Editorial

Intensive insulin management of inpatient hyperglycemia: the time for implementation is now

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It is now well-established that glycemic control in patients with diabetes mellitus (DM) reduces the long-term complications of DM but transient increases in glucose in the setting of acute illness were largely ignored. However, in recent years, it has become apparent that hyperglycemia that develops acutely due to illness and stress is associated with poor patient outcomes in hospital inpatients, even in those with no history of DM, and that correction of this hyperglycemia is associated with improved outcomes. These clinical findings are supported by a wealth of information that suggests that such glycemic improvement suppresses inflammation at the cellular and tissue levels.

A number of observational trials have defined the prevalence of inpatient hyperglycemia as well as established an association between serum glucose and poor patient outcomes during hospitalization. Importantly this association was not limited to individuals with a prior history of DM. In a series of 2030 consecutive adults admitted to Grady Medical Center in Atlanta, Georgia, 38% were found to be hyperglycemic, as defined by a fasting blood glucose of > 126 mg/dl or a random serum glucose of > 200 mg/dl (1). Hyperglycemia was associated with a greater than 5 fold increase in mortality and individuals without a prior history of diabetes proved to be at the highest risk of death (1). Admission serum glucose is directly related to mortality following acute myocardial infarction (2) and stroke (3) independent of diabetes status. In a prospective analysis of 4684 individuals undergoing coronary artery bypass surgery, Furnary and colleagues demonstrated a direct relationship between the average serum blood glucose in the peri-operative period and the development of post-operative deep sternal wound infections (4) and mortality (5).

These data, though intriguing, describe an associative relationship between hyperglycemia and worse hospital outcome; causality cannot be established. The stress of acute illness results in an excess secretion of hormones such as glucocorticoids and epinephrine known to counteract insulin effect, inevitably leading to hyperglycemia. This "stress hyperglycemia" was accepted as a consequence of illness; however important clinical questions remained, namely whether hyperglycemia is directly harmful to patients and if attempts to lower serum glucose would reduce morbidity and mortality. Intervention trials designed to aggressively treat inpatient hyperglycemia, have been conducted to shed light on these questions.

Diabetes mellitus (DM) is associated with increased morbidity and mortality following cardiothoracic (CT) surgery (6-9). The incidence of deep sternal wound infection (DSWI), a potentially life-threatening post-operative complication, is 2.5 times greater among those with diabetes compared to the non-diabetic population (6, 7). A group from Portland, Oregon has shown a direct correlation between hyperglycemia following CT surgery and morbidity and mortality (5, 7). The investigators conducted a historical evaluation of the effect of intensive post-operative glycemic control via an intravenous insulin proto-

col given for 3 days postoperatively in the intensive care unit on surgical outcomes compared to their prior conventional approach of glycemic control with a "sliding scale" insulin regimenr (4,5). Intensive hyperglycemia control post-operatively reduced the incidence of DSWI by 57% among 2467 individuals (4) and reduced mortality by 66% among 3554 individuals with DM (5). The resultant effect was a normalization of the diabetes associated increased risk of DSWI and mortality following CT surgery.

The benefit of intensive insulin therapy is not limited to those with DM but extends to those with critical illness- induced hyperglycemia. In a landmark, randomized, prospective study from Belgium, van den Berghe et al showed that the use of an intensive intravenous insulin protocol designed to maintain serum blood glucose between 80-110 mg/dl significantly decreased morbidity and mortality following admission to the surgical intensive care unit (SICU). Compared to a conventional approach to hyperglycemia (mean blood glucose of 153 mg/dl), intensive hyperglycemia management (mean blood glucose 108 mg/dl) was associated with statistically significant decreases in mortality, sepsis, need for dialysis, need for blood transfusion, the development of post-intubation polyneuropathy, and length of stay in the ICU (10). Of note, only 13% of the individuals in the study had a previously known diagnosis of diabetes, showing that hyperglycemia was common following SICU admission and glycemic control was beneficial regardless of diabetes status.

In a similarly designed study among 1200 individuals admitted to the medical intensive care unit (MICU) the same group was able to show a reduction in new onset renal injury, MICU and hospital length of stay, as well as an improved ability to wean off mechanical ventilation in those individuals randomized to intensive insulin therapy (11). Among the entire cohort in this study no statistically significant improvement in mortality was demonstrated by the use of intensive insulin therapy. However among the subset of individuals requiring a MICU stay of > 3 days duration (n = 767), intensive glycemic control was associated with a significant 33% reduction in mortality and a greater reduction in morbidity end points. Obviously it is impossible to predict which individuals will require a longer MICU stay at the time of admission; however, the salient benefits in morbidity demonstrated by this study would suggest that all individuals admitted to the MICU should receive therapy to achieve euglycemia.

One of the potential hurdles to achievement of euglycemia in the critically ill is the labor intensive changes in patient care policies necessary to attain these goals. Particular concern lies in the ability of inpatient care providers to develop and implement successful insulin protocols. Intravenous insulin administration is effective and appropriate in some inpatient populations but arguably administration of insulin subcutaneously is less nursing intensive and a more familiar hyperglycemia treatment option. Could insulin administered subcutaneously, once clinically advised, achieve similar glycemic targets and clinical benefits as reported with the use of intravenous insulin protocols?

Schmeltz and colleagues were able to normalize the aforementioned increase in morbidity and mortality reported among diabetic patients undergoing cardiothoracic surgery to that of the non-diabetic population using a hyperglycemia protocol which consisted of intravenous insulin in the immediate post-operative period followed by a conversion to subcutaneous insulin on average 28 hours after surgery. (12) In a subset of CABG only patients (n = 159), 0% mortality was reported among those with DM and no significant difference in the incidence of DSWI was seen between the DM and non-DM cohorts. These results came despite a higher prevalence of comorbidities traditionally associated with increased cardiovascular risk, such as obesity, hypertension, hyperlipidemia, smoking, and renal insufficiency, in the DM group. Though it is difficult to make comparison across surgical institutions, this group was able to attain glycemic targets using a less labor-intensive insulin regimen and achieve post-operative outcomes similar to those reported using extended intravenous insulin protocols (4, 5).

Why is hyperglycemia so deleterious to the hospitalized patient? And why does insulin have such a palliative effect? Hyperglycemia may accentuate cellular toxicity in the critically ill. Non-insulin dependent cellular glucose uptake may be increased in critical ill-

ness (13). Increased intracellular glucose concentrations lead to an increase in cytotoxic free radical end products of oxidative phosphorylation (14). Hyperglycemia has been associated with polymorphonuclear cell migratory dysfunction (15) and glycation of immunoglobulin leading to a decrease in bactericidal activity (16) and an increase in the risk of infection. Achievement of euglycemia would ameliorate these harmful intracellular scenarios.

Critical illness is associated with the increased release of hormones such as cortisol, epinephrine and growth hormone that are counter-regulatory to insulin action, leading to a state of relative insulin resistance. In turn insulin resistance is associated with lipolysis and hypertriglyceridemia. Reduced insulin action at the cellular level leads to decreased utilization of glycolytic substrates for energy and a greater dependence on free fatty acid metabolism. Intramyocardial accumulation of free fatty acids and their breakdown products has been shown to decrease cardiac contractility (17) and be arrhythmogenic (18), possibly increasing the risk of cardiac injury or death. Indeed after multivariate analysis, an improvement in lipid status was a better predictor of clinical outcome than serum glucose in the Belgian SICU study (19).

Insulin may have salutary properties independent of its known metabolic effects. Insulin administration has been shown to promote vasodilatation (20, 21), decrease pro-inflammatory cytokine production (22, 23) and suppress pro-coagulant factors (24, 25) all putatively beneficial in the treatment of severe illness.

In summary, the growing body of literature mandates the use of insulin as standard of care to achieve strict glycemic targets in the hospitalized population. It is likely that there are multiple mechanisms that account for the clinical benefits seen. In all of the studies in which intensive glycemic management was carried out, the risk of severe hypoglycemia was not increased. The American Diabetes Association and the American College of Endocrinology recommend an inpatient glycemic target of 110 mg/dl with an acceptable glycemic range of 80-180 mg/dl (26). The use of insulin in both the intravenous and subcutaneous routes of administration is safe and effective at reducing hospital morbidity and mortality.

References

1. Umpierrez G, Isaacs S, Barzagan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87: 978-82.
2. Bolk J, van der Ploeg T, Cornel J, et al. Impaired glucose metabolism predicts mortality after a myocardial infarction. *Int J Cardiology* 2001; 79: 207-14.
3. Capes S, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patient: a systematic overview. *Stroke* 2001; 32: 2426-32.
4. Furnary A, Zerr K, Gunkmeier G, et al. Continuous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg* 1999; 67: 352-62.
5. Furnary A, Gao G, Gunkmeier G, et al. Insulin infusion reduces mortality in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003; 125: 1007-21.
6. Gadaleta, D, Risucci, D, Nelson, R, et al. Effects of morbid obesity and diabetes on risk of coronary artery bypass grafting. *Am J Cardiol* 1992; 70; 1613-14.
7. Zerr, K, Furnary, A, Grunkmeire, G, et al. glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg* 1997; 63: 356-61.
8. Edwards F, Grover F, Shroyer A, et al. The Society of Thoracic Surgeons National Cardiac Surgery Database: current risk assessment. *Ann Thorac Surg* 1997; 63: 903-8.
9. Thourani V, Weintraub W, Stein B, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. *Ann Thorac Surg* 1999; 67; 1045-52.
10. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345: 1359-67.
11. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354; 449-61.
12. Schmeltz L, DeSantis A,Thiyagarajan T, et al. Reduction in surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. *Diabetes Care* 2007; 30: 823-8.
13. Van den Berghe G. How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* 2004; 114: 1187-95.
14. Aulak K, Koeck T., Crabb J, et al. Dynamics of protein nitration in cells and mitochondria. *Am J Physiol Heart Circ Physiol* 2004; 286: 1130-8.
15. Rassias A, et al. Insulin infusion improves neutrophil functionin diabetic cardiac surgery patients. *Anesth Analg* 1999; 88: 1011-6.
16. Black C, Hennessey P, Andrassy R. Short term hyperglycemia depresses immunity through non-enzymatic glycosylation of circulating immunoglobulins. *J Trauma* 1990; 30: 830-32.

17. Mjos O. Effects of free fatty acids on myocardial function and oxygen consumption in intact dogs. *J Clin Invest* 1971; 50: 1386-91.
18. Oliver M, Opie L Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. *Lancet* 1994; 343: 155-8.
19. Mesotten D, Swinnen J, Vanderhoydonc F, et al. Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. *J Clin Endocrinol Metab* 2004; 89: 219-26.
20. Grover A, Padginton C, Wilson M, et al. Insulin attenuates norepinephrine-induced venoconstriction. *Hypertension* 1995; 25: 779-84.
21. Tripathy D, Mohanty P, Sandeep D, et al. Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. *Diabetes* 2003; 52: 2882-7.
22. Dandona P, Aljada A, Mohanty P , et al. Insulin inhibits intranuclear nuclear factor kB and stimulates IkB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 2001; 86; 3257-65.
23. Das U. Is Insulin an anti-inflammatory molecule? *Nutrition* 2001; 17: 409-13.
24. Dandona P, Aljada A, Mohanty P, et al. Insulin suppresses plasma concentration of vascular endothelial growth factor. *Diabetes Care* 2003; 26: 3310-14.
25. Chaudhuri A, Janicke D, Wilson M, et al. Anti-inflammatory and profibrinolytic effect of insulin in acute ST-segment-elevation myocardial infarction. *Circulation* 2004; 109: 849-54.
26. Garber, et al American College of Endocrinology and American Diabetes Association Consensus Statement on Inpatient Diabetes and Glycemic Control *Diabetes Care* 2006; 29: 1955-62.

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