SEE INZUCCHI AND ROSENSTOCK (P. 976)

Point: Inpatient Glucose Management

The emperor finally has clothes

In January 2004, a panel convened by the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) issued a position statement on the management of glucose in hospitalized patients (1). This panel included representation by the American Diabetes Association (ADA), the Endocrine Society, the American Heart Association, the Society of Critical Care Medicine, the Society of Thoracic Surgeons, The American Association of Diabetes Educators, The American Society of Anesthesiologists, and The Society of Hospital Medicine, all of whom were cosignatories to the ensuing document. The position statement recommended that a preprandial target level of 110 mg/dl (6.0 mmol/l) be set for the plasma glucose level of all hospitalized patients, regardless of the presence or absence of a prior diagnosis of diabetes (1).

The impetus for establishment of a position on this issue largely arose from the publication of two major prospective controlled intervention trials that demonstrated significant reductions in serious morbidities and mortality in hospitalized patients in whom glycemia was tightly regulated (2,3). These trials were in turn undertaken to further address the findings of prior observational studies, which showed a strong correlation between hyperglycemia and poor clinical outcomes in a variety of inpatient settings (4–8). Until recently, it seemed intuitively obvious that hyperglycemia manifested under physiologically stressful situations was a consequence of the primary illness and a marker of its severity, rather than directly contributing additional morbidity to it. While the former may indeed be the case, it came as a surprise to many that prospective trials addressing the hyperglycemia alone, or to be more specific, addressing it by the administration of insulin, improved multiple immediate clinical outcomes, including reducing sepsis, renal failure, transfusion requirements, and polyneuropathy (3,9). Moreover, in one study, in-hospital mortality was reduced by >50% (10). Consequent upon the favorable effects on morbidity, there was a reduction in the length of hospital stay and overall cost of care (6).

The presence of diabetes as a comorbidity has been calculated to add an average $11,500 to the cost of a hospital admission in 1997 dollars (11), and between 1997 and 2000 its identification increased from 9.5 to 12.4% of hospital admissions or >4.5 million admissions annually (12,13), although this is almost certainly a considerable underestimate of the true prevalence (14). Of additional interest was the finding that long-term outcomes were also improved by the intervention of intensive glycemic control, which reduced mortality by 25% >3 years after the initial treatment in one study (2). Interestingly, mortality was reduced by an even greater extent (45%) in patients who had not previously been treated for diabetes (2).

The biochemical and physiologic basis for these beneficial effects is not yet fully understood. Furthermore, it is not clear whether the reduction in plasma glucose or the therapeutic administration of insulin is the major contributor to this treatment effect, since in one study (2), the subgroup with the greatest benefit from the intervention had been treated with oral antidiabetic agents before admission. The multiple metabolic actions of insulin make it an attractive candidate for the mechanism producing the favorable changes. Insulin lowers catecholamine-induced free fatty acid release and acutely regulates the vasomotor function and contractility of the myocardium and the vasculature (15,16), as well as stimulating nitric oxide production, improving endothelial function, and lowering inflammatory and prothrombotic mediators and cytokines (17,18). On the other hand, it has long been known that hyperglycemia per se impairs immune function in several ways: neutrophil function is reduced, complement binding is attenuated, and monocyte phagocytic function is disrupted (19). Moreover, hyperglycemia has been shown to induce a proinflammatory and prothrombotic state in human studies (20–22). It is therefore possible, and even likely, that the combined effects of increased insulinemia and reduced glycemia act in a complementary, or possibly synergistic, manner at different sites to bring about overall improvements in hemodynamic, immune, and metabolic functioning.

As momentum gathers to implement programs designed to achieve intensive glycemic control in hospitalized patients nationwide, it has been pointed out that the favorable impact of tight glycemic regulation with insulin has hitherto been achieved in the artificial setting of unblinded, albeit controlled, clinical trials in high-risk patients in intensive care units (ICUs) in academic medical centers and that the findings are unproven in the nonresearch general clinical care setting. It has even been suggested that the improvements may have resulted from the increased attention and vigilance that is necessarily given to such patients, in whom the potential for insulin administration to cause hypoglycemia, with its own adverse clinical impact, is significant. It has been argued that extrapolation of these data to implementation of widespread clinical interventions in less controlled settings is premature, risky, and expensive. Furthermore, the findings of a recently published major prospective interventional study (Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction [DIGAMI]-2 [23]) did not reproduce the benefits of the original DIGAMI trial (2).

These criticisms have no legitimate basis in fact, since the conclusions primarily derive from randomized controlled trials, which are the only valid method for hypothesis testing and can only be performed in attentive clinical care settings. Results of randomized prospective interventional clinical trials constitute the most widely accepted and rigorous level of evidence leading to acceptance of new therapies into general

clinical use. They permit the calculation of a benefit-to-risk ratio applicable to the clinical setting that is more precise than other forms of evidence. For example, in one major trial incorporating a large number of patients, there was still a 50% reduction in mortality despite the occurrence of hypoglycemia associated with insulin treatment (3).

Similar concerns have been raised regarding the use of intravenous insulin in the coronary care unit setting, owing to the potential for hypoglycemia. However, in the first DIGAMI study, despite 43 episodes of hypoglycemia, mortality was 30% lower in the insulin treatment arm (2). DIGAMI-2 did not achieve its treatment goals or its target enrollment numbers and was thus underpowered to show any treatment effect whatsoever (23). Indeed, it was concluded prematurely due to low enrollment. It must also be pointed out that treatment advances are made primarily for the benefit of patients and not for considerations of convenience. If, by this intervention, lives cannot only be saved but immediate health care costs can also be reduced, there can surely be no reasonable justification for failure to implement such a program wherever and whenever feasible and at the earliest opportunity. To further put this in perspective, it is worth recalling that, at any moment in time, >5,000,000 Americans are using insulin on a continuous (outpatient) basis and young children often self-administer it with relatively minor supervision.

The benefits seen in these prospective trials have been so dramatic that if even a small fraction of these are seen in the clinical setting, they translate into many thousands of lives saved per annum and many millions of dollars saved by our already financially overburdened health care system. Furthermore, with significant reductions in length of stay come more effective utilization of costly hospital beds and increased bed availability in regions where capacity is limited. Of course, inpatient treatment programs for hyperglycemia should not be implemented without careful planning, nor should they take place in hospital environments where the basic requirements for safe implementation cannot be met. The multiorganizational consensus statement and subsequent actions of some of its sponsoring bodies have addressed this issue in two ways. First, the consensus statement recommends that treatment protocols be used and advises that a team approach be employed (1). Second, the AACE, as well as the ADA, have announced a series of courses to be held over the coming year in more than a dozen major U.S. cities, beginning in December 2004, to help interested parties design and implement programs successfully (24). A comprehensive slide kit giving practical guidance on these programs has also been prepared by the AACE and the ADA. Although not specifically addressed by the consensus statement, to this we would add the practical recommendation that such programs should generally be phased in incrementally in terms of glycemic target levels, which should be initially set at a level that allows for safe establishment of program structure, while minimizing the risk of hypoglycemia during this phase. After the components of a program are in place and functioning satisfactorily, the stringency of glycemic targets can be increased. In parallel, selected patient groups can initially be included and inclusion criteria gradually expanded as program goals are reviewed and are seen to be met safely.

Finally, a recent report of the results of implementation of such a program in a community hospital indicates that the expected benefits of tight glycemic control were indeed reproduced in this setting (25). This study comprised evaluation of outcomes of 800 patients admitted to a medical surgical ICU in a university-affiliated community teaching hospital after institution of an intensive glucose management protocol, as compared with an equal number admitted immediately before implementation. A treatment target for plasma glucose was set at ≤140 mg/dl. No significant increase in the prevalence of hypoglycemia occurred (0.35 vs. 0.34%). The incidence of new onset of renal insufficiency diminished by 75% in those on the intensive protocol, and there was also a significant reduction in the number of patients who required blood transfusion. The most significant favorable findings were the reduction in hospital mortality (29%, $P = 0.002$) and length of stay in the ICU (11%, $P = 0.01$). Significantly improved outcomes were seen specifically in septic shock, neurological diseases, and general surgical cases. No increase in registered nurse staffing requirements occurred in the protocol-implementation period.

Seldom does an opportunity present itself in the field of health care to implement a relatively straightforward and safe intervention that utilizes existing therapeutic agents and technology and provides such potential for favorable short- and long-term health benefit for so many. It is fair to say that this can be compared with the benefit seen with major immunization programs or the introduction of the principal classes of antibiotics. This intervention is based on carefully designed and conducted clinical trials, and initial reports have confirmed favorable outcomes in a clinical care setting. Moreover, the planned intervention is theoretically soundly based on a large body of experimental data, obtained both in vitro and in vivo, attesting to the multiple deleterious metabolic and immunologic effects of both long- and short-term hyperglycemia and to the beneficial actions of insulin administration to reverse these effects in varied clinical conditions, including major surgery, stroke, and myocardial infarction.

Therefore, the issue at hand is not so much whether we can justify moving forward with full implementation of programs based on the ACE/AACE Consensus Statement but whether we can justify not doing so. Not to do so is likely to result in perpetuating the status quo of unnecessary morbidity and mortality for a significant percentage of hospitalized patients, both during admission and after discharge, and contribute to our inability to put novel constraints on the upward spiral of health care costs. Furthermore, available evidence points to an increasing burden of this avoidable cause of morbidity for the foreseeable future. All acute care hospitals should be able to implement these recommendations at least in part and target them to the patient groups for whom they have clearly been shown to be beneficial, while many should be able, over time, to implement them in full. Happily then, the emperor finally is wearing clothes and should soon be seen in them throughout the land.

MICHAEL BRYER-ASH, MD, FRCP[1,2]
ALAN J. GARBER, MD, PHD[3]

From the [1]Gonda (Goldschmied) Diabetes Center, Division of Endocrinology, Diabetes and Hypertension, David Geffen School of Medicine at UCLA, Los Angeles, California; the [2]Section of Endocrinology, West Los Angeles Veterans Administration Medical Center, Los Angeles, California; and the [3]Division of Endocrinology, Baylor College of Medicine, Houston, Texas.

Address correspondence to Michael Bryer-Ash, David Geffen School of Medicine at UCLA, Division

of Endocrinology, Diabetes and Hypertension, 900 Veteran Ave., Suite 24-130, Los Angeles, CA 90095. E-mail: mbryerash@mednet.ucla.edu.

References

1. Garber AJ, Moghissi ES, Bransome ED Jr, Clark NG, Clement S, Cobin RH, Furnary AP, Hirsch IB, Levy P, Roberts R, Van den Berghe G, Zamudio V, American College of Endocrinology Task Force on Inpatient Diabetes Metabolic Control: American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 10:77–82, 2004
2. Malmberg K, Norhammar A, Wedel H, Ryden L: 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* 99:2626–2632, 1999
3. Van den Berghe G, Wouters P, Weekers F, VerWaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in critically ill patients. *N Engl J Med* 345: 1359–1367, 2001
4. Capes SE, Hunt D, Malmberg K, Gerstein HC: Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 355:773–778, 2000
5. Kiers I, Davis SM, Larkins R, Hopper J, Tress B, Rossiter SC, Carlin J, Ratnaike S: Stroke topography and outcome in relation to hyperglycaemia and diabetes. *J Neurol Neurosurg Psychiatry* 55:263–270, 1992
6. Furnary AP, Chaugle H, Zerr KJ, Grunkmeier GL: Postoperative hyperglycemia prolongs length of stay in diabetic CABG patients (Abstract). *Circulation* 102:II-556, 2000
7. Krinsley JS: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 78:1471–1478, 2003
8. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsch IB, the Diabetes In Hospitals Writing Committee: Management of diabetes and hyperglycemia in hospitals (Technical Review). *Diabetes Care* 27:553–591, 2004
9. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A: Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thoracic Surg* 67:352–360 (discussion 360–362), 1999
10. Furnary AP, Gao G, Grunkmeier GL, Wu Y, Zerr KJ, Bookin SO, Floten HS, Starr A: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 125:1007–1021, 2003
11. American Diabetes Association: Economic consequences of diabetes in the U.S. in 1997. *Diabetes Care* 21:296–309, 1998
12. Elixhauser A, Yu K, Steiner CA: *Hospitalization in the United States, 1997: Healthcare Costs and Utilization Project Fact Book Number 1*. Washington, DC, Agency for Healthcare Research and Quality, 2000 (AHRQ publication 00-0031, ISBN 1-58763-005-2)
13. Centers for Disease Control and Prevention: *National Hospital Discharge Survey Database 2000*. Atlanta, GA, Centers for Disease Control and Prevention, Division of Diabetes Translation, 2003
14. Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE: Unrecognized diabetes among hospitalized patients. *Diabetes Care* 21:246–249, 1998
15. Chaudhuri A, Kanjwal Y, Mohanty P, Rao S, Sung BH, Wilson MF, Dandona P: Insulin-induced vasodilatation of internal carotid artery. *Metabolism* 48:1470–1473, 1999
16. Ramanathan T, Shirota K, Morita S, Nishimura T, Huang Y, Hunyor S: Glucose-insulin-potassium solution improved left ventricular mechanics in diabetes. *Ann Thoracic Surg* 73:582–587, 2002
17. Jain SK, Nagi DK, Slavin BM, Lumb PJ, Yudkin JS: Insulin therapy in type 2 diabetic subjects suppresses plasminogen activator inhibitor (PAI-1) activity and proinsulin-like molecules independently of glycemic control. *Diabet Med* 10:27–32, 1993
18. Hansen T, Thiel S, Wouters P, Christiansen J, Van den Berghe B: Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannosegind lectin levels. *J Clin Endocrinol Metab* 88:1082–1088, 2003
19. Bagdade JD, Root RK, Bulger RJ: Impaired leukocyte function in patients with poorly controlled diabetes. *Diabetes* 23:9–15, 1974
20. Gresele P, Guglielmini G, DeAngelis M, Ciferri S, Ciofetta M, Falcinelli E, Lalli C, Ciabattoni G, Davi G, Bolli G: Acute short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus. *J Am Coll Cardiol* 41:1013–1020, 2003
21. Morohoshi M. Fujisawa K, Uchimura I, Numano F: Glucose-dependent interleukin 6 and tumor necrosis factor production by human peripheral blood monocytes in vitro. *Diabetes* 45:954–959, 1996
22. Davi G, Catalano I, Averna M, Notabartolo A, Strano A, Ciabattoni G, Patrono C: Thromboxane synthesis and platelet function in type II diabetes mellitus. *N Engl J Med* 322:1769–1774, 1990
23. Scheen AJ, Radermecker RP, Philips JC: Effects of intensive insulin therapy after an acute myocardial infarction in patients with type 2 diabetes: results of the DIGAMI-2 trial. *Rev Med Liege* 59:534–539, 2004
24. American Association of Clinical Endocrinologists: Diabetes and metabolic control physician champion course [article online], 2004. Available at http://www.aace.com/edu/symposia.php. Accessed 16 November 2004
25. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 79:992–1000, 2004