

Molecular mechanisms of hyperglycemia and cardiovascular-related events in critically ill patients: rationale for the clinical benefits of insulin therapy

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Abstract: Newly recognized hyperglycemia frequently occurs with acute medical illness, especially among patients with cardiovascular disease (CVD). Hyperglycemia has been linked to increased morbidity and mortality in critically ill patients, especially when it is newly recognized. Increased rates of reinfarction, rehospitalization, major cardiovascular events, and death in CVD patients have also been found. An expanding body of literature describes the benefits of normalizing hyperglycemia with insulin therapy in hospitalized patients. This article reviews several underlying mechanisms thought to be responsible for the association between hyperglycemia and poor outcomes in critically ill patients and those with cardiovascular events, as well as the biologic rationale for the benefits of insulin therapy in these patients.

Keywords: hyperglycemia, diabetes, cardiovascular disease, critical illness, insulin

Introduction

Estimates from 2007 indicate that 23.6 million people in the United States (7.8%) have diabetes, among whom 5.7 million are undiagnosed.¹ An additional 57 million American adults may have prediabetes (based on the prevalence of impaired fasting glucose).¹ Hyperglycemia also frequently occurs as a result of medical illness, even without previously recognized diabetes – especially among critically ill patients with cardiovascular disease (CVD).^{2,3} For example, the Euro Heart Survey found that 36% of patients without a history of diabetes who presented with acute manifestations of coronary artery disease had impaired glucose tolerance; another 22% had newly diagnosed diabetes.³ Likewise, in a prospective analysis of patients presenting with acute myocardial infarction (MI) and no history of diabetes, 35% had impaired glucose tolerance and 31% had unrecognized diabetes.²

Even normoglycemic patients or those with well-controlled diabetes before illness onset may develop hyperglycemia in response to acute metabolic stress, suggesting an irregularity in homeostatic regulation mechanisms that worsens with severity of illness.⁴ In a prospective cohort study of 100 patients admitted to a medical intensive care unit (ICU), including 51 patients with normal glucose levels at baseline, nearly all experienced some degree of hyperglycemia.⁴ The substantial influence of even small increases in glucose levels was evident in that patients with glucose levels in the higher ranges of normoglycemia before admission had more frequent and more severe hyperglycemia in the ICU than did those with glucose levels within the lower range of normoglycemia (Figure 1).⁴

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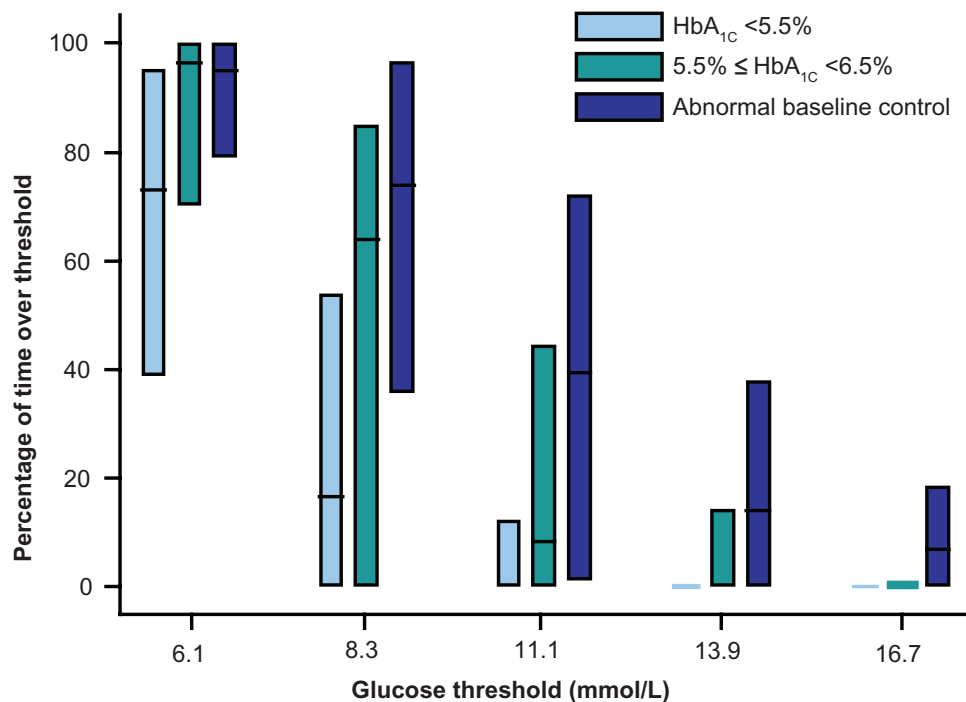


Figure 1 Percentage of time (median and quartile bounds) over glucose thresholds varied in patients admitted to the medical intensive care unit according to low-normal ($HbA_{1c} < 5.5\%$), high-normal ($5.5\% \leq HbA_{1c} < 6.5\%$), and abnormal baseline glucose levels. Glucose threshold values can be converted to conventional units (mg/dL) by multiplying by the conversion factor 0.0555. Copyright © 2004. Adapted with permission from AM College of Chest Medicine. Cely CM, Arora P, Quartin AA, Kett DH, Schein RM. Relationship of baseline glucose homeostasis to hyperglycemia during medical critical illness. *Chest*. 2004;126(3):879–887.⁴
Abbreviation: HbA_{1c}, glycated hemoglobin.

It is now recognized that uncontrolled hyperglycemia has a negative effect on clinical outcomes in hospitalized patients. Many studies over the past 2 decades have demonstrated that short- and long-term mortality rates following acute MI are significantly higher when hyperglycemia is present, with or without established diabetes.^{5–11} This suggests that hyperglycemia, rather than diabetes status, influences morbidity and mortality risk. In fact, a study by Umpierrez and colleagues observed that hospitalized patients (admitted to general wards) with newly discovered hyperglycemia had significantly higher in-hospital mortality than those with normoglycemia or previously diagnosed diabetes (16% versus 1.7% and 3%, respectively, $P < 0.01$). Newly recognized hyperglycemia was also associated with worse functional outcomes.¹² Patients exhibiting stress hyperglycemia upon admission with acute MI have been shown to have a heightened risk of congestive heart failure (CHF) or cardiogenic shock compared with patients without hyperglycemia.¹¹ This association between stress hyperglycemia and risk of CHF or shock has been observed in patients without diabetes and not present in patients with diabetes.¹¹ In a retrospective study of 197 patients with acute MI without diabetes, admission plasma glucose level was an independent predictor

of hospitalization for heart failure ($P = 0.0034$).⁹ In addition, a recent study showed that insulin resistance is an independent predictor of left ventricular diastolic disorder (LVDD) prevalence and severity in patients without diabetes. Insulin resistance was associated with: metabolic syndrome, LVDD, and obesity. The authors indicated that in patients with insulin resistance, the risk for LVDD is already elevated, even before the development of diabetes, therefore, these patients may be a target group for heart failure prevention.¹³

Several landmark studies have demonstrated that aggressive treatment of hyperglycemia with insulin therapy can reduce morbidity and mortality in critically ill patients,^{14,15} patients undergoing coronary artery bypass graft (CABG),¹⁰ and post-MI patients with diabetes.¹⁶ These data have increased emphasis on managing hyperglycemia in hospitalized patients – especially the critically ill and those with CVD – and have led the American Diabetes Association (ADA) to update its guidelines for managing in-hospital hyperglycemia. The ADA 2010 Standards of Medical Care in Diabetes now recommend that insulin therapy be initiated for persistent hyperglycemia starting at ≤ 10.0 mmol/L (≤ 180 mg/dL).¹⁷ Blood glucose levels should be maintained at 7.8 to 10.0 mmol/L (140 to 180 mg/dL) for most critically

ill patients and are most effectively achieved via intravenous insulin protocols.¹⁷ The 2009 American Association of Clinical Endocrinologists/ADA Consensus Statement on Inpatient Glycemic Control recommends a starting threshold no higher than 10.0 mmol/L (180 mg/dL). Once IV insulin therapy has begun, blood glucose should be maintained between 7.8 and 10.0 mmol/L (140 and 180 mg/dL), with targets <6.1 mmol/L (<110 mg/dL) not recommended.¹⁸

It should be noted that insulin therapy is not without potential harm. One meta-analysis found that tight glucose control in critically ill patients resulted in an increased risk of hypoglycemia.¹⁹ A small (N = 13) study of healthy males designed to determine the body's response to the stress of hypoglycemia found an increase in proinflammatory cytokines, markers for lipid peroxidation, reactive oxygen species, and leukocytosis. Further examination is necessary to determine whether this is an adaptive response to the body's efforts to maintain glucose homeostasis under such stress.²⁰

This paper reviews the underlying mechanisms believed to be responsible for the association between hyperglycemia and poor outcomes in critically ill patients and patients with cardiovascular events, as well as the biologic rationale for the benefits of insulin therapy in these patients.

Hyperglycemia, inflammation, and atherogenesis

Many data from in vitro and epidemiologic studies have suggested that insulin is potentially atherogenic.^{21–23} This arose from the finding that most patients with diabetes and at risk for vascular complications exhibit hyperinsulinemia due to compensation for insulin resistance, which is associated with atherogenic risk (eg, dyslipidemia, hypertension, pro-coagulant state). The notion that insulin itself is cardiotoxic or vasculotoxic, however, is inconsistent with more recent clinical outcomes, especially those observed in long-term follow-up of studies such as the United Kingdom Prospective Diabetes Study (UKPDS).²⁴ Researchers now believe that hyperglycemia rather than the hyperinsulinemia of diabetes actually induces inflammatory changes and oxidative stress, which harm cardiovascular and endothelial function.^{25–29} Shown in Table 1 are the deleterious effects of hyperglycemia on endothelial and vascular function in patients with type 1 and type 2 diabetes with associated hyperlipidemia and insulin resistance.³⁰

Insulin resistance, one of the 2 major contributors to type 2 diabetes, appears to play an important role in chronic cardiovascular risk. Its exact influence in atherogenesis is poorly understood, but several relationships appear to be

Table 1 Deleterious effects of hyperglycemia on endothelial and vascular function (as seen in patients with type 2 diabetes in association with dyslipidemia and insulin resistance)⁶¹

↑ AGEs activation	↑ Vascular permeability
	↑ Inflammatory cytokines
	↑ Tissue factor
	↑ Thrombomodulin
↓ Nitric oxide	↑ Vasoconstriction
	↑ Platelet adhesion
	↑ Leukocyte adhesion
	↑ Vascular smooth muscle cell growth
↑ PKC activation	↑ Endothelin-I
	↑ Renin-angiotensin system
	↑ Vascular permeability
↑ Platelet and coagulation system activation	↑ IIB/IIIa receptors
	↑ Clotting factors
	↑ PAI-I
	↓ Antithrombin III
↓ PPAR activation	↑ NFκB
	↑ ROS
	↑ Inflammatory cytokines

Abbreviations: AGEs, advanced glycation end products; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; IIB/IIIa, glycoproteins IIB/IIIa; PAI-I, plasminogen activator inhibitor-I; NFκB, nuclear factor κB; ROS, reactive oxygen species.

involved. Insulin resistance, inflammation, and atherogenesis are linked by a common series of metabolic defects, including dyslipidemia and hypercoagulability.³¹ With insulin resistance, especially in patients with 4 or 5 aspects of the metabolic syndrome, deregulation of proinflammatory and anti-inflammatory cytokine production (eg, increased levels and activity of interleukin-6 and tumor necrosis factor-α) contributes to oxidative stress. The resultant generation of reactive oxygen species, combined with hypercholesterolemia and insulin resistance, apparently contributes to endothelial dysfunction.

Mechanisms involved in endothelial dysfunction in patients with diabetes, its impact on vascular complications, and potential targets of therapeutic intervention have been reviewed elsewhere.^{28,29} Relatively acute endothelial dysfunction and longer-term endothelial damage result from oxidative stress. Insulin therapy may reverse short-term endothelial dysfunction.³² Figure 2 shows a schematic of how insulin infusion therapy to treat hyperglycemia during critical illness may protect the endothelium by downregulation of inducible nitric oxide synthase.³² Subanalysis of a large, randomized controlled study of intensive insulin therapy in critically ill patients demonstrated how intensive insulin therapy suppressed inducible nitric oxide synthase gene expression in postmortem liver and skeletal muscle (via reduced nuclear factor κB [NF-κB] activation), and reduced circulating nitric oxide levels in survivors and nonsurvivors. Biochemical changes reflected

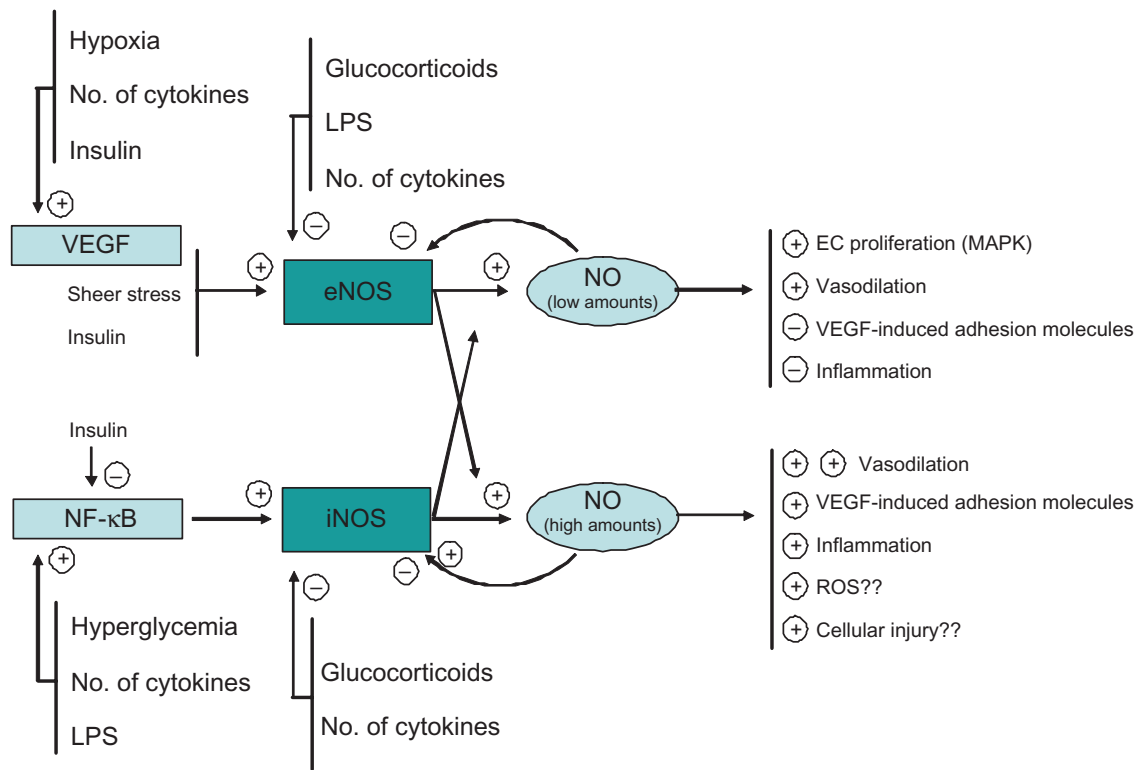


Figure 2 Model for effects of intensive insulin therapy on endothelial function in critically ill patients. Low concentrations of nitric oxide (NO), normally generated by endothelial nitric oxide synthase (eNOS), are likely to be beneficial for the endothelium and organ function. However, high concentrations of NO produced by upregulation of inducible nitric oxide synthase (iNOS) may contribute to excessive vasodilation, endothelium dysfunction, and tissue injury. Prevention of hyperglycemia during critical illness via insulin infusion may protect the endothelium by modifying eNOS and/or iNOS expression and activity. Copyright © 2005. Reprinted with permission from American Society for Chemical Investigation. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest.* 2005;115(8):2277–2286.³²
Abbreviations: EC, endothelial cell; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor κB; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

reduced endothelial activation, which contributes to the risk of organ failure and death in critically ill patients. The endothelial effects in this subanalysis explained a statistically significant portion of improved patient outcomes clinically associated with intensive insulin therapy.^{32,33}

Using a model of critical illness, Ellger et al suggested that glycemic control helps maintain proper endothelial vasodilatory function indirectly through the actions of arginine and asymmetrical-dimethylarginine.³⁴ Asymmetrical-dimethylarginine primarily cleared by dimethylarginine-dimethylaminohydrolase is an endogenous inhibitor of nitric oxide synthetase that increases during critical illness and predicts mortality and morbidity. Although insulin does not directly affect dimethylarginine-dimethylaminohydrolase, glucose control restores its activity, whereas uncontrolled hyperglycemia reduces it. Additionally, inhibition by insulin of plasminogen activator protein-1, an inhibitor of fibrinolysis, may help dissolve clots that form in acute MI.³⁵

Longer-term biochemical or structural endothelial damage (see revised classic model of atherosclerosis in Ross³⁶) can

initiate a cascade of atherogenic activity in the vascular wall, including entrapment of atherogenic molecules, triggering of immunologic activity, promotion of adhesion molecules, and development of lipid-laden foam cells that form the basis for plaque production.³¹ Thus insulin resistance initiated by poor control of glycemic levels, rather than by insulin itself, may stimulate atherosclerosis. In the UKPDS intensive-treatment arm neither insulin nor insulin secretagogues were associated with increased vascular events, MI, or death.³⁷ Interestingly, the long-term outcome of the UKPDS intensive glucose policy for sulfonylureas and insulin has recently been reported to show improvement in all-cause mortality, diabetes-related death, and significant reduction in MI. The reduction occurred despite the intensive policy group having had similar glycemic control over the past 10 years; it may represent a “legacy effect” of earlier glycemic control.^{24,38}

Clinical studies have shown that patients with chronically elevated insulin levels due to insulin therapy have reduced insulin resistance but no increased risk of atherosclerosis or CVD. In some cases, individuals benefit from

insulin exposure, experiencing reduced oxidative stress and improved endothelial function (ie, anti-inflammatory benefit).^{37,39} de Jager and colleagues linked the development of type 2 diabetes to the combination of endothelial dysfunction and low-grade inflammation, reporting a >40% increased risk of cardiovascular mortality with this combination.⁴⁰

Furthermore, elevated glucose levels have been shown to promote the production of reactive oxygen species, significantly increasing its generation by both mononuclear and polymorphonuclear cells within 3 hours after glucose challenge.^{41,42} Oral glucose intake (glucose tolerance test) also significantly increased binding of the transcription factor NF- κ B in mononuclear cell nuclear extracts, indicating that pro-oxidant and proinflammatory activity follows the intake of excessive macronutrients.⁴² In another study, oxidative stress, as estimated from urinary excretion of free 8-iso prostaglandin F₂ α , was higher in patients with hyperglycemia resultant from type 2 diabetes than in nondiabetic controls matched for age and sex.⁴³ These pathophysiologic findings confirm a relationship between variations in glucose exposure, endothelial dysfunction, and atherogenesis independent of insulin levels. When 1548 patients admitted to a surgical ICU received insulin infusion or conventional therapy to achieve blood glucose levels of 4.4 to 5.6 mmol/L (80 to 100 mg/dL), lowering blood glucose rather than insulin dose reduced mortality ($P < 0.0001$).⁴⁴

The role of insulin infusion versus glucose-insulin-potassium (GIK) therapy to achieve glycemic control and improve outcomes in critically ill patients has been investigated and debated.^{27,45} In general, GIK infusions may induce hyperglycemia, offset insulin's beneficial effects, and fail to control glucose levels. Insulin infusions may lower the proinflammatory effects of glucose and induce the anti-inflammatory effects of insulin.^{27,45}

Recent studies in patients with type 2 diabetes have examined the hypothesis that insulin infusions may affect toll-like receptors (TLRs), major determinants of inflammatory response to viral, fungal, and bacterial pathogens.²⁷ Insulin infusions significantly suppressed messenger RNA levels by >25% for several of these receptors, including TLR-1, -2, -4, -7, and -9, within 2 hours ($P < 0.05$ for all). DNA binding of PU.1, a major transcription factor regulating many TLR genes, was also suppressed ($24\% \pm 10\%$, $P < 0.05$).⁴⁶

Role of insulin in cardiovascular disease

Several investigators have studied the impact of insulin on markers of atherosclerosis, indicating a compelling benefit.

A number of studies have shown a significant reduction in C-reactive protein increase in patients with CVD who were treated with insulin, during ST-segment elevation MI ($P < 0.05$) and CABG surgery ($P < 0.05$).^{47,48} These results indicate that insulin is associated with a decrease in the systemic inflammatory response. In a recent study involving 88 patients with a first MI who were scheduled to undergo CABG surgery (50 hyperglycemic patients and 38 normoglycemic [control] patients),³³ hyperglycemic patients were randomized to intensive glycemic control (IGC; $n = 25$; glucose 4.4 to 7.8 mmol/L [80 to 140 mg/dL]) or conventional glycemic control (CGC; $n = 25$; glucose: 10.0 to 11.1 mmol/L [180 to 200 mg/dL]) for 3 days before surgery. Results showed that, compared with IGC patients, CGC patients had significantly higher infarct segment length ($P < 0.05$), myocardial performance index ($P < 0.02$), and wall motion scores ($P < 0.01$) but lower ejection fraction ($P < 0.05$). In the immediate postinfarct period, IGC was associated with a significant reduction of inflammatory cytokines, NF- κ B activation, oxidative stress, and apoptotic cell death compared with CGC.³³ It is likely that treatment of hyperglycemia with insulin acts to counteract inflammatory response and poorer outcomes in critically ill patients by a dual mechanism of a direct anti-inflammatory effect of insulin as well as lowering the proinflammatory effects of glucose.²⁷

Patients with type 2 diabetes randomized to placebo metformin, placebo metformin and insulin glargine, metformin only, or metformin and insulin glargine achieved significant reductions in blood glucose and glycated hemoglobin (HbA_{1c}) levels and C-reactive protein in all treatment groups. However, reductions in C-reactive protein were not significantly different among patients using insulin (change from baseline: -11.8%; 95% confidence interval [CI]: -18.7% to -4.4%) compared with no insulin (-17.5%; 95% CI: -23.9% to -10.5%) (for difference, $P = 0.25$), or among patients using metformin (-18.1%; 95% CI: -24.4% to -11.1%) compared with placebo (-11.2%; 95% CI: -18.1% to -3.7%) (for difference, $P = 0.17$). The authors note this study was limited to outpatients with stable type 2 diabetes and results may not pertain to the potential anti-inflammatory effects of insulin in critically ill patients.⁴⁹

Thus far, no clinical studies examining the effects of insulin detemir on cardiovascular variables including lipid parameters or changes in carotid intima-media thickness have been published. However, the Copenhagen Insulin and Metformin Therapy (CIMT) trial will measure the change in carotid intima-media thickness, and other cardiovascular variables, following 18 months of treatment with insulins

detemir and aspart.⁵⁰ Carotid intima-media thickness often serves as a proxy for progression of macrovascular disease. The technique involves imaging an arterial wall segment of the common carotid arteries.⁵⁰ Vehkavaara and Yki-Jarvinen studied the vascular effects of insulin glargine added to metformin in 11 patients whose type 2 diabetes was poorly controlled by metformin monotherapy.⁵¹ The patients receiving glargine experienced improvement in both endothelial-dependent and endothelial-independent vasodilation at 3.5 years compared with noninsulin-treated control patients with diabetes ($P < 0.02$ for both treatment comparisons).⁵¹ In another study, insulin aspart improved endothelial function in patients with type 2 diabetes by preserving flow-mediated vasodilation after a standard test meal ($P < 0.01$).⁵² Lautamaki and coworkers studied the effects of insulin infusion on endothelial activity in 43 patients with type 2 diabetes and a history of angina.⁵³ Using traditional and nuclear imaging techniques, they observed increased myocardial blood flow in both ischemic and nonischemic regions, which helps improve endothelial function and preserve cardiac health.⁵³

Finally, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, an observational follow-up of the Diabetes Control and Complications Trial (DCCT), evaluated how aggressive insulin therapy affects cardiovascular architecture in patients with insulin-treated type 1 diabetes.⁵⁴ Patients randomly assigned to conventional diabetes therapy (611; HbA_{1c} goal, $<9.0\%$) were compared with patients receiving aggressive treatment (618; HbA_{1c} goal, $<7.2\%$). Aggressive insulin therapy significantly reduced the degree of progression of intima-media thickening in the carotid artery (0.032 versus 0.046 mm; $P = 0.01$) and in the combined common and internal carotid arteries (-0.115 versus 0.007 mm; $P = 0.2$) after 6 years, compared with conventional diabetes therapy.⁵⁴ Although this change has not been linked directly to cardiovascular outcome rates, the findings suggest a potential CVD benefit.

The major cardiovascular event rate has also been shown to be reduced in long-term follow-up of the EDIC study. During a mean 17 years of follow-up in the DCCT, 46 CVD events occurred in 31 patients intensively treated with a mixed-intermediate or rapid-acting insulin, compared with 98 events in 52 patients who received conventional treatment. There was a 42% decrease in cardiovascular events and a 57% decrease in the risk of nonfatal MI, stroke, or death from CVD in the intensive treatment group.⁵⁵ Significant reductions in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels also have been observed in the intensive-treatment group ($P \leq 0.01$), as

well as a reduction in the development of LDL cholesterol levels >4.1 mmol/L.⁵⁶

Ongoing studies, such as the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial will determine if maintaining normoglycemia with insulin glargine can reduce the risk of cardiovascular morbidity and/or mortality among outpatients with impaired fasting glucose, impaired glucose tolerance, or early type 2 diabetes who are at high risk for vascular disease.⁵⁷ The ACCORD (The Action to Control Cardiovascular Risk in Diabetes)⁵⁸ and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation)⁵⁹ study groups have recently published data indicating that intensive glycemic control (HbA_{1c} $< 6.0\%$ or $\leq 6.5\%$, respectively) in patients with type 2 diabetes (ACCORD; mean age, 62 years; duration of diabetes, 10 years; ADVANCE; mean age, 66 years; duration of diabetes, 8 years) at high cardiovascular risk failed to reduce major cardiovascular events, and that it was actually associated with higher mortality (the ACCORD study). The implications of these results are not yet clear. Although future studies are unlikely to show improvements in CVD outcomes when HbA_{1c} values are $\leq 6.5\%$, current evidence justifies maintaining HbA_{1c} goals at $<7.0\%$ to reduce microvascular and neurologic morbidity and suggests that doing so may reduce CVD complications in the long term.⁶⁰ It is important to note, however, that these studies examined outpatients with type 2 diabetes, as opposed to critically ill patients with hyperglycemia (discussed in this review) treated with a variety of glucose-lowering drugs, and the studies were therefore not specifically testing the effects of insulin therapy. Only 40.5% of patients in the intensive control arm of the ADVANCE study were prescribed insulin.⁵⁹ Furthermore, more time may be needed for glycemic control to realize the reduction of MI risk. The 10-year follow-up of the UKPDS reported patients with type 2 diabetes who control glucose by intensive therapy (sulfonylurea or insulin, or metformin in overweight patients) had significant risk reductions for MI (15%, $P = 0.01$) and death from any cause (13%, $P = 0.007$) in the sulfonylurea-insulin group when compared with patients receiving conventional therapy (dietary restrictions); the metformin group also had significant risk reductions for MI (33%, $P = 0.005$).²⁴

Summary

Hyperglycemia substantially increases the risk of morbidity and mortality among critically ill patients with CVD. Contrary to previous theories, the negative effect of hyperglycemia related to stress or uncontrolled diabetes on long-term

outcomes in this patient subpopulation appears to be linked to the proinflammatory, oxidant stress, endothelial dysfunction, and atherogenic effects of hyperglycemia rather than to any metabolic alteration associated with hyperinsulinemia. Recognition of this alternative pathophysiologic paradigm and improved outcomes in patients treated with insulin have led to widespread interest in maintaining adequate glucose control in critically ill patients, and intense investigation into the best means by which to achieve relative normoglycemia throughout periods of acute illness.

Acknowledgment

The contents of the paper and opinions expressed within are those of the author, and it was the decision of the author to submit the manuscript for publication. The author contributed to the writing of this manuscript, including critical review and editing of each draft, and approval of the submitted version.

Disclosure

Editorial support was provided by Peter Mathisen, PhD, of Embryon and was funded by sanofi-aventis, US.

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