Diabetes and hyperglycemia: Strict glycemic control

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Objective: **To critically review recent evidence on pathophysiology, diagnosis, and control of acute and chronic hyperglycemia in medical and surgical intensive care unit (ICU) patients.**

Data Source and Study Selection: **A MEDLINE/PubMed search (1966 through February 2006) with manual cross-referencing was conducted, including all relevant articles published on blood glucose control in intensive care patients. An emphasis was placed on more recent clinical trials investigating the effects of tight glycemic control in ICU patients and on basic science studies investigating the pathophysiology and systemic effects of transient hyperglycemia in nondiabetic patients.**

Data Extraction and Synthesis: **Original articles, selected reviews, letters to the editor, and chapters of selected textbooks were extracted. The reviewed information was then analyzed with respect to the prevalence of hyperglycemia in ICU patients, the pathophysiology of hyperglycemia in nondiabetics, and evidence on glycemic control in various subgroups of ICU patients. The risk of iatrogenic hypoglycemia in the ICU and potential future research directions are discussed at the end of the review.**

Conclusions: **Recent evidence shows direct improvements in patient mortality and in-hospital morbidity with strict control of even short-term elevations of glucose levels in certain subgroups of ICU patients. However, precisely defined target glucose levels, subgroup analyses of different patient populations and treatment interventions, and the avoidance of hypoglycemic episodes during insulin therapy remain incompletely resolved and warrant future investigation. (Crit Care Med 2006; 34[Suppl.]:S291–S300)**

Key Words: hyperglycemia; hypoglycemia; blood glucose; diabetes; critical illness; stress; sepsis syndrome

Physician awareness of the need to control even short-term elevations of blood glucose levels in both medical and surgical intensive care units (ICUs) has increased noticeably in recent years. The rising worldwide prevalence of type 2 diabetes and a series of well-conducted clinical trials on the benefits of tight glucose control in hyperglycemic patients have made the control of inpatient blood glucose levels a performance measure for clinicians. At the same time, basic research has increased our insight into the potential mechanisms by which glucose and insulin modulate the host response to critical illness, inflammation, and infection.

This article is meant to give a current review of the literature on tight glycemic control in ICU patients, while providing an additional focus on the pathophysiology of hyperglycemia in previously nondiabetic, critically ill patients. It is important to note, however, that many of the studies cited in this review were not conducted in critically ill patients and may therefore not directly apply to this group of patients. In addition, pathogenic mechanisms studied in diabetic patients may not pertain to the larger group of nondiabetic patients with hyperglycemia due to critical illness.

Methods

We have conducted a MEDLINE/PubMed literature search including all relevant articles published on the pathophysiology of acute hyperglycemia and glycemic control in the intensive care setting until February 2006. A broad range of search terms was used, including "hyperglycemia," "glucose," or "insulin" in combination with specific search terms for the individual sections of this review. No limitations as to publication types, languages, or subsets were applied. Manual cross-referencing followed the electronic search to identify further articles of interest. Review articles were included, but whenever possible, original sources are cited in our text. Units of measurement are stated as used by the original authors. No meta-analysis or subset analysis was undertaken, and data are presented only as originally published.

Hyperglycemia: The Extent of the Problem

Worldwide Prevalence and Effect of Diabetes Mellitus. Diabetes mellitus has reached epidemic proportions and affects >170 million individuals worldwide, 90% of whom have type 2 diabetes (1). In 2002, diabetes mellitus affected 6.3% of the American population (18.2 million), a percentage that has increased more than four-fold in the past 50 yrs (2, 3). Taking undiagnosed diabetes into account, the true prevalence was estimated to be closer to 10% for the entire U.S. population (4, 5). In the 2002 survey, 45% of diabetics were >65 yrs of age, and the rate of diabetes was two to four times higher in minority races and ethnic groups such as Hispanic, African-American, or native Americans (2, 3). The incidence of type 1 diabetes is increasing to a much lesser extent and varies among different ethnic populations, from 0.1/100,000 per year in certain regions in China to >40/100,000 per year in Finland (6).

Age-adjusted mortality among adults with diabetes is reported to be twice that of people who do not have diabetes (7, 8), and life expectancy is reduced by approximately 13 yrs in the average diabetic

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person (9), making diabetes the sixth most common cause of death in the United States (10). In addition to the loss of life, total national healthcare expenditures for the treatment of diabetes-related healthcare problems were recently stated to be as high as $132 billion per year (3). In this estimate, direct medical costs accounted for $92 billion and indirect costs (disability, work loss, premature mortality) made up the remaining $40 billion per year. To make matters look worse, projections of diabetes into the 21st century predict an increase in diagnosed cases of diabetes to nearly 10% of all Americans in 2050, both due to an increase in the population exceeding 65 yrs of age and rising incidence rates of diabetes among younger age groups (11).

Prevalence of Transient Hyperglycemia in Previously Nondiabetic ICU Patients. There are discrepancies in the definition of stress hyperglycemia in critical illness, mainly with respect to the cut-off value by which one defines hyperglycemia, in-homogeneity of study populations, and varied timing of blood sampling; therefore, the prevalence of stress-induced hyperglycemia is difficult to assess. With more studies demonstrating benefits of tight glucose control in perioperative and critically ill patients emerging every year, the previously accepted threshold of 200 mg/dL plasma glucose (12) has been lowered by most investigators to 110–150 mg/dL (13–17).

In a large series of mixed surgical ICU patients, Van den Berghe et al. (17) reported 75% of all patients, including diabetics, had blood glucose levels exceeding 110 mg/dL at admission, and 12% of all patients were actually >200 mg/dL. Latham et al. (18) found that 21% of cardiothoracic surgery patients developed postoperative blood glucose levels of >200 mg/dL and reported a direct correlation between the degree of hyperglycemia and the rate of infections. Wide variations are observed in nondiabetic patients with acute myocardial infarction, with stress hyperglycemia reported in 3% to 71% of patients (19).

In 2,471 Canadian, non-ICU patients admitted with community-acquired pneumonia, only 5% of patients without a previous diagnosis of diabetes showed blood glucose levels of >11 mmol/L (200 mg/dL) (20), which may emphasize the pathogenic importance of critical illness in the development of stress hyperglycemia. In pediatric emergency room patients, hyperglycemic admission values were lower but still occurred in 3.8–5.0% of patients (21, 22), whereas mean plasma glucose levels in pediatric ICU patients were reported to be as high as 230 mg/dL in a study of 50 critically ill children (23).

Pathophysiology of Hyperglycemia in Diabetes Mellitus

Classic type 1 diabetes is thought to result from an autoimmunologic destruction of the insulin-producing islet beta cells. Accordingly, these patients have absolute insulin deficiency and invariably require insulin treatment. The onset of type 1 diabetes is not limited to young age. Specifically, 5–30% of adult patients initially diagnosed with type 2 diabetes actually have type 1 diabetes, as suggested by the finding of circulating glutamic acid decarboxylase antibodies directed toward the patients' islets of Langerhans (24). Furthermore, patients with type 1 diabetes can also express autoantibodies to islet cell cytoplasm or autoantibodies to insulin (25). Concomitant autoimmune endocrinopathies such as thyroid dysfunction or especially adrenal insufficiency (Addison's crisis) have to be considered in type 1 diabetics, particularly in the unstable ICU patients with unexplained altered mental status, hypotension, or weakness (26).

Type 2 diabetes has a completely different, multifactorial pathophysiology. It is typically accompanied by the metabolic syndrome. This includes not only glucose intolerance but also insulin resistance, central obesity, dyslipidemia, and hypertension, all well-documented risk factors for cardiovascular disease (27). However, not only lifestyle factors but also genetic elements are involved in the pathogenesis of type 2 diabetes, which is evident considering the 2.4-fold increased risk in individuals with a positive family history (28). Given the high prevalence of environmental and genetic risk factors, it is not surprising that type 2 diabetes is now being increasingly diagnosed in obese young and adolescent people, particularly in western nations (1, 29).

In contrast to type 1 diabetes, the main problem in patients with type 2 diabetes is not absolute insulin deficiency but, rather, insulin resistance with ensuing relative insufficiency of insulin production. Insulin resistance is said to be present when the biological effects of insulin are less than expected for both glucose disposal in skeletal muscle and suppression of endogenous glucose production in the liver (30). Type 2 diabetes can be treated with a calorie-restricted diet, oral hypoglycemic agents, or insulin. It is usually a progressive disease, and even if it can be controlled by oral hypoglycemic agents initially, may ultimately require insulin treatment (26).

Pathophysiology of Hyperglycemia in Critical Illness

Cellular Glucose Transport. Despite large timely fluctuations in supply and demand, plasma glucose levels are normally controlled within a narrow range between 80 and 125 mg/dL in a fasting state. Interestingly, 80% of systemic glucose utilization occurs by non–insulin-mediated glucose uptake under basal conditions, mainly by the central nervous system (31, 32). Muscle glucose uptake accounts for only about 20% in a resting state, half of which occurs as insulin mediated. Another 30–40% of total glucose uptake is stored in the liver in the form of glycogen.

Glucose transport into cells occurs as facilitated diffusion using one of five different glucose transporter (GLUT) channel proteins. GLUT 1–mediated insulin-independent transport occurs in most tissues and accounts for basal glucose uptake, whereas the membrane presence of GLUT 4 is specifically and reversibly up-regulated by insulin. On a cellular level, insulin binds to the insulin receptor, causing autophosphorylation and tyrosine-kinase–mediated phosphorylation of insulin receptor substrate second messenger molecules 1 and 2. Insulin receptor substrate 1 then activates the phosphatidylinositol 3-kinase system, which is a required step for the translocation of preformed and intracellularly stored GLUT 4 transporter molecules to the cell membrane. During moderate hyperglycemia, cells usually respond with an internalization of GLUT transport molecules to protect themselves from glucose overloading (33). Interestingly, although, total body glucose uptake is typically increased in critical illness, which has mainly been attributed to non–insulin-mediated glucose uptake in tissues such as the central nervous system or blood cells (12, 34). Several factors typically observed in critical illness, including proinflammatory cytokines, endothelin-1, transforming growth factor-β, or tissue hypoxia, were shown to upregulate GLUT 1 and GLUT 3 isoforms in various tissues, thereby leading to concentration-dependent cellular glucose uptake

and compromising the protective response against hyperglycemia (35–38).

Metabolic Stress Response. In general, the degree of the systemic response to stress correlates with the intensity of the challenge. Critically ill patients commonly enter a hypermetabolic state, with distinct alterations of their carbohydrate metabolism as part of the physiologic stress response. The classic endocrine reaction to a stressful challenge consists of the activation of the sympathoadrenal and the hypothalamopituitary-adrenal axis, leading to increased plasma levels of catecholamines and glucocorticoids, both of which help induce hyperglycemia in critical illness (12). Other hormones, such as corticotrophin, growth hormone, and glucagons, are also found to be elevated in response to physiologic stress (39). These counter-regulatory hormones inhibit hepatic glycogenesis and peripheral glycolysis while promoting gluconeogenesis, hepatic and muscle glycogenolysis, and peripheral lipolysis (12). Glucagon, which mainly promotes hepatic glycogenolysis and gluconeogenesis, was shown to be a major factor for the development of hyperglycemia in burn patients (40). Peripheral glycolysis and the breakdown of glycogen, lipids, and later, muscle protein provides the substrates for hepatic gluconeogenesis in the form of pyruvate, glycerol, and alanine (34). Figure 1 provides a simplified overview of the glucose metabolism during stress.

Peripheral and Hepatic Insulin Resistance. Proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 were both shown to have the potential to induce a state of peripheral and hepatic insulin resistance (41–43). Tumor necrosis factor-α has been well studied in this regard and supposedly promotes insulin resistance through compromised tyrosine phosphorylation of insulin receptor substrate 1/2, this in turn leading to an impaired activation of the phosphatidylinositol 3-kinase second messenger pathway (42–46) necessary for the membrane expression of GLUT 4 transporters. Counter-regulatory hormones such as epinephrine, cortisol, or growth hormone have also been associated with peripheral insulin resistance, although the precise mechanisms for this effect are less well understood (47–50).

Other Factors Promoting Stress Hyperglycemia. Increased gluconeogenesis fueled by proteolytic, lipolytic, and glucolytic metabolites combined with hepatic insulin resistance are considered the main

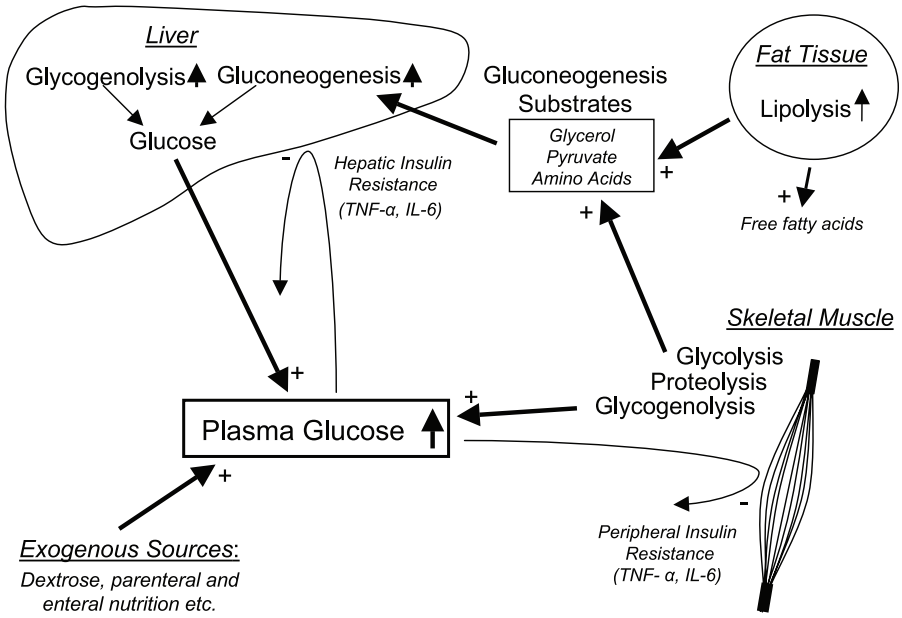

Figure 1. In critical illness, transient hyperglycemia results from a combination of peripheral and hepatic insulin resistance, increased glycogenolysis, and gluconeogenesis fueled by the enhanced peripheral breakdown of substrates. Increased levels of counter-regulatory hormones such as cortisol and exogenous sources of glucose further promote already increased blood glucose levels (see text for details). *TNF-α*, tumor necrosis factor-α; *IL-6*, interleukin-6.

causes of stress-induced hyperglycemia, but more obvious factors such as exogenous dextrose, enteral or total parenteral nutrition, and simple bed rest can further aggravate this picture. Dextrose administered at a rate of >4 mg·kg^{-1}·min^{-1} in patients with total parenteral nutrition was shown to increase the rate of hyperglycemia in nondiabetic patients by 50% (51). Age has also been associated with higher glucose levels in trauma patients (52). Bed rest alone, even in the absence of obvious disease, leads to impaired skeletal muscle glucose uptake combined with increased fasting plasma insulin concentrations, both hallmarks of peripheral insulin resistance (53).

Mechanism of Intensive Insulin Therapy and Improved Outcome in Critical Care

Maintenance of normoglycemia by use of insulin has been shown to significantly reduce morbidity and mortality of critically ill patients. The exact mechanisms by which these beneficial effects occur due to intensive insulin therapy have been investigated, and a number of potential hypotheses have been delineated.

Strict glycemic control with intensive insulin therapy prevented or reversed ultrastructural and functional abnormalities of hepatocyte mitochondria in the liver samples obtained after death in patients who were randomly assigned intensive (normoglycemia) or conventional (hyperglycemia) insulin therapy and who were similar in terms of admission diagnosis and cause of death (54).

Asymmetric dimethylarginine, an L-arginine analog that inhibits nitric oxide formation and thereby can impair vascular function (55), has been shown to be a strong and independent predictor of mortality in critically ill patients with clinical evidence of organ dysfunction. Interestingly, in a study comparing asymmetric dimethylarginine concentrations in patients randomized to receive either conventional or intensive insulin therapy, the mean daily insulin dose was inversely associated with the asymmetric dimethylarginine concentration in the intensive insulin group. The authors concluded that modulation of asymmetric dimethylarginine concentrations by insulin at least partly explains the beneficial effects found in critically ill patients receiving insulin therapy (56).

Intensive insulin therapy may also protect the endothelium of critically ill patients. In a preplanned subanalysis of the large randomized controlled study comparing intensive vs. conventional insulin therapy, intensive insulin therapy lowered circulating levels of intercellular adhesion molecule-1 and tended to re-

duce E-selectin levels in patients with prolonged critical illness, which reflected reduced endothelial activation. This effect was not brought about by altered levels of endothelial stimuli, such as cytokines or vascular endothelial growth factor, or by up-regulation of endothelial nitric oxide synthase. In contrast, prevention of hyperglycemia by intensive insulin therapy suppressed inducible nitric oxide synthase gene expression in postmortem liver and skeletal muscle, possibly in part via reduced nuclear factor kappa B activation, and lowered the elevated circulating nitric oxide levels in both survivors and nonsurvivors. Maintenance of normoglycemia with intensive insulin therapy during critical illness therefore seems to protect the endothelium, likely via inhibition of excessive inducible nitric oxide synthase–induced nitric oxide release, and thereby contributes to prevention of organ failure and death (Fig. 2) (57).

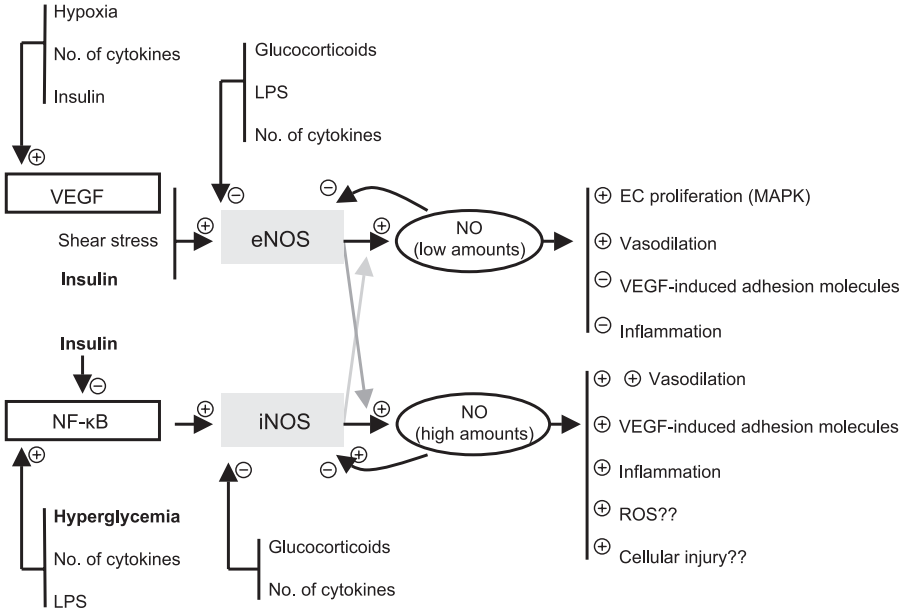

Figure 2. Simplified concept and rationale of the study by Langouche et al (57). Low concentrations of nitric oxide (*NO*), normally generated by endothelial NO synthase (*eNOS*), are likely to be beneficial for the endothelium and organ function, whereas high concentrations of NO, generated via inducible NO synthase (*iNOS*) induction, may contribute to endothelium dysfunction, excessive vasodilation, extravasation, and tissue injury. Insulin-titrated prevention of hyperglycemia during critical illness may theoretically protect the endothelium via its effects on eNOS and iNOS expression and activity. *VEGF*, vascular endothelial growth factor; *LPS*, lipopolysaccharide; *EC*, endothelial cell; *MAPK*, mitogen-activated protein kinase; *ROS*, reactive oxygen species; *NF-κB*, nuclear factor kappa B. Reproduced with permission from Langouche et al (57).

Glycemic Control in Critically Ill Diabetic Patients

Diabetic patients must be hospitalized more frequently, are more prone to develop complications, and have longer hospital stays and higher hospital costs than nondiabetic patients. They also have higher morbidity and mortality rates when acutely ill (58). The preoperative evaluation of all patients with diabetes should include careful screening for asymptomatic cardiac or renal disease and other secondary complications (e.g., retinopathy, neuropathy).

Hospitalization of the diabetic patient interrupts the usually tolerable outpatient balance of medications, diet, and exercise and may lead to either hyperglycemia or hypoglycemia. The perioperative control of blood glucose in known diabetic patients can be achieved by a number of different ways. However, in recent years, most authors would recommend the use of perioperative insulin infusions or glucose-insulin-potassium solutions, which offer better and more rapid glycemic control without the inadvertent risk of hypoglycemia by long-acting subcutaneous insulin. Typical recommendations for perioperative glucose control in diabetics can be found in Table 1, but the specific literature provides more detailed information on perioperative glycemic control.

Diabetics are occasionally admitted to the ICU for management of an acute diabetes-related process such as life-threatening hypoglycemia, hyperglycemia, diabetic ketoacidosis, or nonketotic hyperosmolar state (59). However, most diabetic patients are admitted to the ICU for other medical reasons. Various studies report that 13–26% of ICU patients have a history of diabetes at the time of ICU admission (13, 17, 60).

In critically ill patients with type 1 diabetes, a continuous intravenous insulin infusion is the favored means of management. As an alternative, basal insulin

Table 1. Perioperative insulin therapy in diabetic patients

Insulin infusion	Hold all insulins on the morning of surgery. Obtain a blood glucose and start an insulin infusion at 1–2 units/hr, along with 5% dextrose in H_2O or 5% dextrose in 0.45% normal saline at 75–100 cc/hr (approximately 5 g of glucose/hr). Administration of glucose during surgery helps to prevent ketosis, hypoglycemia, and catabolism.
	The dextrose solution is not intended for volume replacement. Any additional fluid necessary for volume resuscitation should not contain dextrose.
	Blood glucose should be checked every 1–2 hrs and the insulin infusion adjusted to achieve a blood glucose between 100 and 150 mg/dL.
Intermediate-acting insulin use	Give half to two thirds of intermediate- to long-acting insulin on the morning of surgery.
	Dose with regular insulin intravenously, from 1 to 4 units/hr, with a goal blood glucose of 100–150 mg/dL.
Potassium supplementation	Glucose-insulin-potassium (GIK) regimen: patients with normal renal function and normal potassium levels may receive dextrose-containing fluids with additional potassium (10–20 mEq/L) in addition to the insulin infusion.
Insulin pump	Options are to turn the pump off and use a continuous insulin infusion or continue the pump at a basal rate supplemented with dextrose and potassium, as needed, with rate adjustment based on serial blood glucose measurements.

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may be given with long-acting insulins (e.g., insulin glargine) and additional short-acting insulin, dependent on individual demand, every 4 to 6 hrs. Because it is increasingly accepted that lower blood glucose levels are beneficial for critically ill patients, intravenous insulin regimens best maintain glycemic control in the setting of the often variable clinical and metabolic status. Nonetheless, intravenous insulin management requires frequent, sometimes hourly, glucose monitoring and adaptations in the insulin dose, which is of concern to less adequately staffed or trained institutions.

In patients admitted to the ICU with an implanted insulin pump, the pump should generally be discontinued because many doctors and nurses are not accustomed to programming the insulin pump (26). In critically ill patients with type 2 diabetes, all oral agents should be discontinued when the patient is admitted to the ICU. Most oral antidiabetic drugs (i.e., metformin and thiazolidinediones) begin to lower blood glucose only after several weeks; thus, these drugs are not helpful for the acute glycemic management of critically ill patients in any ICU. In addition, all hypoglycemic agents represent a major risk for drug side effects and drug interactions. Specifically, sulfonylurea agents increase the risk of hypoglycemia, and patients treated with the biguanide metformin carry the risk for lactic acidosis, particularly if renal insufficiency is present. Conversely, thiazolidinedione agents precipitate volume expansion and may exacerbate heart failure in predisposed patients (61). After discontinuing oral hypoglycemic agents, elevated blood glucose levels in critically ill patients with type 2 diabetes should be managed with insulin alone. Depending on actual glucose levels, these patients can be managed with basal insulin and short-acting insulin to cover the prandial blood glucose peaks. Optimally, however, a continuous insulin infusion should be provided in critically ill patients with type 2 diabetes.

Management of the Diabetic Ketoacidotic and Hyperosmolar Coma. Diabetic ketoacidosis and hyperosmolar hyperglycemia are the most common acute metabolic emergencies in patients with diabetes mellitus. The mortality rate in patients with diabetic ketoacidosis is usually <5%, whereas the mortality rate in patients with hyperosmolar hyperglycemic state remains at a high 15%, perhaps reflecting the severity of the associated cardiovascular co-morbidities, secondary complications, and the increased age of many of these patients. Precipitating factors in the development of hyperglycemic crises in diabetic patients are mainly infections, but other common factors include noncompliance and new-onset type 1 diabetes. Further precipitating factors are alcohol abuse, cerebrovascular events, pancreatitis, myocardial infarction, trauma, and drugs such as glucocorticoids (62).

Diabetic ketoacidosis most often occurs in patients with type 1 diabetes, but patients with type 2 diabetes are also susceptible to ketoacidosis under stressful conditions, particularly trauma, infections, or surgery (63, 64). The annual prevalence of diabetic ketoacidosis is between 1% and 5% in the typical type 1 diabetic patient and seems to have remained fairly constant during the past decade. Admission rates for hyperosmolar hyperglycemia are lower than those for diabetic ketoacidosis and account for <1% of admissions related to diabetes (65).

The treatment for the two conditions, both of which should be viewed as parts of the same spectrum of metabolic complications of diabetes, is principally the same. The aims of treatment are adequate correction of dehydration with careful avoidance of hypervolemia (potential preexisting ischemic heart disease); the correction of hyperglycemia, ketoacidosis, and electrolyte deficiencies; and the identification and treatment of any co-morbid precipitating event. Importantly, this requires frequent glucose monitoring. Low-dose regular insulin should be given intravenously, usually 0.1–0.2 units/kg as a loading dose, followed by 5–10 units/hr intravenously. The precise management of hyperglycemic coma is nicely reviewed elsewhere (66).

Diabetic Patients and Cardiovascular Disease. Cardiovascular disease accounts for almost 80% of the mortality in diabetic patients. Diabetes is considered a major cardiovascular risk factor, similar as smoking, hyperlipidemia, and hypertension (67). Diabetic patients have an almost two-fold higher mortality from myocardial infarction as compared with nondiabetics.

In 1995, the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study was the first trial to randomize diabetic patients with acute myocardial infarction to receive either intensive insulin therapy or standard treatment (68). Intensive insulin therapy consisted of an intravenous infusion of glucose and insulin as soon as possible after the myocardial infarction and continued for 48 hrs. Thereafter, patients in the intensive insulin group had stricter blood glucose control and regimens for about 3 months after discharge as compared with the standard treatment group. With this intervention, blood glucose levels after 24 hrs were decreased from a mean of 11.7 mmol/L (210 mg/dL) in the standard treatment group to 9.6 mmol/L (172 mg/dL) in the intensive treatment group. One-year mortality was reduced by almost 30% in the intensive treatment group (68). Similarly, the rate of reinfarction and heart failure was significantly decreased. During an average follow-up of 3.4 yrs, patients in the intensive insulin group had a lower mortality than controls. Thereby, the authors concluded that admission glucose levels represented an independent risk factor for long-term mortality after myocardial infarction (69). These data suggest that even moderately improved glycemic control in diabetic patients with acute myocardial infarction is highly beneficial.

A recent analysis of long-term follow-up data by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study provides further striking evidence for the benefits of strict glycemic control in known type 1 diabetics (70). The DCCT, a randomized, controlled trial conducted between 1983 and 1993, compared the effects of an intensive diabetes treatment regimen (mean glycosylated hemoglobin of 7.4%) vs. a conventional treatment group (mean glycosylated hemoglobin of 9.1%) (71). In 2005, after a mean follow-up of 17 yrs and 11 yrs after the conclusion of the DCCT trial, the authors still recorded a 42% reduced risk of a cardiovascular event in patients having received intensive insulin treatment during the DCCT study. Similarly, the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease was reduced by 57% in the intensive insulin treatment group, an effect that exceeds the reductions in risk achieved by other pharmacologic interventions, including the treatment of high cholesterol or high blood pressure (70).

Glycemic Prevention and Control in Nondiabetic Critically Ill Patients

Acute hyperglycemia as a response to stress is defined as hyperglycemia in pre-

viously euglycemic patients that corrects once the acute process resolves. This "diabetes of injury" was once considered a compensatory response that seemed to demonstrate the mandatory metabolic rearrangements required to cope with critical stress. However, it is now known that it imposes a range of adverse effects, including abnormal immune function (72, 73), increased infection rate (74), and hemodynamic and electromyocardial disturbances (75). In addition, severe physical stress leads to insulin resistance of peripheral tissues and, thus, an increase in insulin requirements. Dependent on the individual's capabilities to meet this increasing insulin demand, a hyperglycemic state ensues.

A number of studies have shown a direct relationship between the extent of stress hyperglycemia and mortality in ICU patients. A meta-analysis of 15 observational studies showed that among critically ill nondiabetic patients undergoing myocardial infarction, those with glucose levels in the range of 6.1–8.0 mmol/L (110–144 mg/dL) had an almost four-fold higher risk of death than patients who had lower glucose values (19). Similarly, after stroke, a meta-analysis of 32 observational studies found that acute hyperglycemia was associated with an increased risk of in-hospital mortality and increased risk of poor functional recovery (76).

The same association was also shown in nondiabetic women after coronary artery bypass grafting (77, 78). Women with glucose levels in the upper two quartiles had a four-fold higher mortality rate compared with the lower quartiles. Using multivariate analysis, glucose levels at admission were confirmed to be an independent risk factor for increased mortality in one of these studies (78).

Similarly, in children with brain injuries, the mean blood glucose level at admission was significantly higher (288 mg/dL) in patients with poor outcome (death or vegetative state) when compared with those patients who recovered better (194 mg/dL) (79). Likewise, children with burn injuries and hyperglycemia (>7.8 mmol/L/140 mg/dL blood glucose) at admission had a higher likelihood of positive blood cultures, a lower skin graft success rate, and a >20% higher mortality (80).

An increased risk of adverse outcome was also noted for patients with newly detected hyperglycemia as compared with both diabetics and normoglycemic individuals in a study of 2,030 consecutively admitted patients of a general medical center (58). In this study, hyperglycemia was also associated with increased ICU admission rates.

Based on these observational studies, Van den Berghe et al. (17) demonstrated the value of tight glycemic control (80–110 mg/dL, controls received insulin only when blood glucose levels were >215 mg/dL) in a randomized intervention trial of 1,548 consecutive surgical ICU patients. Intensive insulin therapy reduced the overall in-hospital mortality by 34%, blood stream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, and transfusion requirements by 50%. Patients receiving intensive insulin treatment were also less likely to require prolonged mechanical ventilation and intensive care. Although this was a single-center study of primarily surgical patients, the mortality and morbidity benefit observed warrant the consideration of aggressive glucose control for all ICU patients who experience hyperglycemia (81).

A recent meta-analysis included randomized controlled trials that reported mortality data on critically ill hospitalized patients in different settings who were treated with insulin (82). Overall insulin treatment in 35 trials decreased short-term mortality by 15%. However, most *early* studies were performed in surgical ICU patients, and less evidence exists on glycemic control in medical ICU patients. Because medical patients tend to stay in the ICU longer than surgical patients, some have hypothesized that tight glucose control might even be more favorable. Accordingly, in a study by Krinsley (16) that was conducted in a more heterogeneous population of critically ill patients in a mixed medical–surgical ICU, an intensive glucose management protocol resulted in a significantly reduced overall mortality, organ dysfunction, and length of ICU stay as compared with patients who were admitted before the introduction of a standardized glucose monitoring protocol.

To better assess the benefits of tight glycemic control in medical ICU patients, Van den Berghe and colleagues group has subsequently conducted a randomized, controlled trial similar to her 2001 study in a medical ICU setting (83). In this trial, the authors found that intensive insulin therapy (target glucose range, 80–110 mg/dL) significantly reduced morbidity and shortened the length of ICU and hospital stay but did not reduce mortality among the 1,200 patients included in the intention-to-treat analysis. Further *post hoc* analysis, however, showed that, indeed, the mortality of patients staying in the ICU for >3 days was reduced from 52.5% to 43% ($p < .01$), despite the authors' inability to identify this subgroup of patients at admission to the ICU. From these data, it seems advisable to shift the metabolic management toward a tighter glucose control with the present data, although further randomized trials in more heterogenous ICU populations are necessary to confirm these preliminary data and to identify patient subgroups with the greatest benefit from tight glycemic control.

Another often discussed question is how to explain the wide range of clinical benefits with strict control of glycemia. These effects may potentially be attributable to either the avoidance of hyperglycemia, the administration of insulin, or the combination of glucose control and exogenous insulin (84–86). Van den Berghe et al. (17, 87) hypothesized that strict control of hyperglycemia may be the decisive factor, rather than the exogenous administration of insulin. This is supported by a prospective observational study of 531 critically ill ICU patients by Finney et al. (13), in which the authors found a correlation between the amount of insulin given and ICU mortality, regardless of the prevailing blood glucose levels. Apart from specific pathophysiologic causes, precise glycemic control may also be a surrogate marker of exceptionally attentive patient care and thereby indirectly be associated with better outcomes in general.

It must be emphasized that insulin requirements in individual patients vary widely, depending on insulin production reserves, insulin sensitivity before and during critical illness, caloric intake in the ICU, and the severity and nature of the underlying illness. In addition, the presence of infections and different medications, such as corticosteroids, further affect insulin sensitivity (88). Thus, any algorithm for insulin dosage is only a recommendation and has to be adapted to the individual response of any patient. A possible algorithm for intensive insulin therapy in the ICU has been proposed by Van den Berghe et al (17, 88) (Table 2). Thereby, patients with high glucose levels at ICU admission should be treated with a relatively high starting dose, whereas patients with less severe hyperglycemia require lower initial doses. Spe-

Table 2. Suggested algorithm for glycemic control in intensive care unit (ICU) patients

Test	Result	Action
Measure glucose at entry to ICU	BG >11.1 mmol/L (200 mg/dL)	Start insulin 2–4 IU/hr
	BG 11.1–6.1 mmol/L (220–110 mg/dL)	Start insulin 1–2 IU/hr
↓	BG <6.1 mmol/L (110 mg/dL)	Don't start insulin but continue BG monitoring every 4 hrs
Measure glucose every 1–2 hrs until in normal range	BG >7.8 mmol/L (140 mg/dL)	Increase insulin dose by 1–2 IU/hr
	BG 6.1–7.8 mmol/L (110–140 mg/dL)	Increase insulin dose by 0.5–1 IU/hr
↓	BG approaching normal range	Adjust insulin dose by 0.1–0.5 IU/hr
Measure glucose every 4 hrs	BG approaching normal range	Adjust insulin dose by 0.1–0.5 IU/hr
	BG normal	Insulin dose unchanged
	BG falling steeply	Reduce insulin dose by half and check more frequently
	BG 3.3–4.4 mmol/L (60–80 mg/dL)	Reduce insulin dose and check within 1 hr
	BG 2.2–3.3 mmol/L (40–60 mg/dL)	Stop insulin infusion, ensure adequate baseline glucose intake, and check BG within 1 hr
	BG <2.2 mmol/L (40 mg/dL)	Stop insulin infusion, ensure adequate baseline glucose intake, administer glucose per 10-g intravenous boluses, and check BG within 1 hr

BG, blood glucose. Modified with permission from Van den Berghe (88).

cial attention has to be given to patients with acute renal failure or in whom a reduction or interruption of caloric intake occurs. Achieving the goal of stable glycemic control requires extensive nursing efforts, frequent bedside capillary glucose monitoring, and the implementation of complex insulin infusion protocols. A detailed review of the literature fails to produce a comprehensive validated insulin infusion protocol that is both complex enough to achieve strict glucose control and practical enough to be easily implemented by ICU nurses without the need for expert supervision or frequent deviation from protocol (89). A simplified insulin infusion protocol has therefore been propagated by Goldberg et al. (89), which would allow safe yet tight blood sugar control with minimal physician supervision. In their own analysis on medical ICU patients, euglycemia could be achieved within 9 hrs, and hypoglycemia of <60 mg/dL occurred in a mere 0.3%.

How High Is the Risk of Hypoglycemia as a Result of Blood Glucose Control?

Tight glycemic control in critically ill patients, especially with the low target ranges proposed by recent trials, invariably carries a risk of inadvertent hypoglycemic episodes. The reported rate of hypoglycemia ranges from 0% to >30% in the studies reviewed, but differences as to its precise definition make direct comparisons difficult. The meta-analysis by Pittas et al. (82), in which data on the prevalence of hypoglycemia from ten studies were combined and analyzed, found that patients receiving insulin therapy were three times more likely to develop hypoglycemia than those without insulin therapy (relative risk, 3.4; 95% confidence interval, 1.9–6.3). In addition, hypoglycemic events were usually recorded more frequently in studies that used a protocol aimed at maintaining euglycemia as compared with those aimed at merely avoiding excessive hyperglycemia. Similarly, Moeniralam et al. (90) found that the implementation of tight glycemic control regimens increased the prevalence of hypoglycemic (<4.4 mmol/L) blood values from 13% to 39% in a retrospective analysis of general ICU patients treated between 1999 and 2003. Interestingly, despite the obvious increase in hypoglycemic events, no adverse clinical outcomes associated with hypoglycemia were reported in any of these studies. High rates of hypoglycemic events, as defined by any glucose value of <60 mg/dL, were seen in the study by Grey and Perdrizet (14), in which the authors randomized patients to receive either strict (80–120 mg/dL) or conservative (180–220 mg/dL) blood glucose control. Hypoglycemia occurred in 32% of patients receiving strict glucose control as compared with only 7.4% of control patients.

Some investigators have tried to pinpoint risk factors for the occurrence of hypoglycemia in insulin-controlled patients, such as low target ranges, a lack of adequately staffed ICU personnel, or insufficient routine in the management of critically ill hyperglycemic patients. Although certain of these factors may seem apparent and logically justified, a lack of clear data precludes absolute statements. The use of standardized insulin protocols have been described, and their use in both reaching target glucose levels more rapidly and avoiding hyperglycemic events are well documented (88, 91–93). Some evidence also suggests better avoidance of hypoglycemic events using standardized insulin regimens as compared with on-demand insulin orders (91), but, although plausible, this is questioned in the literature (92).

To facilitate insulin therapy and to decrease both hypoglycemic and hyperglycemic excursions, several recent studies have assessed the value of glucose sensing devices that would allow frequent, less invasive blood glucose measurements (94, 95). Such devices typically require subcutaneous placement of a sensor tip connected to a Walkman-sized monitor device, which provides near–real-time glucose sensing for up to 72 hrs. Additional noninvasive devices, such as transcutaneous near infrared spectroscopy, are under investigation for continuous glucose monitoring. Initial studies show promising results, but further evaluation of these sensors is necessary before widespread recommendations may be made.

Conclusion

Where Is Tight Blood Glucose Control in 2006? Diabetes mellitus has long been associated with significant morbidity and mortality and with adverse outcome in critically ill patients. Glycemic control in this group has been an accepted performance measure in past years. However, its real threat may lie in the almost epidemic increase in prevalence of diabetes mellitus in western nations, where type 2 diabetes has already become a common diagnosis in the adolescent age group.

On the other side, acute hyperglycemia associated with severe stress is now increasingly recognized to be a potential

harbinger of aggravated illness and outcome. With the current increase in insulin-resistant conditions such as old age, obesity, or the metabolic syndrome, coupled with studies suggesting that the adverse effects of hyperglycemia can be altered, we are now challenged to consider an alternative clinical paradigm. Although pancreatic beta-cell function should normally be adequate to overcome insulin resistance, stress-induced hyperglycemia may result from a combination of high levels of counter-regulatory hormones, proinflammatory cytokines, oxidative stress, beta-cell dysfunction, iatrogenic measures (steroids, dextrose, etc.) and from a genetic predisposition for diabetes mellitus.

The need for tighter glycemic control in critically ill diabetic and nondiabetic patients is increasingly recognized by critical care physicians. However, more data from randomized controlled trials are needed to determine the effects of tight glucose control on clinical outcome in different subgroups of patients. We must identify the right degree or target range of glycemic control for different patient populations and, ideally, define treatment standards with which to facilitate intensive insulin therapy without compromising patient safety. Institutional standardizations of insulin infusion protocols, with special emphasis on efficiency, safety, and nursing workload, are important measures to ensure safe and adequate glycemic control in both diabetic and nondiabetic ICU patients.

REFERENCES

1. Nathan DM: Clinical practice: Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med* 2002; 347:1342–1349
2. Harris M, Cowie C (Eds): Prevalence and Incidence of Non-Insulin-Dependent Diabetes. Bethesda, National Institutes of Health, 1995
3. Centers for Disease Control and Prevention: National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States. Atlanta, US Department of Health and Human Services, Centers for Disease Control and Prevention, 2003
4. Mokdad AH, Ford ES, Bowman BA, et al: Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; 289:76–79
5. Sullivan PW, Morrato EH, Ghushchyan V, et al: Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000–2002. *Diabetes Care* 2005; 28:1599–1603
6. Onkamo P, Vaananen S, Karvonen M, et al: Worldwide increase in incidence of Type I diabetes: The analysis of the data on published incidence trends. *Diabetologia* 1999; 42:1395–1403
7. Engelgau MM, Geiss LS, Saaddine JB, et al: The evolving diabetes burden in the United States. *Ann Intern Med* 2004; 140:945–950
8. Geiss LS, Herman WH, Smith PJ: Mortality among persons with non-insulin dependent diabetes. *In:* Diabetes in America. Second Edition. Harris M, Cowie C, Stern M, et al (Eds). Bethesda, National Institutes of Health, 1995, pp 233–258
9. Manuel DG, Schultz SE: Diabetes health status and risk factors. *In:* Diabetes in Ontario: An Institute for Clinical Evaluative Sciences Practice Atlas. Toronto, Canadian Diabetes Association, 2002, 4.77–4.94
10. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; 26(Suppl 1):S5–S20
11. Honeycutt AA, Boyle JP, Broglio KR, et al: A dynamic Markov model for forecasting diabetes prevalence in the United States through 2050. *Health Care Manag Sci* 2003; 6:155–164
12. McCowen KC, Malhotra A, Bistrian BR: Stress-induced hyperglycemia. *Crit Care Clin* 2001; 17:107–124
13. Finney SJ, Zekveld C, Elia A, et al: Glucose control and mortality in critically ill patients. *JAMA* 2003; 290:2041–2047
14. Grey NJ, Perdrizet GA: Reduction of nosocomial infections in the surgical intensive-care unit by strict glycemic control. *Endocr Pract* 2004; 10(Suppl 2):46–52
15. Krinsley JS: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003; 78:1471–1478
16. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; 79:992–1000
17. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345:1359–1367
18. Latham R, Lancaster AD, Covington JF, et al: The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. *Infect Control Hosp Epidemiol* 2001; 22:607–612
19. Capes SE, Hunt D, Malmberg K, et al: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. *Lancet* 2000; 355:773–778
20. McAlister FA, Majumdar SR, Blitz S, et al: The relation between hyperglycemia and outcomes in 2,471 patients admitted to the hospital with community-acquired pneumonia. *Diabetes Care* 2005; 28:810–815
21. Bhisitkul DM, Morrow AL, Vinik AI, et al: Prevalence of stress hyperglycemia among patients attending a pediatric emergency department. *J Pediatr* 1994; 124:547–551
22. Valerio G, Franzese A, Carlin E, et al: High prevalence of stress hyperglycaemia in children with febrile seizures and traumatic injuries. *Acta Paediatr* 2001; 90:618–622
23. Xu F, Yang X, Lu Z, et al: Evaluation of glucose metabolic disorder: Insulin resistance and insulin receptors in critically ill children. *Chin Med J* (*Engl*) 1996; 109:807–809
24. Turner R, Stratton I, Horton V, et al: UKPDS 25: Autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. *Lancet* 1997; 350:1288–1293
25. Atkinson MA, Eisenbarth GS: Type 1 diabetes: New perspectives on disease pathogenesis and treatment. *Lancet* 2001; 358:221–229
26. Boord JB, Graber AL, Christman JW, et al: Practical management of diabetes in critically ill patients. *Am J Respir Crit Care Med* 2001; 164:1763–1767
27. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 2005; 365:1415–1428
28. Stumvoll M, Goldstein BJ, van Haeften TW: Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet* 2005; 365:1333–1346
29. Sinha R, Fisch G, Teague B, et al: Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002; 346:802–810
30. Dinneen S, Gerich J, Rizza R: Carbohydrate metabolism in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1992; 327: 707–713
31. Baron AD, Brechtel G, Wallace P, et al: Rates and tissue sites of non-insulin- and insulin-mediated glucose uptake in humans. *Am J Physiol* 1988; 255:E769–E774
32. Mizock BA: Alterations in fuel metabolism in critical illness: Hyperglycaemia. *Best Pract Res Clin Endocrinol Metab* 2001; 15:533–551
33. Klip A, Tsakiridis T, Marette A, et al: Regulation of expression of glucose transporters by glucose: A review of studies in vivo and in cell cultures. *FASEB J* 1994; 8:43–53
34. Mizock BA: Alterations in carbohydrate metabolism during stress: A review of the literature. *Am J Med* 1995; 98:75–84
35. Clerici C, Matthay MA: Hypoxia regulates gene expression of alveolar epithelial transport proteins. *J Appl Physiol* 2000; 88: 1890–1896
36. Pekala P, Marlow M, Heuvelman D, et al: Regulation of hexose transport in aortic endothelial cells by vascular permeability factor and tumor necrosis factor-alpha, but not by insulin. *J Biol Chem* 1990; 265:18051–18054
37. Sanchez-Alvarez R, Tabernero A, Medina JM: Endothelin-1 stimulates the translocation and upregulation of both glucose transporter and hexokinase in astrocytes: Relationship with gap junctional communication. *J Neurochem* 2004; 89:703–714
38. Vanhorebeek I, Langouche L, Van den Berghe G: Glycemic and nonglycemic effects of insulin: How do they contribute to a better outcome of critical illness? *Curr Opin Crit Care* 2005; 11:304–311
39. Rolih CA, Ober KP: The endocrine response

to critical illness. *Med Clin North Am* 1995; 79:211–224
40. Wolfe RR: Herman Award Lecture, 1996: Relation of metabolic studies to clinical nutrition. The example of burn injury. *Am J Clin Nutr* 1996; 64:800–808
41. Bastard JP, Maachi M, Van Nhieu JT, et al: Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. *J Clin Endocrinol Metab* 2002; 87:2084–2089
42. Borst SE: The role of TNF-alpha in insulin resistance. *Endocrine* 2004; 23:177–182
43. Rotter V, Nagaev I, Smith U: Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem* 2003; 278:45777–45784
44. Borst SE, Lee Y, Conover CF, et al: Neutralization of tumor necrosis factor-alpha reverses insulin resistance in skeletal muscle but not adipose tissue. *Am J Physiol Endocrinol Metab* 2004; 287:E934–E938
45. Cheung AT, Wang J, Ree D, et al: Tumor necrosis factor-alpha induces hepatic insulin resistance in obese Zucker (fa/fa) rats via interaction of leukocyte antigen-related tyrosine phosphatase with focal adhesion kinase. *Diabetes* 2000; 49:810–819
46. Ma Y, Toth B, Keeton AB, et al: Mechanisms of hemorrhage-induced hepatic insulin resistance: Role of tumor necrosis factor-alpha. *Endocrinology* 2004; 145:5168–5176
47. Bessey PQ, Brooks DC, Black PR, et al: Epinephrine acutely mediates skeletal muscle insulin resistance. *Surgery* 1983; 94:172–179
48. James DE, Burleigh KM, Kraegen EW: In vivo glucose metabolism in individual tissues of the rat: Interaction between epinephrine and insulin. *J Biol Chem* 1986; 261:6366–6374
49. Smith TR, Elmendorf JS, David TS, et al: Growth hormone-induced insulin resistance: Role of the insulin receptor, IRS-1, GLUT-1, and GLUT-4. *Am J Physiol* 1997; 272: E1071–E1079
50. Venkatesan N, Lim J, Bouch C, et al: Dexamethasone-induced impairment in skeletal muscle glucose transport is not reversed by inhibition of free fatty acid oxidation. *Metabolism* 1996; 45:92–100
51. Rosmarin DK, Wardlaw GM, Mirtallo J: Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. *Nutr Clin Pract* 1996; 11: 151–156
52. Desai D, March R, Watters JM: Hyperglycemia after trauma increases with age. *J Trauma* 1989; 29:719–723
53. Stuart CA, Shangraw RE, Prince MJ, et al: Bed-rest-induced insulin resistance occurs primarily in muscle. *Metabolism* 1988; 37: 802–806
54. Vanhorebeek I, De Vos R, Mesotten D, et al: Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005; 365:53–59
55. Boger RH, Maas R, Schulze F, et al: Elevated levels of asymmetric dimethylarginine (ADMA) as a marker of cardiovascular disease and mortality. *Clin Chem Lab Med* 2005; 43:1124–1129
56. Siroen MP, van Leeuwen PA, Nijveldt RJ, et al: Modulation of asymmetric dimethylarginine in critically ill patients receiving intensive insulin treatment: A possible explanation of reduced morbidity and mortality? *Crit Care Med* 2005; 33:504–510
57. Langouche L, Vanhorebeek I, Vlasselaers D, et al: Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005; 115:2277–2286
58. Umpierrez GE, Isaacs SD, Bazargan N, et al: Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87:978–982
59. Coursin DB, Connery LE, Ketzler JT: Perioperative diabetic and hyperglycemic management issues. *Crit Care Med* 2004; 32:S116–S125
60. Van den Berghe G: Neuroendocrine pathobiology of chronic critical illness. *Crit Care Clin* 2002; 18:509–528
61. Kermani A, Garg A: Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc* 2003; 78: 1088–1091
62. Kitabchi AE, Umpierrez GE, Murphy MB, et al: Hyperglycemic crises in diabetes. *Diabetes Care* 2004; 27(Suppl 1):S94–S102
63. Pitteloud N, Philippe J: Characteristics of Caucasian type 2 diabetic patients during ketoacidosis and at follow-up. *Schweiz Med Wochenschr* 2000; 130:576–582
64. Umpierrez GE, Kitabchi AE: Diabetic ketoacidosis: Risk factors and management strategies. *Treat Endocrinol* 2003; 2:95–108
65. English P, Williams G: Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad Med J* 2004; 80:253–261
66. Magee MF, Bhatt BA: Management of decompensated diabetes: Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. *Crit Care Clin* 2001; 17:75–106
67. Grundy SM, Benjamin IJ, Burke GL, et al: Diabetes and cardiovascular disease: A statement for healthcare professionals from the American Heart Association. *Circulation* 1999; 100:1134–1146
68. Malmberg K, Ryden L, Efendic S, et al: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): Effects on mortality at 1 year. *J Am Coll Cardiol* 1995; 26:57–65
69. Malmberg K, Norhammar A, Wedel H, et al: Glycometabolic state at admission: Important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction. Long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 1999; 99: 2626–2632
70. Nathan DM, Cleary PA, Backlund JY, et al: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353:2643–2653
71. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329:977–986
72. Perner A, Nielsen SE, Rask-Madsen J: High glucose impairs superoxide production from isolated blood neutrophils. *Intensive Care Med* 2003; 29:642–645
73. Turina M, Fry DE, Polk HC Jr: Acute hyperglycemia and the innate immune system: Clinical, cellular, and molecular aspects. *Crit Care Med* 2005; 33:1624–1633
74. Khaodhiar L, McCowen K, Bistrian B: Perioperative hyperglycemia, infection or risk? *Curr Opin Clin Nutr Metab Care* 1999; 2:79–82
75. Marfella R, Nappo F, De Angelis L, et al: The effect of acute hyperglycaemia on QTc duration in healthy man. *Diabetologia* 2000; 43: 571–575
76. Capes SE, Hunt D, Malmberg K, et al: Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke* 2001; 32:2426–2432
77. Norhammar AM, Ryden L, Malmberg K: Admission plasma glucose: Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. *Diabetes Care* 1999; 22:1827–1831
78. Zindrou D, Taylor KM, Bagger JP: Admission plasma glucose: an independent risk factor in nondiabetic women after coronary artery bypass grafting. *Diabetes Care* 2001; 24: 1634–1639
79. Michaud LJ, Rivara FP, Longstreth WT Jr, et al: Elevated initial blood glucose levels and poor outcome following severe brain injuries in children. *J Trauma* 1991; 31:1356–1362
80. Gore DC, Chinkes D, Heggers J, et al: Association of hyperglycemia with increased mortality after severe burn injury. *J Trauma* 2001; 51:540–544
81. Vincent JL, Abraham E, Annane D, et al: Reducing mortality in sepsis: new directions. *Crit Care* 2002; 6(Suppl 3):S1–S18
82. Pittas AG, Siegel RD, Lau J: Insulin therapy for critically ill hospitalized patients: A meta-analysis of randomized controlled trials. *Arch Intern Med* 2004; 164:2005–2011
83. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
84. Dhatariya K: Hyperglycemia in acute illness. *JAMA* 2003; 289:1244
85. Evans TW: Hemodynamic and metabolic therapy in critically ill patients. *N Engl J Med* 2001; 345:1417–1418
86. Montori VM, Bistrian BR, McMahon MM: Hyperglycemia in acutely ill patients. *JAMA* 2002; 288:2167–2169
87. Van den Berghe G, Wouters PJ, Bouillon R, et al: Outcome benefit of intensive insulin

therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med* 2003; 31:359–366
88. Van den Berghe G: Beyond diabetes: Saving lives with insulin in the ICU. *Int J Obes Relat Metab Disord* 2002; 26(Suppl 3):S3–S8
89. Goldberg PA, Siegel MD, Sherwin RS, et al: Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care* 2004; 27:461–467
90. Moeniralam H, Spronk P, Graat M, et al: Tight glycemic control increases the incidence of hypoglycemia in intensive care unit patients. Abstr. *Crit Care* 2005; 9:S162
91. Kanji S, Singh A, Tierney M, et al: Standardization of intravenous insulin therapy improves the efficiency and safety of blood glucose control in critically ill adults. *Intensive Care Med* 2004; 30:804–810
92. Markovitz LJ, Wiechmann RJ, Harris N, et al: Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract* 2002; 8:10–18
93. Preiser JC, Devos P, Van den Berghe G: Tight control of glycaemia in critically ill patients. *Curr Opin Clin Nutr Metab Care* 2002; 5:533–537
94. De Block C, Rogiers P, Keenoy B, et al: Intensive insulin therapy in the intensive care unit: Assessment by continuous glucose monitoring. Abstr. *Crit Care* 2005; 9:S159
95. Farmer M, Kornfeld H: Assessment of glycemic control in critical illness using a continuous glucose monitoring system. Abstr. *Chest* 2004; 126:873