Inpatient Diabetes Control: Rationale

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This is the first of two articles on the Consensus Development Conference on Inpatient Diabetes Control, which was sponsored by the American College of Endocrinology and held in Washington, DC, 14–15 December 2003.

Donald Bergman (New York, NY), President of the American Association of Clinical Endocrinologists, suggested the importance of endocrinologists beginning “to partner . . . for practical reasons,” perhaps in this one fashion emulating trial lawyers and the National Rifle Association by finding strength in numbers! Nathaniel Clarke, on behalf of the American Diabetes Association, which cosponsored the meeting, stressed the importance of developing common conclusions and guidelines. Representatives of the Endocrine Society, the American Association of Diabetes Educators, the Society of Hospital Medicine, and the American Society of Anesthesiologists agreed on the importance of the topic. Alan Garber (Houston, TX), who moderated the conference, pointed out the frequency of diabetes among hospitalized persons and noted that at his institution, approximately one-third of persons in the coronary care unit have diabetes, with one-third of this group having glucose levels ≥200 mg/dl. There are, he noted, few existing standards for glycemic control of persons with diabetes in hospital.

Glycemia and cardiovascular disease

Robert Frye (Rochester, MN) gave “a historical perspective” of the rationale for the Bypass Angioplasty Revascularization Investigation (BARI) study of patients with multivessel coronary disease, with objective evidence of ischemia and without prior revascularization. At the time of patient enrollment in the study, the majority of patients were considered unsuitable for angioplasty, so that only a minority of potential patients were randomized, leading to some uncertainty as to whether the results can be fully generalized. Diabetes was prespecified as a subgroup by the data monitoring and safety group, with 19% of those enrolled having treated diabetes, although diabetes was not prespecified for analysis of outcome, which has been another source of controversy about the interpretation of the study. Frye noted that almost half of the enrolled patients had had a prior myocardial infarction, so that these patients were being treated “relatively late.” In the absence of treated diabetes, angioplasty and bypass were of equal benefit. Patients with treated diabetes, however, had worse outcome than those without diabetes, and for this group mortality was higher with angioplasty than with bypass surgery among persons who had an internal mammary artery graft, although not among those who only had vein grafts (1). Insulin use at baseline was an independent predictor of mortality, regardless of the revascularization procedure. The protective effect of internal mammary artery graft among women with diabetes remained at 5 years but appeared to be lost after 10 years. Repeat revascularization was higher among those randomized to angioplasty, and this was particularly the case among persons with treated diabetes. Cost was higher among persons with treated diabetes than among those without diabetes, regardless of the procedure utilized (2). Persons with treated diabetes did particularly poorly with incomplete revascularization, which occurred more commonly with angioplasty than with bypass surgery. Restenosis of angioplasty occurred more frequently in persons with diabetes, but occlusion of bypass grafts did not occur more frequently than in the nondiabetic group.

Important questions to be addressed include how outcome could be improved for the overall group of persons with treated diabetes, whether earlier intervention would be beneficial, and whether improvements in angioplasty methodology will improve outcome with this approach. The BARI 2 Diabetes (BARI-2D) is a study that will include 2,300 persons with type 2 diabetes using a 2 × 2 trial design studying the effect of insulin sensitizers versus insulin provision, with goal HbA1c <7%, as well as whether to use aggressive medical management as the initial approach versus early revascularization. Frye noted that mortality of persons with diabetes and coronary disease has increased over the past decade, despite the increasing use of revascularization; therefore, studies such as BARI-2D are important (3).

Klaus Malmberg (Stockholm, Sweden) discussed coronary disease among persons with diabetes and reviewed the findings of the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (4). “Why,” he asked, “is it so important to lower glucose in acute coronary syndromes (ACSs)?” In the 1980s, the 1-year mortality of persons with diabetes and ACS was 50%. Using the central Swedish Coronary Care Unit registry of acute myocardial infarction (AMI), of 25,000 persons in 1998, 21% had diagnosed diabetes, with similar statistics in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry (5). In a study of 160 consecutive persons with AMI without diagnosed diabetes, however, oral glucose tolerance tests just before and 3 months after discharge showed that only one-third had normal glucose tolerance (6). Mortality of persons with myocardial infarction and for those with ACSs is increased as much as fivefold with diabetes. Hyperglycemia is itself a risk factor, with admission glucose levels a risk factor in both persons with and without diabetes. In the DIGAMI study, in fact, the admission glucose was a...
risk factor for both early and late mortality. Myocardial pump failure is the most common cause of death in this group, and reinfarction the next most common cause, presumably reflecting the more extensive coronary disease of persons with diabetes. Improved glucose oxidation and decreased free fatty acid (FFA) levels may, Malmberg suggested, underlie the benefits of improved glycemic control. Sixty to 70% of myocardial energy comes from FFAs, but with diabetes this approaches 90%, with mitochondrial fatty acid oxidation particularly occurring during stress, while glucose oxidation is decreased, leading to lactic acid accumulation. In persons with diabetes without evidence of coronary artery disease (CAD), there is a 33% decrease in myocardial energy stores, correlated with FFAs and glucose levels, which may contribute to the development of heart failure. Persons with and without diabetes have similar ejection fraction on admission for myocardial infarction, but the former have greater subsequent development of congestive heart failure (CHF).

The DIGAMI study tested the hypothesis that improving metabolic control would lead to improved outcome. Persons with diabetes and glucose >11 mmol/l (or >13 mmol/l if not with known diabetes) were randomized to treatment using intravenous followed by subcutaneous insulin versus standard glycemic treatment, with stratification based on prior myocardial infarction and prior insulin treatment (those with both had 41% 1-year mortality vs. 13% with neither). In the study population, 40% had a prior myocardial infarction, 50% prior angina, 20% heart failure, 50% hypertension, and 20% cigarette use, with mean HbA1c at randomization 8%. The initial blood glucose was 15.7 mmol/l, decreasing at 24 h to a greater degree in the insulin group. At discharge, 90% of those randomized to the infusion group received insulin, and at 1 year, 72% continued with this, while in the control group 44% were discharged on insulin, with some increase at 1 year, thereby diluting the effect of the intervention. One-year mortality was 19% vs. 26% and 3.4-year mortality 33 vs. 44%, for an absolute decrease in mortality of 11% (a relative decrease of 28%). Of persons aged <65 years not previously treated with insulin and without prior myocardial infarction (the relatively lower-risk group), 81 vs. 15% and 66 vs. 24% received insulin treatment at discharge and at 1 year. This group had an absolute lowering of mortality at 3.4 years by 15%. The most common cause of death was CHF in the control group, with no effect of the intervention on nonfatal reinfarction.

Malmberg noted the similar treatment effect of glucose-insulin infusion in nondiabetic persons with myocardial infarction and suggested that the approach is particularly beneficial for persons without CHF, for whom the volume infused is less likely to have adverse consequence. He noted that additional potential benefits of glycemic control may be to decrease inflammation, improve endothelial function, and provide fibrinolytic effects. The DIGAMI 2 trial is soon to be completed, to address questions of the mechanism of benefit and whether acute or chronic glycemnic treatment is of greater benefit, in a three-arm study of persons with type 2 diabetes or initial glucose >11 mmol/l, as well as AMI, comparing the full DIGAMI regimen with only the acute insulin infusion.

Richard Nesto (Boston, MA) discussed the potential effects of diabetes on AMI. Persons with diabetes have a myriad of cardiac complications: twice the early mortality with ACS, greater likelihood of prehospital death, a higher rate of reinfarction and greater impairment of coronary flow after percutaneous intervention (PCI), more periprocedural complications and higher rate of restenosis despite similar initial procedural outcomes, greater likelihood of myocardial infarction during the first year after PCI, greater risk for early and late CHF after myocardial infarction, longer intensive care unit (ICU) and hospital stay, and the possibility of adverse cardiac effect of sulfonylureas, which has been cited as an explanation of the findings of the DIGAMI study. Nesto noted that 70% of recurrent events occur at a site separate from the initial lesion, confirming our knowledge that atherosclerosis is a diffuse process. Understanding of the adverse effects of diabetes on myocardial infarction has been growing over more than 70 years, although evidence of a direct relationship between the level of glycemia and adverse outcome has been rather slow in developing. Initial studies suggested that although diabetes is a risk factor, there was only a weak relationship between myocardial infarct size and admission glucose in persons without diabetes (7). Nesto noted, however, that it has long been appreciated that persons with apparently small infarct who have marked hyperglycemia are at risk of cardiogenic shock.

Recent studies have confirmed prior observations, with evidence that the adverse effect on long-term outcome of having diabetes is similar to that of having an AMI (8). Analysis of the CARE (Cholesterol and Recurrent Events) study showed diabetes as a major predictor of late CHF and death in survivors of myocardial infarction (9). In this study, mortality risk increased 6% per year of age and 3% per 1% decrease in ejection fraction. Regular physical exercise was associated with a 33% decrease in death and CHF in the study. Hypertension was associated with a 34% increase in mortality, prior myocardial infarction with a 42% increase, Killip cardiac function class >II with a 36% increase, and diabetes with a 50% increase in adverse outcome, thus showing it to be a major risk factor.

In addition to diabetes, insulin resistance without diabetes appears to convey increased risk, with the metabolic syndrome emerging as a major contributor to myocardial infarction in persons aged <45 years. Insulin resistance increases the risk of plaque disruption and thrombosis and hence of myocardial infarction and is associated with increased plaque formation, increased sympathetic and decreased parasympathetic tone, increased procoagulant levels, and increases in inflammatory mediators CD-40 and CD-40 ligand (10), as well as in C-reactive protein (CRP) and matrix metalloproteinases (MMPs). In a sense, Nesto pointed out, “the notion that coronary atherosclerosis is the big problem has been exaggerated,” as the extent of CAD is similar in young persons with and without diabetes (or with and without the metabolic syndrome) who have myocardial infarction. Furthermore, the extent of left ventricular dysfunction is a more important determinant of prognosis than the extent of angiographic CAD (11). There must therefore be “other targets for treatment.” The “dominant feature,” Nesto noted, is “tubular progressive moderate [arterial] disease,” associated with the presence of vulnerable atherosclerotic plaques, which are prone to rupture leading to thrombosis. Visualization of lipid deposits within the arterial wall with angioscopy and with intravascular ultrasound further demonstrates the association of diabetes with...
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Multiple vulnerable plaques, perhaps explaining the benefits of treatment with statins and insulin. In a study (12) of carotid endarterectomy specimens, those from persons with diabetes showed more inflammatory infiltrates, colocalizing on immunohistochemical study with MMP and the receptor for advanced glycation end products (AGEs). Diabetes may be associated with ACS, then, because of plaque instability and disruption caused by inflammatory erosion of the fibrous cap. Microparticles representing residua of necrotic or apoptotic inflammatory cells lead to increased tissue factor expression in patients with type 2 diabetes, lending support to this concept (13).

Cardiac autonomic neuropathy may mimic the effect of myocardial infarction, leading to worsening electrical instability and worsening cardiac contractile function in the absence of injury. CHF is the major cause of adverse outcome following ACS, with the OASIS data suggesting association between diabetes and total mortality, cardiovascular disease death, new myocardial infarction, stroke, and most markedly with increased new onset of CHF. Left ventricular expansion and hypokinesis of noninfarcted segments is seen in 25% of persons following myocardial infarction and is particularly common in persons with diabetes. Maladaptive remodeling could be responsible for the high rate of heart failure following myocardial infarction in persons with diabetes. Nesto speculated that the noninfarct zone may be crucial in the pathogenesis of diabetic cardiac disease. For any degree of myocardial infarction, the person with diabetes has lower regional ejection fraction of noninfarcted areas (14). Causes of CHF may include silent myocardial infarction, autonomic neuropathy, endothelial dysfunction, hypertension, lipotoxicity, AGEs, and diabetic cardiomyopathy, and Nesto pointed out that “there’s more [cardiomyopathy] out there than people want to believe.” In addition, diabetes affects the infarct zone by decreasing fibrinolysis and collateral formation. Mechanisms promoting left ventricular remodeling and dysfunction in insulin resistance include increased cellular lipids, nonenzymatic glycation, altered myocardial protein degradation, altered intracellular matrix remodeling, and IGF-mediated effects. “Fortunately,” Nesto stated, “ACE inhibitors really help these patients.” Most of the benefit of these agents in large trials has been due to their effect in persons with diabetes. In the TRACE (Trandolapril Cardiac Evaluation) study, for example, the effect of trandolapril on CHF progression after myocardial infarction was modest and only began after 2 years in the nondiabetic group, decreasing CHF by 19%, while among persons with diabetes “ACE inhibitors have a remarkable benefit right out of the gate,” lowering CHF rates by 61% (15).

Hyperglycemia may be important as a therapeutic target, with a recent study suggesting that in-hospital mortality is associated with the admission glucose level rather than the presence of diagnosed diabetes. With hyperglycemia in the absence of clinical diabetes carrying with it the same risk as hyperglycemia with diabetes, and persons with diabetes without marked hyperglycemia having lesser risk (16). In an animal study, myocardial infarction size increased in streptozotocin-induced diabetic rats and similar effect was demonstrable in an isolated heart preparation incubated with high glucose, which could be reversed by incubation with glutatione, suggesting a role of oxidative stress. “Maybe,” Nesto said, “glucose is the problem … and interventions directed against the glucose” could be of benefit. Hyperglycemia is associated with “no-reflow,” a major factor affecting PCI outcome in AMI and that is felt to reflect impaired microvascular flow. In the PAMI (Primary Angioplasty in Myocardial Infarction) trials of 3,362 patients having angioplasty in AMI, on multivariate analysis diabetes was the most influential factor related to decreased flow despite successful PCI (17). The phenomenon is associated with higher blood glucose on hospital admission rather than with increased HbA1c, suggesting an effect of acute hyperglycemia. Recovery of wall motion 3 months following myocardial infarction is greatly decreased in this state, with increased catecholamines, leukocyte plugging, microthrombosis, oxidative stress, loss of benefits of ischemic preconditioning, decreased endothelial nitric oxide (NO) production associated with vasospasm and endothelial injury, and intracellular and interstitial edema potential reasonable targets. There is evidence of benefit of dichloroacetate, which triggers pyruvate dehydrogenase and lowers glycolysis, reducing posts ischemic cardiac dysfunction (18). Other metabolic approaches include etomoxir and ranolazine, which may partially inhibit fatty acid oxidation, propionyl l-carnitine, which may increase mitochondrial carnitine levels, and thiazolidinediones.

Meta-analysis of studies with administration of intravenous glucose, insulin, and potassium to persons without diabetes shows a 24% reduction in mortality following myocardial infarction (19). In the ECLA (Estudios Cardiologicos Latinoamerica) pilot trial of patients with myocardial infarction undergoing reperfusion, 139 control subjects were compared with 268 subjects treated with glucose, insulin, and potassium in low (ineffective) and high (effective) doses, with 66% benefit in the latter group (20). Nesto discussed a recent randomized study of 940 persons receiving glucose, insulin, and potassium or placebo for 8–12 h, showing benefit only in those without CHF, suggesting that approaches will need to be developed that minimize the volume of infused fluid. He suggested that intracoronary insulin might be an effective treatment to avoid volume load. This would not lead to systemic metabolic effects such as the reductions in FFAs seen with glucose, insulin, and potassium but would be effective if insulin has direct cardioprotective actions, which could be antiapoptotic, anti-inflammatory, and antithrombotic, perhaps acting by decreasing reactive oxygen species (ROS), decreasing antiplatelet action and generation of tissue factor and plasminogen activator inhibitor-1, increasing in NO synthase, decreasing intracellular nuclear factor-κB and early growth response gene (egr)-1, and reducing expression of tumor necrosis factor-α, interleukin-6, intracellular adhesion molecule, vascular cell adhesion molecule, monocyte chemoattractant protein-1, MMPs, and CRP (21).

Recent controlled studies of persons with AMI show that insulin attenuates the increase in CRP, plasminogen activator inhibitor-1, and creatine kinase–myocardial band, the latter suggesting a decrease in infarct size. Furthermore, in AMI, hyperglycemia (whether in diagnosed diabetes or as “new hyperglycemia”) is associated with inflammatory markers (interleukin-18 and CRP), the presence of cytotoxic rather than suppressive T-cells, and greater degrees of cardiac injury, as indicated by troponin I levels. Studies in animal models of myocardial infarction show decreases in left ventric-
ular remodeling and heart failure with decreased myocyte hypertrophy with both rosiglitazone (22) and pioglitazone (23), and potential mechanisms include antiinflammatory effects and decreased ROS. There is, however, some concern about potentiation of CHF withTZDs (24), so that such treatment must be carefully assessed in persons with myocardial infarction.

Anthony Furnary (Portland, OR) discussed the impact of hyperglycemia and insulin infusion on cardiac surgery outcomes. The lifetime risk of CAD, he stated, is 54% in diabetic individuals but 6% in those without diabetes. Persons with diabetes constitute 6.2% of the total population but 29% of cardiac surgery subjects. Diabetes is associated with a 3.8 vs. 0.8% rate of sternal wound infection, an 8.7– vs. 6.9-day mean length of stay, and worse long-term prognosis. The Portland Diabetic Project, begun in 1987, has endeavored to “eliminate the unfair disadvantage,” seeking to normalize perioperative glycemia in a prospective nonrandomized ongoing interventional study. A total of 4,864 persons with diabetes who have undergone cardiac surgery (83% with coronary artery bypass graft) have been included in the study, representing 23% of the overall cardiac surgery population. Before admission, treatment was with insulin plus combination treatment in 33%, oral agents alone in 51%, and diet in 11%, and 5% were untreated or not previously diagnosed. An early study compared the effectiveness of subcutaneous insulin given to 968 patients before 1992, with outcome of 3,896 patients treated with an intravenous insulin infusion protocol beginning in 1992. The protocol (see http://www.starrwood.com/research) has been effective, with 47% of the subcutaneous group but 88% of the intravenous group having a median glucose during the first 24h after surgery of <200mg/dl (25). The protocol has been modified over the years, with target glucose levels of 150–200mg/dl in 1992–1995, with treatment only in the ICU, whereas in 1996–1998 treatment was begun in the operating room and continued under after discharge from the ICU to the telemetry unit. From 1999 to 2000, the glucose target was 125–175mg/dl; from 2001 to 2003, it was 100–150mg/dl; and currently the glucose target is 80–120mg/dl in the ICU and 100–150mg/dl in the telemetry unit.

With this approach, the rate of wound infection in diabetic persons has been similar to that in nondiabetic persons. In a study of the relationship between postoperative hyperglycemia and deep sternal wound infection, the rates of wound infection in patients whose mean glucose during the first 48h following surgery averaged <150, 150–175, 175–200, 200–225, 225–250, and >250 mg/dl were 0.6, 0.8, 1, 1.5, 2.2, and 3.9%, respectively (26). In multivariate analysis, obesity, the use of an internal mammary artery graft, and glucose >200 were significant independent predictors of infection. Respective mortality rates in the six glucose groups were 0.6, 1.4, 2.4, 4, 5.6, and 14%, with the effect of hyperglycemia on mortality significant in multivariate analysis, although explained in part by an association between requirement for pressor therapy and hyperglycemia. There was little association between hyperglycemia and noncardiac mortality, with the increase in mortality due to increased frequency of heart failure and arrhythmia. Comparing 942 subcutaneous with 2,612 intravenous insulin patients, mortality was 5.3 vs. 2.5%, with a 50% lower risk-adjusted mortality in the intravenous insulin group, currently reaching levels similar to those in persons without diabetes (27).

Furnary presented an economic analysis suggesting that wound infection has important consequence in persons with diabetes, increasing the length of stay to 24.8 days from the average of 8.8 days without infection, associated with a total cost of $54,600 vs. $28,200, and with hospital mortality 18.8% vs. 4%. Estimates based on the 742,000 open-heart surgery procedures performed in the U.S. in 1998, with 20% diabetes prevalence and a 2% incidence of deep sternal wound infection in these patients, suggest that 2,968 wound infections occurred. The current rate of wound infection among patients with diabetes treated with intravenous insulin is 0.7%. Extrapolating to the 1998 cardiac surgery population, this suggests that 1,929 infections could be avoided, with attendant decrease in cost and improvement in outcome. Each 10mg/dl increase in glucose might therefore be associated with a 0.2-day greater length of stay, with average length of stay 7.5, 8.8, 9.5, and 10.5 days for glucose <150, 150–200, 200–250, and >250 mg/dl.

When asked whether he thought that failing to have a controlled study and comparing data from 1987 to 1992 to current data constituted an important weakness, Furnary replied that the use of continuous quality improvement techniques has allowed conclusions to be drawn without a randomized controlled trial, which his institution now believes would not be ethical, although one must note that similar use of historical controls led for a number of years to the incorrect belief that combined estrogen-progestone one therapy reduced cardiovascular disease in postmenopausal women rather than (as has been currently found) increasing such events (28).

Claresa Levethan (Philadelphia, PA) discussed the relationship between glycemich control and stroke outcome. Intracellular acidosis caused by hyperglycemia increases lactate, leading to gial and neuronal membrane damage, due to ROS generation and impaired vasodilation. Potentially viable neurons in the ischemic penumbra are more likely to infarct under conditions of hyperglycemia, and there is evidence of disruption of the blood-brain barrier, associated with greater degrees of hemorrhage and cerebral edema. Hyperglycemia with or without diagnosis of diabetes is associated with transformation from ischemic to hemorrhagic stroke.

In the U.S., 500,000 strokes occur annually, with stroke the third leading cause of death and disability in the developed world. No current standards exist for glycemich control (the American Stroke Association recommends that only glucose be maintained at <300mg/dl), despite the costs of hyperglycemic patients with stroke exceeding those that would occur in persons with normal glucose by ~$300 million. Questions have been raised by some neurologists as to whether a larger stroke causes hyperglycemia as an epiphenomenon, although the degree of hyperglycemia is not correlated with catecholamine levels and insulin has been shown to decrease stroke size, suggesting that hyperglycemia is an independent mediator. There is relatively little variability of glycemia in normal persons, and “stress” is as likely to be associated with decreased as with increased blood glucose, so that “stress hyperglycemia” in stroke is likely previously undiagnosed diabetes. Hyperglycemia without history of diabetes in persons with acute stroke accounts for 12–53% of all hyperglycemic
stroke patients, with more than half of these patients found in one study to have HbA1c >10% (29). Levetan noted that hyperglycemia is an independent marker of in-hospital mortality, with mortality in hyperglycemic hospitalized persons without known diabetes considerably greater than that in persons with known diabetes (30). In her studies, 37.5% of persons on the medical service and 33% of those on the surgical service with glucose >200 mg/dl had no history of diabetes, and unrecognized diabetes was associated with 12% of in-hospital mortality (31).

In the Paris Prospective and Whitehall studies, both diagnosed and undiagnosed diabetes were associated with increased vascular mortality. A meta-analysis showed that admission glucose predicted poor outcome, with a threefold increase in risk of in-hospital mortality for persons without prior diabetes diagnosis having admission glucose >108–144 mg/dl (depending on the study) (32). In other studies, admission glucose >148 mg/dl was associated with a doubling of mortality independent of age, stroke type, and stroke severity (33); admission glucose >120 mg/dl predicted disability and ability to return to work in hyperglycemic patients regardless of prior diabetes status (34); and persistent hyperglycemia was associated with worse outcome (35). A linear relationship has been found between admission glucose and mortality among persons with stroke (36). Diabetes is associated with a mean $1,400 increase in hospital charges and a longer length of stay, suggesting that there may be excess cost of $300 million in additional hospital charges for patients with hyperglycemia. Stroke risk may be particularly high among diabetic women. In a comment following Levetan’s presentation, Malmberg noted that there had been a trend to decrease in stroke in the DIGAMI intensive insulin intervention (37).

**Effects of hyperglycemia in the ICU**

Neil Gray (Hartford, CT) discussed the relationship between glycemic control and nosocomial infection in the surgical ICU. There are, he noted, 2.3 cases of sepsis per 100 hospital discharges, and in a case control study of 97 persons with 107 episodes of sepsis, a 3.31-fold increase in mortality was demonstrated, with a 2.7-fold increase in length of stay and a 3.7-fold increase in ICU days, leading to an extra cost of $33,268 per patient and of $40,890 per survivor (38). Hyperglycemia decreases leukocyte chemotaxis, decreases the polymorphonuclear cell oxidative burst (39), impairs polymorphonuclear phagocytosis and bactericidal function (40), impairs complement fixation, and may alter immunoglobulin function through the production of AGEs, and insulin may have direct beneficial effects independent of its glucose-lowering actions. In a retrospective review of 241 patients with diabetes, documented infection correlated with increase in mean plasma glucose, without relationship to age, diabetes duration, or diabetes complications (41). Recent studies have confirmed that hyperglycemia is associated with increased risk for postoperative infection at sites such as the radial artery (42), as well as sternal wound infection after coronary artery bypass graft (see above discussion by Furnary).

In the Hartford Hospital ICU, approximately one-third of patients have diabetes, with hyperglycemia also common in persons not known to have diabetes. In a prospective study of persons with glucose >140 mg/dl, a standard insulin regimen with target glucose 180–220 mg/dl was compared with intensive insulin with target glucose 80–120 mg/dl. A total of 943 persons were screened, of whom 340 were eligible and 61 agreed to participate in the study. Thirty-four of these subjects received intensive treatment and 27 the standard regimen. The patients’ mean age was 55 years and BMI 27.7 kg/m², and there were high severity of illness scores. Twelve percent had diagnosed diabetes. The 30-day mean glucose was 125 vs. 179 mg/dl, with hyperglycemia noted to begin after nutritional support with hyperalimentation or enteral feedings were begun, usually several days after ICU admission. Hypoglycemia was seen in 32 vs. 7.4% of the patients, without serious adverse effect. The standard group had a significant increase in all nosocomial infections, with a 10-fold increase in intravascular device and blood stream infection and a 7-fold increase in surgical site infection, leading Gray to conclude that strict control decreases nosocomial infection and therefore that glucose levels exceeding 140 mg/dl require treatment. He recommended that intravenous solutions not contain dextrose and that insulin be used liberally, with a target glucose of <130 mg/dl, and noted that this will require revision of current insulin protocols.

Greet Van den Bergh (Leuven, Belgium) discussed the role of intravenous insulin therapy in critically ill patients. The majority of ICU patients are discharged in ≤5 days and have 2.5% mortality, but 30% stay for >5 days and have 20% mortality and 10% stay >21 days and experience 30% mortality. The early concept that hyperglycemia might be “adaptive” in providing additional glucose for brain, red cells, and wounds and that treatment should only be given with glucose >215 mg/dl has been called into question by numerous studies, with Van den Bergh showing evidence that high IGFBP-1 was associated with low insulin levels and adverse outcome (43). Thus, her group carried out a prospective randomized controlled trial of 1,548 persons, enrolling all mechanically ventilated adult patients admitted to ICU, 62% of whom had had cardiac surgery, comparing glucose targets of 180–200 vs. 80–110 mg/dl (44). Of patients, 13% had diabetes before admission and 12% glucose >200 mg/dl on admission to ICU. Nutritional support was begun on day 1, gradually increasing over 1 week, with glucose differences seen after the first day. Hypoglycemia was seen in 0.8 vs. 5.2% and tended to occur with interruption of feedings, suggesting the need for frequent “point of care” glucose measurement, ideally with accurate continuous glucose monitoring.

Conventional treatment was associated with more deaths in every stratum of severity of illness. Among 451 persons spending >5 days in the ICU, mortality decreased from 20.2 to 10.6%. Among persons with a history of diabetes, mortality was 5.8 vs. 3.9%; after cardiac surgery, it was 5.1 vs. 2.1%. For noncardiac surgery, mortality was 13.1 vs. 8.7%. Multiple organ failure with sepsis caused 33 vs. 8% of deaths in the two groups, and blood stream infection decreased 46%, renal failure 41%, critical illness polynuropathy (based on weekly electromyographic screening) 44%, mechanical ventilation >14 days 37%, and ICU stay >14 days 27%. Among 63 persons admitted after neurosurgery, diabetes insipidus occurred in 70 vs. 30%, seizures in 13 vs. 3%, and Karnofsky function score was increased at 12 months.

To address the question of whether glycemic control or pharmacologic insu-
lin treatment per se was the operative factor. Van den Berge noted that multivariate analysis correcting for additional risk factors showed that both the daily insulin dose and the mean glucose were associated with significant effect, but with higher insulin dose actually associated with greater risk of adverse outcome, suggesting the benefit to be due to the glycemic effect. When CRP and other inflammatory markers were included in the multivariate analysis, insulin effect was not seen, suggesting that this adverse effect reflected insulin resistance. However, as mean glucose increased from $<110$ to $110–150$ to $>150 \text{ mg/dl}$, there was progressive increase in adverse outcome, particularly demonstrable for critical illness polyneuropathy (45). There is evidence that hepatic gluconeogenesis is the major mediator of the glycemic effect, and anti-inflammatory effects might mediate the outcome benefits.

Glycemic control during pregnancy
Lois Jovanovic (Santa Barbara, CA) discussed the effects of glycemic control during pregnancy, labor, and delivery. Maternal glucose is the major nutrient of the fetus, readily crossing the placenta, with the fetus responding to persistent hyperglycemia by secreting large quantities of insulin, which leads to excess fat deposition and premature delivery, which can be prevented by maintaining euglycemia. Infant mortality has progressively decreased among women with diabetes as improved glycemic control has been achieved. Retinopathy progression during pregnancy and in particular during delivery has been a concern, with both HbA_1c and retinopathy stage being risk factors, and regular ophthalmologic evaluation during pregnancy. Jovanovic noted, is crucial. In nondiabetic pregnant women at week 28, the normal fasting glucose is $50–65 \text{ mg/dl}$, while postprandial glucose is $<90 \text{ mg/dl}$ and, at the end of the third trimester, peak levels rarely exceed $110 \text{ mg/dl}$. Jovanovic has taken these levels as goals for women with diabetes. Normal HbA_1c during pregnancy is $<5\%$, further suggesting the need for close glycemic control. “It’s the worst blood glucose that predicts macromania,” Jovanovic suggested, since she recommends 1-h postprandial testing to optimize outcome and notes that carbohydrate restriction is required ($<40\%$ in all women and $<30\%$ in more overweight women), even with insulin analogs. Insulin requirements are $0.7$, $0.8$, and $1.0 \text{ units/kg}^{-1} \text{ day}^{-1}$ during the first, second, and third trimesters, respectively. Using such approaches, women with diabetes can be allowed to go into labor and have vaginal delivery.

Laborition appears to be related to increases in oxytocin and is associated with increases in cortisol, with delivery often followed in normal women by mild elevation in blood glucose. Hypergonic glucose infusions were at one time recommended during delivery to provide energy but were shown to cause maternal and fetal hyperglycemia, with adverse outcomes including subsequent neonatal hypoglycemia; therefore, “there is absolute indication to have normal blood glucose during labor and delivery.” Jovanovic recommends that diabetic women stop administering insulin at the onset of labor. Hourly glucose testing is required during labor with administration of parenteral glucose using $10\%$ dextrose (infusing via a large vein to avoid sclerosing effects), as the physical exercise of active labor has glucose-lowering effects. Based on Biostator studies, she recommended a glucose dose of $2.55 \text{ mg} \cdot \text{kg}^{-1} \text{ min}^{-1} (~9 \text{ g glucose/h for a } 60\text{-kg woman})$ for glucose $<80 \text{ mg/dl},$ half this dose for glucose $81–100 \text{ mg/dl},$ saline only for glucose $101–140 \text{ mg/dl},$ and saline with hourly insulin administration, preferably intravenously, for glucose $>140 \text{ mg/dl}$ without administration of insulin.

References


