Inpatient Diabetes Control

Approaches to treatment

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Mechanisms of adverse effect of hyperglycemia

Derek LeRoith (Bethesda, MD) and Irl Hirsch (Seattle, WA) discussed mechanisms by which metabolic control may improve outcomes. Both speakers reviewed physiological and cellular aspects of normal insulin action and glucose homeostasis and molecular aspects of insulin resistance in relation to situations of stress. Insulin has classic actions such as increased glucose uptake, decreased hepatic glucose production (HGP), and antilipolytic effects in skeletal muscle, liver, and adipose tissue, as well as nonclassical vasodilatory effects, proliferative actions on vascular smooth muscle cells (VSMCs), effects on the brain (perhaps related to learning and memory), β-cell actions, and general effects increasing growth and differentiation and decreasing apoptosis. Insulin levels range from <10 to 30–50 μU/ml in the fasting versus fed state. The liver is exposed to portal vein insulin levels triple that in the periphery, with HGP inhibited at levels of 20–25 μU/ml. Lipolysis increases during fasting and is inhibited at levels of 30–50 μU/ml, so that in the fasting state, free fatty acids (FFAs) are available for fuel. A doubling of insulin levels inhibits HGP by 80% and increases glucose utilization by 20%.

The insulin-signaling pathway involves stimulation of cascades of intracellular kinases leading to insulin action. The insulin receptor substrates (IRSs) have metabolic as well as antiapoptotic effects, particularly due to IRS-1 phosphorylation via the phosphatidylinositol-3-hydroxy kinase (PI3K) pathway after activation of the insulin receptor—a process inhibited in situations of insulin resistance. The mitogen-activated protein kinase pathway is involved in gene expression, cell proliferation, and a variety of other anabolic actions. When insulin stimulates glucose uptake, particularly occurring in muscle, which mediates ~80% of insulin-stimulated glucose uptake, PI3K stimulates GLUT4 translocation to the cell membrane, leading to facilitated glucose transport into the cell, a site principally affected by insulin resistance. Two additional "environmental factors" are glucose toxicity (adverse effects of increased glucose on β-cell, liver, muscle, and adipocyte), which worsens the intrinsic abnormalities of type 2 diabetes, and lipotoxicity, perhaps a more important factor than glucose toxicity, with lipolysis-induced increased FFA levels inhibiting insulin action on muscle, liver, and pancreas, further potentiating the state of insulin resistance. Insulin treatment therefore can be shown to improve the insulin resistance of type 2 diabetes (1).

LeRoith noted that a stress-related increase in catecholamines inhibits insulin secretion and blocks insulin action via cAMP and protein kinase A, which increase serine phosphorylation of IRS-1, as well as indirectly via FFAs. Another important feature of the acute and subacute stress state is hypercortisolemia (2). FFAs (which also increase cytokine production) increase intramyocellular fatty acyl-CoA and diacylglycerol (DAG), leading to protein kinase C-ξ and -λ activation, further increasing IRS-1 serine phosphorylation. Normally, serine phosphorylation may represent a negative feedback system to lessening the effects of tyrosine phosphorylation, but this appears to be pathological under situations of cellular "stress." Inflammatory cytokines such as tumor necrosis factor (TNF)-α may be seen as the hormones of the immune system, which appear to be causally related to inflammation (rather than simply markers). Cytokines may further mediate increased serine phosphorylation of IRS-1. Interleukin (IL)-6 is another factor inhibiting insulin-induced tyrosine phosphorylation. Cytokines also act through the Jak/stat/socs kinases. Angiotensin II also inhibits insulin signaling through serine phosphorylation of IRS-1, explaining the improvement in insulin sensitivity with ACE inhibitors and angiotensin receptor blockers.

Acute illness may be seen as a state of "cytokine storm," with nuclear factor-κB (NF-κB) translocating to the nucleus, increasing transcription of adhesion molecules (intracellular adhesion molecule-1 and vascular cell adhesion molecule-1), proinflammatory molecules (TNF-α, IL-6, and IL-1β), and chemokines (monocyte chemoattractant protein-1 and C-reactive protein [CRP]). IL-1 and TNF-α in turn activate acute-phase proteins (APPs), including serum amyloid, CRP, complement factors 3 and 4, fibrinogen, plasminogen, tPa, plasminogen activator inhibitor-1 (PAI-1), and ferritin, as well as inhibiting hepatic albumin and cholesterol synthesis, with these "negative APPs" being important markers of adverse risk, so that in the setting of acute coronary syndrome, a low cholesterol

should not dissuade the clinician from administering statins. Insulin decreases the positive APPs, as well as reducing levels of activator protein 1 and Egr (early growth response)-1.

Some of these considerations may explain improvement in outcome with intensive glycemic treatment. FFAs may be an important mediator (3). Normally, with feeding, utilization of FFAs is reduced while that of glucose increases. Insulin-induced suppression of FFAs is reduced, however, in critical illness. FFAs increase oxygen requirements, and with coronary ischemia, FFAs impair Ca^{2+} transporters and are associated with reperfusion arrhythmias. During myocardial infarction there is catecholamine-induced lipolysis and decrease in insulin secretion, further increasing FFA levels. Therapy with glucose, insulin, and potassium may activate myocardial glucose utilization and, by decreasing FFAs, reduce the likelihood of arrhythmia. In the Paris Prospective Study, FFAs were associated with sudden death, although not with myocardial infarction (4). FFAs cause endothelial dysfunction (5) and increase cardiac sympathetic tone and procoagulant factors such as PAI-1. Postischemic brachial artery dilation is decreased and reactive oxygen species increased by FFAs (6).

The protective effects of insulin may involve nitric oxide (NO), which increases blood flow and inhibits VSMC growth and migration, platelet aggregation and thrombosis, monocyte adhesion, inflammation, and oxidative stress. Insulin increases endothelial NO production (7). Insulin also affects vascular endothelial cells and VSMCs by decreasing the pathological effects of glucose (for example, via advanced glycation end products) and of lipids (via oxidized LDL). Insulin may also directly reduce expression of pathological inflammatory cytokines. Nonclassical effects of insulin, however, might cause proliferation of VSMCs, contributing to atherosclerosis. The insulin effect on NO production involves PI3K, leading to endothelial NO synthase phosphorylation. Insulin resistance may then decrease vasodilation while the mitogen-activated protein kinase pathway is still active, potentially explaining adverse actions (8). Thus, angiotensin II, mechanical injury, and chronic insulin stimulation lead to growth factor effects, causing inflammation, and VSMC migration, ultimately leading to

atherosclerosis. Furthermore, glucose may increase reactive oxygen species, NF-κB, and Egr-1, with insulin potentially reversing these processes, so that insulin therapy would be antiatherosclerotic (9). Thus, acutely, insulin therapy may have a number of benefits, although compensatory hyperinsulinemia in the setting of insulin resistance may have adverse effects. LeRoith speculated that there may also be long-term benefit of insulin therapy via "molecular memory," or via reduction in cytokines and advanced glycation end products, improving long-term positive outcome.

Hirsch cited a placebo-controlled study of insulin treatment effect in 32 persons with acute myocardial infarction, with lower CRP, serum amyloid A, and PAI-1, and peak levels of creatinine phosphokinase-MB isoenzyme seen in the insulin-treated group (10). It appears that the combination of both hyperglycemia and hyperinsulinemia is particularly likely to cause adverse effect, with incubation of VSMCs with hyperglycemia plus hyperinsulinemia increasing NF-κB above that seen with hyperglycemia alone (11). Furthermore, during hyperglycemic clamp studies with octreotide to suppress islet hormones, only slight increases in TNF-α and IL-6 were seen (12); therefore, "you cannot look at insulin and glucose separately."

Approaches to inpatient glucose management

Andrew Ahmann (Portland, OR) addressed the cost-benefit analysis of intensive inpatient glucose management, reviewing evidence that good glucose control reduces cost and length of hospital stay. He cited new statistics from the Centers for Disease Control, showing that there are 18.2 million persons in the U.S. with diabetes, comprising 8.7% of the population over age 20 years, with an annual rate of increase in prevalence of 8%/year. Health care expenditures in 2002 were $132 billion, of which $91.8 billion were direct medical expenses, including $24.6 billion for complications ($17.6 billion for cardiovascular complications). Per capita direct medical costs for persons with versus without diabetes were $13,243 vs. $2,560. Persons with diabetes had 17 million hospital days in 2001, comprising 43% of total direct expenditures for diabetes, with annual per capita inpatient costs of $6,309 (vs. $2,971 for persons without diabetes). Rates of diabetes hospitalization among persons hospi-

talized have increased from ~3 to 5 over the past decade, with most diabetes hospitalizations for general medical conditions (13). Potential benefits of improved glucose control in hospital include reduced mortality (although this may increase costs) and reduced length of stay and overall cost of care for antibiotics, mechanical ventilation, dialysis, diagnostic procedures, ischemic events, rehospitalization, and requirement for extended care. This may occur with aggressive glycemic treatment, although another factor will be improved attention to comorbidities, patient education, and safety of treatment, which may accrue from more intensive treatment of persons with diabetes.

Clara Levetan (Philadelphia, PA) reviewed a number of studies of inpatient care of persons with diabetes, showing that the disease is expensive and provides opportunity for savings, with evidence linking glucose levels and length of stay, but few controlled studies have been performed. In retrospective comparison of in-hospital diabetes treatment with an endocrinology consult versus a diabetes team versus internal medicine physician alone, there were 35 and 56% shorter lengths of stay (LOSs) with the diabetes team than with an endocrinology consult and with an internist alone, respectively, with delay in obtaining consultation associated with longer LOS (14). In a study randomizing 94 vs. 85 persons to usual care versus a diabetes team, those admitted with diabetes as primary diagnosis had a reduction in LOS from 7.5 to 5.5 days. When diabetes was a secondary diagnosis, there was no effect on LOS and no difference in discharge glucose level, but readmission during the subsequent 3 months decreased 55% and outpatient glucose levels were lower (15). In an assessment of 260 persons hospitalized during a 3.5-year period with a primary diagnosis of diabetic ketoacidosis, LOS with versus without endocrine consultation was 3.3 vs. 4.9 days, with $10,109 vs. $5,463 in hospital charges (16). In analysis of outcome of 656 persons with stroke, glucose >130 vs. ≤130 mg/dl was associated with a 7.2- vs. 6-day LOS and with hospital charges of $6,611 vs. $5,262 (17). A study of 1,574 persons having coronary artery bypass graft, 34.6% of whom had diabetes, suggested that for each 50-mg/dl increase in perioperative mean glucose, LOS increased by 0.99 and 0.58 days in persons with and

without diabetes, respectively, with hospital charges increasing $4,320 and $1,552 and actual hospital costs increasing $2,870 and $782, respectively (18). In the Leuven study, the 3-day shortening of intensive care unit (ICU) stay was projected to decrease cost by €2,052,558 annually, with additional savings from prevention of sepsis and improving functional outcome. In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, increased LOS was seen in the insulin infusion group but complications decreased over the subsequent 12 months; therefore, total cost was similar, and insulin treatment increased life expectancy by 1.15 years at cost of €24,100 per quality-adjusted life-year gained, comparing favorably with costs of cholesterol treatment, with glycemic treatment in the U.K. Prospective Diabetes Study, and with costs of air bags or road improvements.

Susan Braithwaite (Chapel Hill, NC) discussed considerations for intravenous insulin infusion therapy initiation and what might be appropriate goals of such treatment. Indications include diabetic ketoacidosis and hyperosmolar coma, and the usual thresholds for initiation of intravenous insulin may be too high. Persons with type 1 diabetes not able to eat (npo) because of intervening illness may benefit, and one should consider whether such treatment would be appropriate for all persons in pre-, intra- and postoperative care, an endeavor that would require participation of anesthesiologists. Stroke, myocardial infarction, and infection may be additional indications. The target for such treatment is uncertain. As she reviewed studies, including those presented earlier in the conference, Braithwaite noted that for prevention of reflow after percutaneous transluminal coronary angioplasty in the setting of myocardial infarction, glucose levels of 159 are better than 209 (19). The DIGAMI study supports levels <180, and the Portland data suggest levels <150 to be optimal in comparison to historical controls, perhaps with a cutoff at <125 for prevention of atrial fibrillation and <175 for prevention of sternal wound infection. An observational study of 531 ICU patients with time-weighted glucose showed survivors to be most often in the 111–144 range, while nonsurvivors were more likely to have glucose >200, suggesting a threshold for critically ill patients of 145 (20).

Stroke data suggest glucose <140, the Hartford study suggests <125, the randomized controlled Leuven trial suggests <110, and pregnancy data suggest glucose <100 mg/dl to be ideal. A recent retrospective analysis of 1,826 consecutive ICU patients showed no threshold, with mortality increasing steadily from <100 to >300 mg/dl glucose (21). She suggested that intravenous insulin be given to persons with myocardial infarction, npo, or gastroparesis with goal glucose <140 mg/dl, considering intravenous insulin necessary if glucose exceeds 180 mg/dl in persons receiving basal insulin plus lispro or aspart supplementation every 2 h. Thresholds might be >140 mg/dl for perioperative care, >110–140 in the surgical ICU, and >140–180 for nonsurgical illness, with glycemic targets of 80–110 for surgical ICU, 110–140 for medical ICU, and 80–100 mg/dl for pregnancy.

Bruce Bode (Atlanta, GA) noted that the currently used hospital treatment approach is, for many persons with diabetes, administration of insulin only if glucose exceeds 200 mg/dl. He suggested use of constant intravenous glucose, varying the insulin based on the blood glucose level, using premixed solutions of glucose, insulin, and potassium only for euglycemic persons. The ideal insulin protocol would be easily ordered and implemented and available throughout the hospital (based on glucose targets), rapidly effective, and safe, with minimal risk of symptomatic hypoglycemia. Requirements are an intravenous line with sufficient flow to keep the vein open, with constant glucose inflow, able to compensate for alterations in enteral nutrient delivery, administering potassium as required, using regular insulin in a 1 unit/ml or 0.5 units/ml concentration (this should be standardized through each hospital) with adjustments in 0.05- to 0.1-unit/h increments, requiring hourly monitoring initially, and 2-h monitoring once the patient is stable. Such an approach requires an algorithm that "seeks" the correct insulin dose via adjustment to the insulin sensitivity of the patient based on glycemic response.

Bode noted the complexity of the intravenous insulin protocols in the DIGAMI, Portland, and Leuven studies, so that "for an outside observer it is difficult to pick up what to do." In the Portland protocol, essentially one doubles or halves the insulin infusion rates for glucose >200 or <100 mg/dl, respectively,

with 0.5-unit/h adjustments under certain circumstances (22). The Leuven protocol allows flexible insulin adjustment based on the experience of the ICU nurse, with insulin increments of 1–2 units/h for glucose >140 mg/dl, 0.5–1 unit/h for glucose 110–140 mg/dl, reduction by half for glucose "falling steeply," and otherwise adjustment by 0.1–0.5 units/h (23). This approach, however, led to 5.2% of glucose levels being <40 mg/dl.

Bode described a protocol based on the following formula: hourly insulin rate = hourly maintenance rate + (blood glucose − [glucose target])/ISF, where the insulin sensitivity factor (ISF) is initially calculated as 1,500 divided by the patient's total 24-h insulin dose (24). Implementation of this approach uses the information depicted in Table. One should "start with column 2, test the glucose hourly, go to a lower column if glucose trends low or is stable for >8 h, and go to higher column if glucose trends high."

A different stepped approach calculates the insulin dose from the following formula: units/h = (blood glucose − 60) × SF (25). One starts with the sensitivity factor (SF) 0.02, although for most persons a higher SF is needed, with severely insulin-resistant persons requiring a SF as high as 0.15. If the blood glucose exceeds 140 mg/dl, one should increase the SF by 0.01; if <100, decrease by 0.01; and if <80 mg/dl, give 50% dextrose intravenous at a dose (in ml) of (100 − blood glucose) × 0.4. This approach lends itself to computerization and is illustrated at www.glucommander.com and www.adaendo.com. Bode stated that the program has been used during 5,802 separate patient care episodes at his institution, where there has been a total of 120,618 glucose determinations and a mean starting glucose of 259 mg/dl. On average, patients have reached stable levels <150 mg/dl after 3 h and remain in the target range for up to 60 h. The correlation between the target and achieved mean glucose is $r^2 = 0.92$, and 2.6% of glucose levels have been <40 mg/dl. The program may become commercially supported, but because intravenous insulin is currently considered by the Food and Drug Administration to be "off label," there has been hesitation on the part of potential supporters.

Discussing conversion to subcutaneous insulin, Bode suggested that patients requiring >0.5 units/h should start insu-

Table 1—*Tabular infusion rates for the protocol of Markovitz et al. (24)*

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6
<70 (off)	<70 (off)	<70 (off)	<70 (off)	<70 (off)	<70 (off)
70–79 (off)	70–79 (off)	70–79 (off)	70–79 (off)	70–79 (0.5)	70–79 (1)
80–89 (off)	80–89 (off)	80–89 (off)	80–89 (0.5)	80–89 (1)	80–89 (1.5)
90–99 (off)	90–99 (off)	90–99 (off)	90–99 (1)	90–99 (1.5)	90–99 (2)
100–109 (off)	100–109 (0.5)	100–109 (1)	100–109 (1.5)	100–109 (2)	100–109 (3)
110–129 (0.5)	110–129 (1)	110–129 (1.5)	110–129 (2)	110–129 (3)	110–129 (4)
130–149 (1)	130–149 (1.5)	130–149 (2)	130–149 (3)	130–149 (4)	130–149 (6)
150–179 (1.5)	150–169 (2)	150–179 (3)	150–169 (4)	150–179 (6)	150–169 (8)
	170–189 (2.5)		170–189 (5)		170–189 (10)
180–209 (2)	190–209 (3)	180–209 (4)	190–209 (6)	180–209 (8)	190–209 (12)
210–269 (3)	210–254 (4)	210–239 (5)	210–229 (7)	210–239 (10)	210–229 (14)
		240–269 (6)	230–269 (8)	240–269 (12)	230–249 (16)
270–329 (4)	255–299 (5)	270–299 (7)	270–309 (10)	270–299 (14)	250–269 (18)
	300–345 (6)	300–329 (8)	310–349 (12)	300–329 (16)	270–309 (20)
330–389 (5)		330–359 (9)		330–359 (18)	310–349 (24)
	346–389 (7)	360–389 (10)	350–389 (14)	360–389 (20)	350–389 (28)
≥390 (6)	≥390 (8)	≥390 (11)	≥390 (16)	≥390 (22)	≥390 (32)

Data are capillary blood glucose level (units/h).

lin glargine at least 2 h before stopping intravenous insulin and that perhaps this would need to be started the night before stopping. There is a linear correlation between the intravenous insulin requirement and subsequent subcutaneous insulin requirement (26), so that one might extrapolate to a 24-h insulin requirement the insulin utilized during the previous 6–8 h, giving half as basal and half as meal bolus doses and giving supplemental insulin correction doses for glucose >140, calculating that 1 unit insulin lowers the blood glucose by (in mg/dl) 1,700/(24-h insulin requirement).

Stephen Clement (Washington, DC) noted the importance of subcutaneous insulin in the treatment of hospitalized persons with diabetes. Much information pertaining to this and the overall topic of intensive treatment of hospitalized persons with diabetes appeared in a recent review (27). Physiological insulin needs can be divided into basal and nutritional components, with the latter related to prandial, enteral, or parenteral feedings and each with different implications in insulin requirement. Parenteral nutrition, for example, increases the insulin requirement to ~100 units/day for persons with type 2 diabetes and to more than twice the usual total daily dose for persons with type 1 diabetes (28).

When used as sole insulin replacement in the insulin-deficient patient, the "sliding scale" typically is ineffective and leads to hypo- followed by hyperglycemia (29). The concept of glucose-related insulin administration is, however, appropriate when administered as a supplement or correction, which becomes the third portion of the hospital insulin-dosing schedule. Illness- or stress-related increases in the insulin requirement need to be apportioned among basal, nutritional, and correctional doses, and all components will decrease as the level of stress decreases. With illness and decreased nutritional intake, the total dose increases while the prandial component decreases. Implementation of such a protocol requires administration and pharmacy support and involvement of medical and nursing staff. Physicians must have "core knowledge" of the impact of glycemia on outcome, accepted glycemic targets, the need to avoid sliding scale alone, and understanding of appropriate approaches in special circumstances. Nurses need to be familiar with bedside glucose monitoring, critical and target glucose, and insulin administration techniques. Patient education is also important, including "survival skills," basic understanding of diabetes and of their prescribed medications, symptoms of high and low glucose, glucose monitoring, hypoglycemia management, approaches to contacting their health care providers, and community education resources.

Current practices are highly variable.

Michelle McGee (Washington, DC) described the approaches to diabetes treatment at a 907-bed urban hospital with ~10,000 annual hospitalizations of diabetic patients. Insulin orders on the Medical service were for a sliding scale for only 40% of patients, a sliding scale plus oral in 13%, a sliding scale plus a standing insulin program in 30%, a program alone in 7%, oral agents alone in 6%, and insulin infusion in 13%. In the ICU, 45% of patients were treated with a sliding scale alone. Thirty-eight percent of glucose levels exceeded 180 mg/dl and 3% exceeded 400 mg/dl, while hypoglycemia was also seen relatively frequently.

Avoidance of hypoglycemia
Richard Hellman (Kansas City, MI) discussed approaches to improving outcomes among persons with diabetes (30) and described a "systems approach" to strategies for error reduction in insulin therapy in the inpatient setting, suggesting that nursing errors may be caused by excessive patient responsibilities or fatigue, illegible physician order writing, hospitals deferring computerized medication orders, hospital finances preventing such systems, federal financial deficits, and a host of other causes, so that one must address the root causes of these errors. Each healthcare provider has their own "scope of awareness," enabling them to recognize and correct some errors, while we may not realize that other ac-

tions we perform could lead to adverse outcome. Hellman suggested that a "culture of safety" must be promoted to create barriers to unintended injuries. In his studies, death from medical errors was most commonly seen when a systems problem was combined with a medical error, as with a misdiagnosis, suggesting the need for "backup systems." Nurses are crucial in implementing patient safety and in finding medication errors made by physicians, although there is danger that economic cutbacks may interfere with this layer of protection.

The sliding scale can in this sense be considered a "rule-based error," as would be a decision to maintain glucose levels >200 mg/dl. "Slips and lapses" must also be addressed, such as a nurse forgetting to measure a blood glucose. Diagnostic errors include lack of awareness of gastrointestinal manifestations of ketoacidosis delaying its recognition. A "latent error" would be inappropriately infrequent glucose monitoring. Prejudices such as the fear of hypoglycemia may interfere with intensive treatment in coronary patients and in the ICU, in part because although hypoglycemia uncommonly causes mortality in an inpatient setting, it is a common cause of uncomfortable symptoms. Furthermore, a defective "culture of safety" often causes hypoglycemia, for example, with lack of coordination between dietary and nursing leading to mistiming of insulin administration with respect to food, inadequate glucose monitoring, or lack of coordination between transportation and nursing. The key is to have frequent glucose monitoring, excellent and well-understood treatment algorithms, and trained teams to administer the algorithm correctly with a backup plan for large glucose variance. Cognitive barriers to safer insulin therapy in hospital settings "is a touchy issue," as there is a wide disparity between the interest and support of various subspecialty groups in accepting the concept of intensive glycemic treatment. "In oncology," Hellman pointed out, "often it's not on the map." Lack of availability of electronic medical records and computerized physician order entry systems is another major error-causing factor.

Lack of uniformity of insulin orders is important. Hellman pointed out that as orders become more complex, there is higher risk of error, so that careful education becomes important. Insulin infusion protocols need to be evaluated not only for efficacy but also for safety, for lack of ambiguity, for sufficient frequency of glucose monitoring, for clarification of when the physician is called for help, and for the minimal concentration of insulin for the patients' anticipated insulin requirements. It will be important for these protocols to be field tested with independent analysis of the implementation approach.

Braithwaite agreed that "the simple mismatch" between nutrient ingestion and insulin administration in hospitalized patients is the most common cause of hypoglycemia. She commented that hypoglycemia is predictable, occurring in association with nausea/vomiting, altered mental status, and oral or enteral nutrient withholding for surgery or diagnostic testing. Additional risk factors include hypoalbuminemia, sepsis, and renal failure, and hypoglycemia may also be caused by physician or nurse error in insulin ordering or administration. Although there is evidence of association of hypoglycemia with increased mortality (31,32), in a study of 5,404 hospitalized persons, of whom 281 experienced hypoglycemia, it appeared that low glucose was a marker of poor health rather than itself being causally related to adverse outcome (33). Thus, if hypoglycemia is a principal barrier to achieving euglycemia in hospital, then an important question is whether it is a real barrier or, as it were, a psychological barrier for the health care provider.

There is uncertainty about the comparative risks and benefits of mild hyperglycemia versus mild hypoglycemia. In a study of 2,030 hospitalized adults, 38% had hyperglycemia, with considerable increase in mortality among those with previously undiagnosed diabetes and those known to be affected by the disease (34), while hypoglycemia appears to be considerably less common, although reported studies may have not ascertained all episodes of hypoglycemia. An approach is to monitor persons at risk, such as the elderly, those receiving high-risk medications, and those with renal failure or malnutrition. In critically ill patients, the Portland, DIGAMI, and Leuven studies suggest that hypoglycemia is not a consequential problem. In the Diabetes Control and Complications Trial and U.K. Prospective Diabetes Study, however, hypoglycemia sometimes did threaten the safety of intensively managed patients. In one study of patients on geneal medical wards, 5,491 patients had 67 mild episodes of hypoglycemia, while 91 had severe hyperglycemia and 13 both hypoglycemia and severe hyperglycemia (31).

Prevention approaches may include allowing self-management in hospital for appropriate patients, although it is important then to formally assess which patients are capable of such self-treatment and what medications, such as sedatives and analgesics, might interfere with patient ability to do so. Braithwaite reemphasized the need to discourage sliding scale monotherapy and for physicians to be responsive to downward trends in glycemia. Basal insulin must be clearly separated from the nutritional and hyperglycemic correction components of the insulin regimen, with clear "hold" parameters for short- or rapid-acting insulin. Consistent carbohydrate intake is not always provided in the hospital diet and must be emphasized. It also is important to establish appropriate nursing protocols in order to respond with appropriate preventive actions for triggering events such as decreased nutrient intake rather than simply having a protocol to treat hypoglycemia after it has happened, so that if insulin or a secretagogue is given and a patient is transported off the ward, has new "npo" status, or has interruption of glucose-containing intravenous treatment or enteral feeds, it is appropriate to take action to provide a safety net to avoid hypoglycemia, closely monitoring glucose. One must, of course, at the same time be certain to identify patients with absolute insulin deficiency to avoid incorrect suspension of basal as well as nutritional insulin administration, perhaps by a specific order on admission so that "the doctor doesn't have the choice to discontinue all insulin." If hypoglycemia does occur, an appropriate preventive oral and intravenous dextrose algorithm must be available.

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