to 25% of STEMI patients. The prevalence of type 2 diabetes mellitus or impaired glucose tolerance may be as high as 65% in myocardial infarction patients without prior diabetes when oral glucose tolerance testing is performed.

High blood glucose concentration may increase risk of death and poor outcome after acute myocardial infarction. Capes SE et al did a systematic review and meta-analysis to assess the risk of in-hospital mortality or congestive heart failure after myocardial infarction in patients with and without diabetes who had stress hyperglycemia on admission. Concluding that acute hyperglycemia with myocardial infarction is associated with an increased risk of in-hospital mortality in patients with and without diabetes; the risk of congestive heart failure or cardiogenic shock is also increased in patients without diabetes (Figure 4)

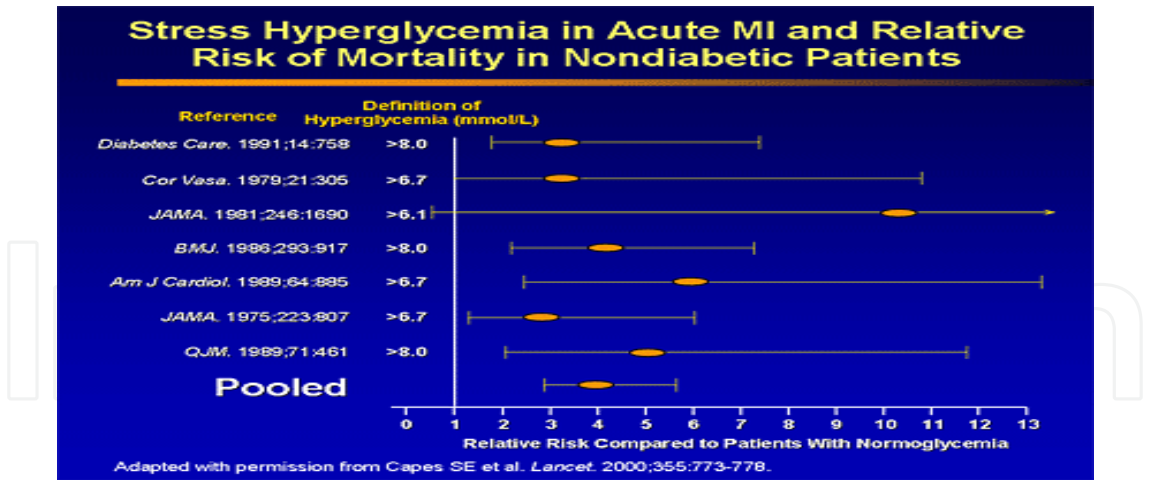


Figure 4. Stress hyperglycemia in acute MI and relative risk of mortality in nondiabetic patients

Acute hyperglycemia is common among patients with acute myocardial infarction. The prevalence of acute hyperglycemia in prior studies varies from <10% to >80%.⁴⁵⁻⁴⁶ It mostly depends on the definition of acute hyperglycemia, which is differs from study to study. Threshold glucose concentration used to define acute hyperglycemia has ranged from 6.1 mmol/L (1 mmol/L=18 mg/dl) to 11.0 mmol/L. There is a linear correlation between the blood glucose level on admission and mortality after acute myocardial infarction. Therefore,

there is no clear cut-off value of blood glucose to predict mortality and no consensus about the appropriate definition of acute hyperglycemia for patients with myocardial infarction. In most of the recent studies, 10.0 mmol/L or 11.0 mmol/L of blood glucose on admission is used to define acute hyperglycemia.

Diabetes has been a consistently powerful risk factor for development of post infarction heart failure, accounting for 66% of mortality during the first year. The combination of diabetes and HF after MI requires preventive action because it is usually not associated with the characteristic left ventricular remodeling. If left ventricular remodeling does develop, it requires appropriate treatment that includes revascularization and metabolically and hemodynamically effective treatment strategies that limit infarct size, cardiac dysfunction, and left ventricle remodeling

In patients without a history of diabetes, there was a linear relation between admission blood glucose level and in-hospital mortality (Figure 5)

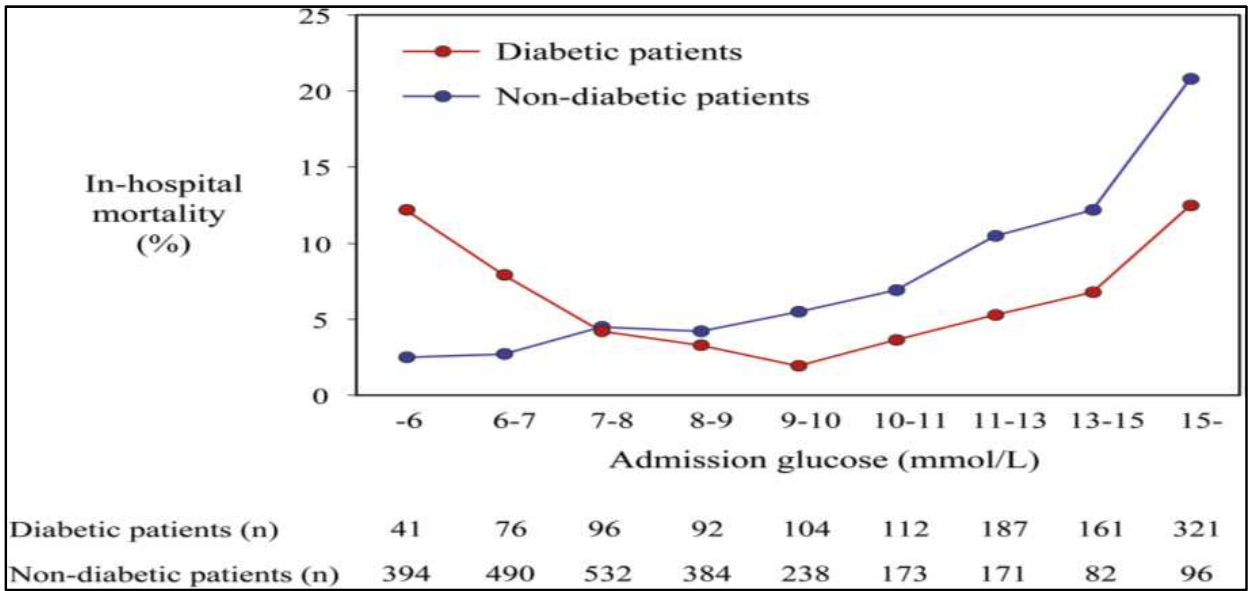


Figure 5. Relationship between admission blood glucose level and in-hospital mortality. It is near-linear in patients without diabetes (blue) but U-shaped in patients with diabetes (red). Adapted from Ishihara M, et al. Am J Cardiol 2009; 104: 769-74

In the presence of hyperglycemia, proteins and lipids are irreversibly glycated by non-enzymatic mechanisms, and these advanced glycated end products accumulate in the cells and extracellular space of blood vessels, enhancing atherogenic processes. A cell surface receptor for this glycated end products (a “RAGE”) has been isolated; binding of AGEs and other pro inflammatory ligands to this signal-transducing receptor has a multitude of effects, including increased smooth muscle cell proliferation, migration and activation of mononuclear phagocytes, induction of cytokines such as TNF- α , and in endothelial cells, increased vascular permeability, oxidative stress, vasoconstriction and expression of adhesion molecules. Glucotoxic effects involve three additional mechanisms for dysfunction in the diabetic heart. These involve:

1. Reactive oxygen species that amplify hyperglycemia induced activation of protein kinase C isoforms.
2. Increased formation of glucose derived advanced glycation end products
3. Increased glucose flux through the aldose reductase pathways

Admission glucose levels have a prognostic role in patients with acute myocardial infarction and in patients with heart failure.⁴⁷⁻⁴⁸

In a Spanish study, the findings highlight a 2-fold increase in mortality risk with hyperglycemia after STEMI, as an additive to clinical parameters. Moreover, it is of interest to note that the probability of mortality was not modified when DM was added in the model, indicating that the predictive influence of DM was marginal.⁴⁹ Similar results were found by Pinto et al.⁵⁰ in a subgroup of patients in CLARITY-TIMI 28 study trial. In 1027 patients with STEMI treated with PCI, with 26% incidence of DM.

6. The effect of hyperglycemia and diabetes in outcomes for thrombolysis, arrhythmias and left ventricle function

In patients with acute STEMI, thrombolysis in myocardial infarction (TIMI) frame counts may show significant variability despite presence of grade 3 TIMI flow after successful reperfusion and lower TIMI frame counts after reperfusion are associated with more favorable prognosis. No data are present regarding TIMI frame counts and admission glucose values in non-diabetic patients with acute ST elevation MI who undergo successful primary percutaneous coronary intervention. In STEMI subjects, acute hyperglycemia is associated with reduced TIMI grade 3 flow before intervention compared with normal glucose blood levels and is the most important predictor of the absence of coronary perfusion.⁵¹ Similarly, diabetic subjects have reduced myocardial blush grades and diminished ST-segment resolution after successful coronary intervention in STEMI, consistent with diminished microvascular perfusion.⁵² Acute hyperglycemia also is associated with impaired microcirculatory function as manifest by “no reflow” phenomenon on myocardial contrast echocardiography after percutaneous coronary intervention.⁵³

Elevated admission glucose levels are associated with increased risk of life-threatening complications, especially arrhythmias in diabetic and non-diabetic AMI patients. This increased risk of complications is one of the possible explanations for the elevated in-hospital mortality in AMI patients presenting with hyperglycemia. In a clinical study by Dziewierz et al⁵⁴ admission hyperglycemia was associated with increased risk of ventricular tachycardia/ventricular fibrillation, atrial fibrillation, second to third atrioventricular block, pulmonary edema. A analysis from the Krakow Registry of Acute Coronary Syndromes database, found that diabetes mellitus and presence of chest pain on admission, as well as heart rate and systolic blood pressure on admission, were independent predictors of new onset of atrial fibrillation⁵⁵

In a Spanish study with the aim to evaluate the impact of glucose levels on admission and high risk ventricular tachyarrhythmia in hospital mortality in patients with acute myocardial

infarction, the admission glucose levels >180 mg/dL had a significantly increased risk in in-hospital only high risk ventricular tachyarrhythmia only in patients without diabetes⁵⁶

Several mechanisms promote metabolic consequences that lead to cardiac dysfunction and heart failure in diabetes. An important mechanism deduced mainly from experimental work is myocardial energy demand/supply mismatch from increased oxygen demand in the diabetic myocardium related to increased vascular stiffness; and decreased energy supply from myocardial underperfusion.

The CARISMA study enrolled patients with a recent MI and LV systolic dysfunction. The patients were implanted with an implantable loop recorder and followed for 2 years allowing continuous monitoring and diagnosis of asymptomatic and symptomatic arrhythmias.⁵⁷ Diastolic dysfunction in post myocardium infarcted patients with moderate-to-severe left ventricle systolic dysfunction predisposes to cardiovascular ischemic events such as re-infarction and stroke. New-onset atrial fibrillation also occurs more frequently in patients with diastolic dysfunction. Re-infarction and stroke were more frequent in patients with new onset atrial fibrillation, but the increased risk of ischemic events was independent of development of atrial fibrillation, suggesting that diastolic dysfunction in infarcted patients by itself is an important risk factor for ischemic events.⁵⁸

Diabetes is associated with a higher risk of death or heart failure hospitalization across the spectrum of left ventricle ejection fraction (LVEF) in high-risk post-myocardial infarction patients. The magnitude of reduction in risk of death or heart failure hospitalization associated with increasing LVEF is significantly attenuated among patients with diabetes when compared to patients without diabetes⁵⁹

VALIANT was a randomized, double-blind trial of the efficacy and safety of Valsartan versus Captopril versus combination therapy following MI complicated by clinical or radiological signs of heart failure, evidence of left ventricle systolic dysfunction (LVEF \leq 35% by echocardiography or \leq 40% by radionuclide ventriculography), or both⁶⁰

7. Glucose variability in acute myocardial infarction

Hyperglycemia is a strong predictor of mortality in patients hospitalized with acute myocardial infarction. Professional society guidelines have accordingly advised glucose control in hyperglycemic patients. These same guidelines also recommend avoiding hypoglycemia, even though the association between hypoglycemia and adverse outcomes in acute myocardial infarction patients is controversial. In a meta-analysis of OASIS-6 and CREATE-ECLA studies Goyal A. et al conclude that both admission and post admission hyperglycemia predict 30-day death in acute myocardial infarction patients. In contrast, only hypoglycemia on admission predicted death, and this relationship dissipated after admission. These data suggest hypoglycemia may not be a direct mediator of adverse outcomes in myocardial infarction⁶¹

Short-term variation in blood glucose levels is a daily challenge for patients with diabetes. It confers a possible increased risk for hypoglycemia, and it has been suggested that glucose

variability is related to cardiovascular risk ^{62–64}. However, reanalysis of the Diabetes Control and Complications Trial (DCCT) and DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) dataset examining the predictive value of glucose variability on microvascular and neurologic complications did not show an effect of glucose variability independent from mean glucose and HbA1c, and randomized controlled trials specifically targeting glucose variability are lacking

Oscillating hyperglycemia also induces apoptosis of cells. Risso et al reported that intermittent high glucose enhanced apoptosis of human endothelial cells that were incubated in media containing different glucose concentrations.⁶⁵ Apoptosis, which was studied by viability assay, cell cycle analysis, DNA fragmentation, and morphological analysis, was enhanced in human umbilical vein endothelial cells exposed to intermittent, rather than constant, high glucose concentrations.

They are secondary to deterioration in microvascular function causing a decrease in myocardial blood flow. In diabetic patients without microvascular or macrovascular complications, postprandial myocardial perfusion defects may represent an early marker of the atherogenic process in the coronary circulation; hence, its reversal constitutes a potential goal of treatment⁶⁶. (Figure 6)

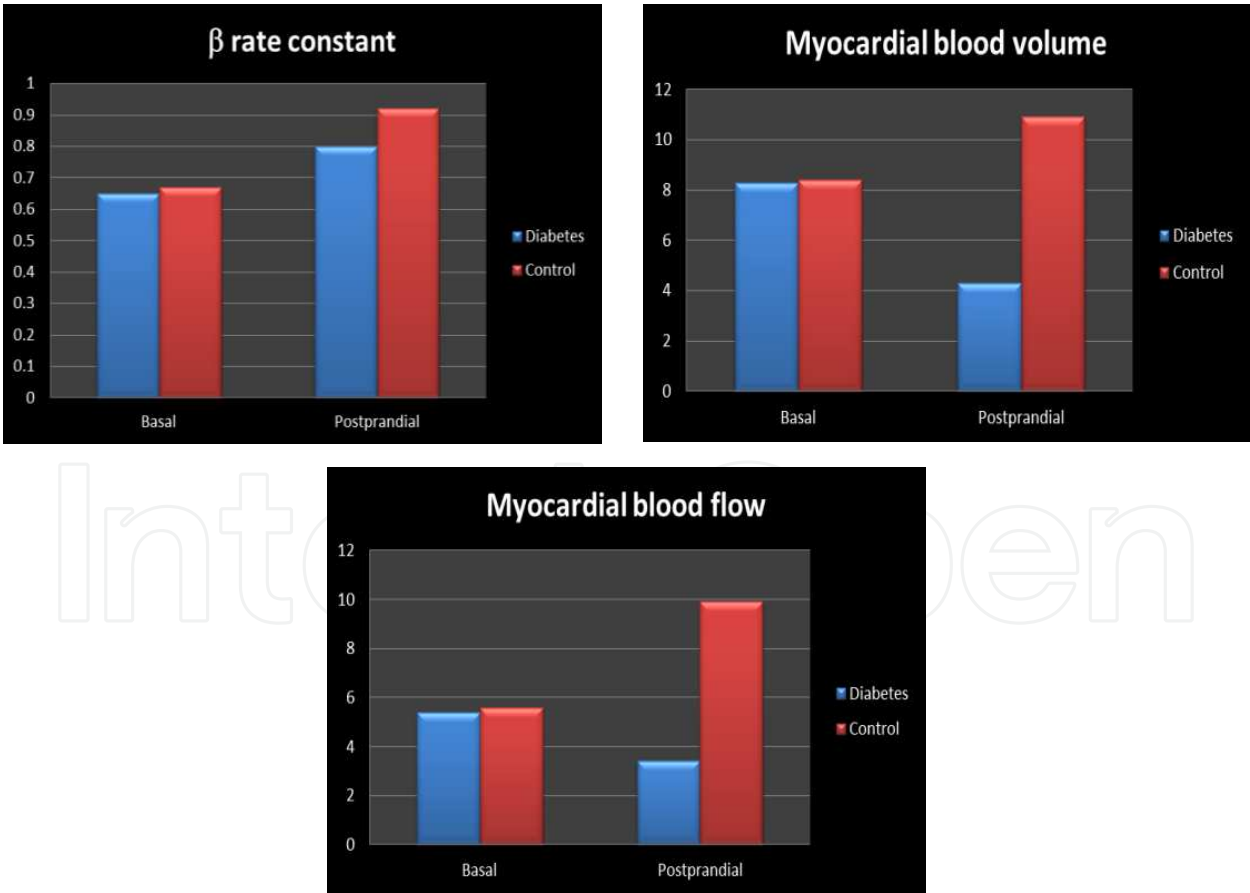


Figure 6. Changes in myocardial perfusion indexes after overnight fasting (baseline) and 120 minutes after standard mixed meal ingestion (postprandial) in type 2 diabetic patients (blue bars) and control subjects (red bars). Adapted from Scognamiglio R et al. *Circulation* 2005;112:179-84.

The American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism prepared a scientific statement summarizing the current understanding of the association between elevated glucose and patient outcomes in acute coronary syndromes and identifying major knowledge gaps that remain for further investigation efforts.

The committee assessed data from the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI), Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5), Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Clinicos Latino America (CREATE-ECLA), and other clinical trials in ACS patients with hyperglycemia.

Most cardiovascular disease risk factors make similar contributions to risk among patients with and without diabetes, and the relationship between fasting plasma glucose or HbA1C levels and macrovascular complications among diabetic patients is not strong. For example, the United Kingdom Prospective Diabetes Study Group (UKPDS) study found that “intensive” control of fasting blood glucose among diabetic patients reduced the relative risk for myocardial infarction by only 16% as compared to conventional, diet-based therapy ($p=0.052$).⁶⁷ What, then, accounts for the greatly increased cardiovascular risk among patients with diabetes? Postprandial hyperglycemia, which captures “spikes” in blood glucose levels that may not be fully reflected in fasting blood glucose or glycosylated hemoglobin levels⁶⁷, has historically been overlooked as a CV risk factor among diabetic patients, those with isolated impaired glucose tolerance and those in the general population.

8. Treatment of acute hyperglycemia in acute myocardial infarction

Many clinicians caring for diabetic patients have a “fasting glucocentric” outlook: they focus on fasting blood glucose and HbA1C levels as the main measures of glycemic status when evaluating a diabetic patient’s cardiovascular risk. However, there is broad epidemiological evidence that just as acute hyperglycemia portends a poorer clinical outcome among critically ill patients, postprandial hyperglycemia predicts cardiovascular disease and mortality not only among patients already identified as diabetic, but also among subjects in the general population. Mounting mechanistic evidence suggests that acute hyperglycemia has myriad adverse effects that are mediated through oxidative stress. Moreover, some available interventional studies suggest that strategies directed toward decreasing postprandial glucose in outpatients and acute hyperglycemia during hospitalizations for cardiovascular events may improve clinical outcomes. Postprandial hyperglycemia determines myocardial perfusion defects in type 2 diabetic patients.

The concept of a metabolic cocktail (GIK) to stabilize cell membranes through potassium influx, promote glucose oxidation, and reduce free fatty acid accumulation to protect the ischemic myocardium dates back to the work of Sodi-Pallares et al.⁶⁸ However, the CREATE-ECLA study showed no benefit of GIK in a large number of STEMI subjects, dampening the enthusiasm for aggressive use of a metabolic cocktail in STEMI⁶⁹

The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study⁷⁰ randomly assigned 6,104 patients admitted to the intensive care unit to undergo either intensive glucose control, with a target blood glucose range of 4.5–6.0 mmol/L or conventional glucose control, with a target of ≤ 10.0 mmol/L. The 90-day mortality was significantly higher in the intensive control group than in the conventional-control group (27.5% vs. 24.9%, $P=0.02$). The difference in mortality between the 2 treatment groups was still significant after adjustment for the predefined baseline risk factors (adjusted odds ratio, 1.14; 95% confidence interval 1.01–1.29; $P=0.04$). Severe hypoglycemia (defined as a blood glucose level ≤ 2.2 mmol/L) was recorded more frequently in the intensive-control group. After these studies, recent guidelines revised their recommendation from intensive glucose control to mild glucose control, avoiding hypoglycemia.

Due as an emerging risk factor for cardiovascular disease, acute hyperglycemia during cardiovascular events may be considered analogous to postprandial hyperglycemia and may carry with it similar adverse clinical implications. Accordingly, several groups, including the American Diabetes Association⁷¹ and the American Heart Association⁷², have encouraged more rigorous control of blood glucose levels during acute hospitalizations for cardiovascular diseases. The clinical trial basis for these recommendations is not yet exceedingly robust.

Although sustained chronic hyperglycemia produces excessive protein glycation, acute fluctuations of glucose may activate oxidative stress and contribute to endothelial dysfunction, which may also participate in the development of diabetes complications. Therefore, reducing postprandial hyperglycemia and glucose variability are now recognized as a priority in treatment of type 2 diabetes. Therapeutic agents acting on postprandial glucose excursions are of particular interest to diminish glucose variability. Emerging therapeutic agents such as the glucagon-like peptide 1 agonists and the dipeptidyl peptidase (DPP)-4 inhibitors are very attractive. Both increase insulin secretion and suppress glucagon release in response to meals, in a glucose-dependent manner. This review will focus on the increasing impact of postprandial hyperglycemia and glycemic variability in developing diabetes complications and the role of DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin) in reducing both defects presenting in people with type 2 diabetes.⁷⁴

In the more recent DIGAMI-2 study ($n=1253$ patients), however, mortality did not differ significantly between diabetic patients randomized to either acute insulin infusion followed by insulin-based long-term glucose control, insulin infusion followed by standard glucose control, or standard management, probably reflecting a lack of difference in glucose control among the three groups.⁷⁵

Because hyperglycemia remained one of the most important predictors of outcome in acute coronary syndromes, however, it appears to be reasonable to keep glucose levels within normal ranges in diabetic patients. Target glucose levels between 90 and 140 mg/dL (5 and 7.8 mmol/L) have been suggested. Care needs to be taken to avoid blood glucose levels

below 80–90 mg/dL (4.4–5 mmol/L), however, as hypoglycemia-induced ischemia might also affect outcome in diabetic patients with acute coronary syndromes⁷⁶

The HI-5 study⁷⁷ attempted to rectify some of the issues that were encountered in DIGAMI-2. It was the first randomized clinical trial of intensive insulin infusion that included hyperglycemic acute myocardial infarcted patients without previously established diabetes. Patients assigned to the intensive insulin-infusion arm received standard insulin and dextrose infusion that was then adjusted to maintain glucose levels between 72 and 180 mg/dL. Patients in the conventional arm received their baseline diabetes medications (including subcutaneous insulin); additional short-acting subcutaneous insulin was permitted for those with a glucose level >288 mg/dL. There was no difference in mortality rates among the groups during hospitalization or at 3 or 6 months. There were, however, statistically and clinically significant reductions in post-myocardial infarction heart failure during hospitalization (10% absolute risk reduction) and in re infarction at 3 months (3.7% absolute risk reduction).

9. Conclusions and recommendations

Concluding, there is currently insufficient evidence to consider glucose control as a quality measure during acute myocardial infarction hospitalization, although this position may change in the future. The recommendations from a scientific statement from the American Heart Association, in hyperglycemia in acute coronary syndromes⁷⁸, are the next:

1. Glucose level should be a part of the initial laboratory evaluation in all patients with suspected or confirmed acute coronary syndrome.
2. In patients admitted to an ICU with acute myocardial infarction, glucose levels should be monitored closely. It is reasonable to consider intensive glucose control in patients with significant hyperglycemia (plasma glucose >180 mg/dL), regardless of prior diabetes history. Although efforts to optimize glucose control may also be considered in patients with milder degrees of hyperglycemia, the data regarding a benefit from this approach are not yet definitive, and regardless of diabetes status. The precise goal of treatment has not yet been defined. Until further data are available, approximation of normoglycemia appears to be a reasonable goal (suggested range for plasma glucose 90 to 140 mg/dL), as long as hypoglycemia is avoided.
3. Insulin, administered as an intravenous infusion, is currently the most effective method of controlling glucose among patients hospitalized in the ICU. Effective protocols for insulin infusion and glucose monitoring have been developed in other patient populations. Care should be taken to avoid hypoglycemia, which has been shown to have an adverse prognostic impact.
4. Treatment should be instituted as soon as feasible, without compromising the administration of life-saving and evidence-based treatments.
5. In patients hospitalized in the non-ICU setting, efforts should be directed at maintaining plasma glucose levels >180 mg/dL with subcutaneous insulin regimens.
6. Acute myocardial infarcted patients with hyperglycemia but without prior history of diabetes should have further evaluation (preferably before hospital discharge) to

determine the severity of their metabolic derangements. This evaluation may include fasting glucose and HbA1C assessment and, in some cases, a post discharge oral glucose tolerance test.

7. Before discharge, plans for optimal outpatient glucose control should be determined in those patients with established diabetes, newly diagnosed diabetes, or evidence of insulin resistance.

The chronic and acute hyperglycemia associated to acute coronary syndromes, mainly in acute myocardial infarction is an independent and determinant factor in the outcome for patients with and without diabetes mellitus. The evidence in clinical trials has showed the importance of admission glucose and glycated hemoglobin, in the evolution, risk for complications, and therapeutic response of patients with acute myocardial infarction. The control of blood glucose levels in patients with acute myocardial infarction, will lead to better outcomes regardless of diabetes status. The precise goal of treatment has not yet been defined. Until further data are available, approximation of normoglycemia appears to be a reasonable goal, as long as hypoglycemia is avoided.

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