Hyperglycemia in-hospital management

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Introduction

Regardless of the etiology of hyperglycemia in hospitalized patients, the finding is an independent risk factor that is strongly associated with adverse outcomes. An estimated 25–35% of all US adult inpatients have hyperglycemia, one third of those do not have a prior diagnosis of diabetes [Levetan *et al.* 1998]. Umpierrez and colleagues presented evidence that unrecognized hyperglycemia in the inpatient setting [Umpierrez *et al.* 2002], even when recognized, did not trigger a treatment plan that was sufficiently altered, in a timely fashion, to improve glycemic levels. Later, Matheny demonstrated that intensification of insulin administration was associated with a decrease in the average daily glucose, while hypoglycemia was uncommon [Matheny *et al.* 2008]. This suggested that increasing the frequency of treatment adjustments could lead to improved glycemic control in hospitalized patients with diabetes.

Trials of intensive insulin management of hyperglycemia to achieve near-normal glycemic levels have shown inconsistent benefits regarding study end points with elevated insulin requirements and frequent iatrogenic hypoglycemia; in particular, severe hypoglycemia is currently regarded the most harmful side effect of interventions in critically ill patients intended to normalize glycemia in the hospital setting [Finfer *et al.* 2009].

Nevertheless, with mounting evidence that supports the notion that rational glycemic control may indeed result in improved clinical outcomes and reduced mortality in hospitalized patients [Clement *et al.* 2004], a Consensus statement from the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA), recommended new targets for glucose levels in hospitalized patients with premeal and random glucose targets of <140 mg/dl (< 7.8 mmol/l) and <180 mg/dl (<10 mmol/l), respectively for non-critically ill patients; and target ranges of 140–180 mg/dl (7.8–10 mmol/l) for critically ill patients [Moghissi *et al.* 2009]. These projections were considered to be '*reasonable, achievable and safe*' in hospitalized patients. However, it is left for future randomized control trials (RCTs) to establish the benefits and risks of these new glycemic goal guidelines.

Hyperglycemia

The precise mechanism(s) by which comorbid hyperglycemia results in increased morbidity and mortality in patients with acute illnesses requiring hospitalization is unknown, but it is likely multifactorial.

Hyperglycemia in the hospital setting is defined as any blood glucose levels greater than 140 mg/dl (>7.8 mmol/l) [American Diabetes Association, 2011; Moghissi *et al.* 2009]. Hyperglycemia, whether stress related, acute, or chronic, has been shown to elicit direct vasoconstrictor effects in nondiabetic renal vessels resulting in endothelial dysfunction. In addition, it induces an exaggerated inflammatory response resulting in deleterious microvascular complications that could contribute to increased morbidity and mortality [Siegelar *et al.* 2010].

Excess intracellular glucose levels also activate oxidative stress through an overproduction of superoxide by the mitochondrial electron-transfer chain, initiating a deleterious metabolic cascade of enhanced polyol activity, increase the formation of advanced glycation end products, activation of protein kinase C and nuclear factor kB. All of these responses are harmful to the health of the endothelium [Monnier *et al.* 2009].

Hyperglycemia at the time of the admission regardless of diabetes status is an independent risk factor for inpatient mortality in trauma and intensive care unit (ICU) patients [Sung *et al.*

2005]. New onset hyperglycemia produces as much damage as long-standing hyperglycemia and should not be overlooked during hospitalization.

In case of hyperglycemia on admission in patients without a diagnosis of diabetes, an HbA1c test can provide a historic perspective of recent prior glycemic levels and help identify long-standing *versus* new hyperglycemia, as well guiding decisions regarding inpatient insulin management.

Interventional studies have linked the reversal of hyperglycemia with insulin therapy to better clinical outcomes in medical and surgical patients, especially in the setting of acute myocardial infarction, cardiac surgical procedures, and critical neurological illness, and is particularly apparent in patients undergoing coronary bypass graft surgery as shown by the reduction in deep wound infection [Furnary *et al.* 2003].

Hypoglycemia

Hypoglycemia is defined as a blood glucose level lower than 70 mg/dl (<~4 mmol/l) with the presence of symptoms, and severe hypoglycemia is defined as a level lower than 40 mg/dl (2.2 mmol/l) [American Diabetes Association, 2011; Moghissi *et al.* 2009].

Prolonged and/or severe hypoglycemia increases the systemic inflammatory response [Dotson *et al.* 2008], induces neuroglycopenia and inhibits the glucocorticoid response to stress [Keller-Wood *et al.* 1983].

Hypoglycemia itself carries a deleterious effect especially in critically ill patients, possibly contributing to cardiac arrhythmias and seizures resulting even in brain damage.

The main question is which of these two events, hyperglycemia or hypoglycemia, is responsible for the increased morbidity and mortality of the hospitalized patient?

Glycemic variability

While normoglycemia is clearly ideal, wide fluctuations in glycemia with extremes of both hyperglycemia and hypoglycemia are common in the hospital setting due to the stress of illness, certain drugs (steroids, antibiotics, etc.), as well as the insulin treatment prescribed. Moreover, the speed of transitions between high and low glycemic values could be very rapid with overcorrection in hyperglycemia or overtreatment for hypoglycemia. This 'rollercoaster effect', seems to be more deleterious than persistent hyperglycemia itself [Kilpatrick *et al.* 2010].

Van den Berghe and colleagues demonstrated that intensive blood glucose management in critically ill surgical patients (target glucose levels of 80–110 mg/dl [4.4–6 mmol/l]) resulted in a 34% reduction in mortality [Van den Berghe *et al.* 2001]. In contrast to these results, the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study showed that increased frequency of hypoglycemia is detrimental in patient outcomes, raising the issue of balance between benefit and risk of these strict glycemic strategies.

A recent study by Monnier and colleagues highlighted the close relationship between oscillating glucose levels with hypoglycemic episodes and increased excretions of isoprostane, a marker of oxidative damage, which could possibly contribute to diabetes-related complications, and represent an independent marker for increased mortality in vulnerable patients [Monnier *et al.* 2006]. Other studies [Ceriello and Ihnat, 2010] have demonstrated evidence of glucose variability contributing to accelerated formation of free radicals. In animal models [Azuma *et al.* 2003], the oxidative stress, specifically increased superoxide production at the mitochondrial level, has been suggested as the key link between hyperglycemia and diabetes complications. Fluctuations in blood glucose concentrations enhance the accelerated macrophage adhesion to endothelial cells and the formation of fibrotic arteriosclerotic lesions produced by hyperglycemia. Reduction of glucose 'swings', on the other hand, was associated with decreased monocyte–endothelial adhesion [Piconi *et al.* 2006].

The available evidence would suggest interventions to correct inpatient hyperglycemia should be directed at reducing blood glucose instability, thus potentially mitigating vascular injury and improving clinical outcomes. Various measures of glucose variability have been proposed; the most recognized is the mean amplitude of glycemic excursion (MAGE) suggested in 1970 [Service *et al.* 1970]. More recently, continuous glucose monitoring (CGM) has become

widespread and offers the opportunity of more complete assessment of glucose fluctuation. Clearly more evidence is needed with RCTs evaluating glucose stability impact on hospital outcomes.

Hospital teams

Educating personnel about appropriate inpatient glycemic management practices and implementing reliable and reproducible measures of glycemic levels with standardized insulin protocols should go a long way towards ensuring greater patient safety and thus decrease morbidity and mortality associated with hyperglycemia. There is a need for the creation of hospital teams responsible for these educational programs with clear guidelines in insulin management for general practitioners and established criteria for considering diabetes specialist consultation [Newton, 2006].

The hyperglycemia team should be a hospital-based group in charge of the coordination of a multidisciplinary effort comprising nursing administration, pharmacy, and nutrition services under physician leadership. Its primary goal should be resource optimization directed to overcome barriers in hyperglycemia management and the prevention of harmful hypoglycemia events.

The identification and documentation of many of the hyperglycemia events occurring in the hospital is still not well established in most hospitals. Optimal glycemic control thus remains a challenge among providers of care in the hospital environment. Practitioners are often aware of diabetes at admission, but the problem is hyperglycemia is often overlooked during hospitalization.

The low rate of documentation and the lack of appropriate therapeutic changes in the hospital setting suggest the need for interventions to improve provider awareness to enhance inpatient diabetes care [Knecht *et al*. 2006]. Frequent glucose monitoring in hospitalized patients is crucial and results must be easily available to health care providers in order to determine proper insulin management. Physiological protocols using basal insulin, correction or supplementation insulin, and insulin coverage for nutrition can assist in achieving proposed glycemic goals in a short period of time after admission without hypoglycemia events [Umpierrez *et al*. 2007].

Other agents used in the outpatient setting may not be appropriate for the hospitalized patient population. Sulfonylureas, for example, tend to have long half-lives and could produce severe and prolonged hypoglycemia episodes when oral nutritional intake is reduced or discontinued. Metformin should be held at hospital admission to prevent adverse accumulation of drug such as can occur with renal impairment in patients with dehydration or exposed to iodine contrast studies during hospital stay.

Best practice efforts start with preprinted friendly order sets and insulin protocols with the elimination of improper abbreviations and notation. These orders should encourage scheduled insulin therapy as a key intervention in the hospitalized patient. They need to promote the use of appropriate basal insulin as well as supplemental scales individualized based on perceived insulin sensitivity. Basal/bolus insulin therapy has been demonstrated in the RABBIT 2 study to be safe in the hospital setting and effective to obtain in a short period of time the target glycemic goals with minimal hypoglycemia [Umpierrez *et al*. 2007].

Safe glycemic management of hospitalized patients with different nutritional requirements is complicated due to variability in the type and duration of nutrition delivery sometimes with unexpected discontinuation, increasing the risk of hypoglycemia. Avoiding long-acting basal insulin agents, in favor of more flexible short-acting insulin preparations to cover nutritional requirements, can mitigate the risk of hypoglycemia if nutrition is interrupted.

Treatment of hypoglycemia in the inpatient setting should be reinforced with preprinted, nurse-directed hypoglycemic treatment protocols to direct immediate response and alert the treating physician to the potential need for treatment adjustment [Magee, 2007].

Coordination of nutrition tray delivery times with prandial insulin administration, as well as documentation and awareness of the status of the patient NPO (nothing by mouth) can reduce the risk of hypoglycemia. These tools must not merely exist; they must be widely disseminated and used.

Special nurse education effort is necessary, recognizing their critical role in patient care.

It is necessary to increase the knowledge, understanding, and skills adherence to insulin order protocols to ensure patient care improves. Computer-based learning modules for medical and nursing staff should be available on a per-need basis allowing training of new staff members or retraining of existing professionals.

Finally, establishing measures for clinical performance is vital to the successful implementation of a targeted glycemic control initiative. The collection and analysis of results are needed to identify opportunities for improvement. It is important to note that these initiatives are not likely to be successful if there is grass roots resistance among front-line caregivers.

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References

American Diabetes Association (2011) Standards of medical care. *Diabetes Care* 34 Supplement 1; S11–S61.

Azuma, K. *et al.* (2003) A new en face method is useful to quantitate endothelial damage in vivo. *Biochem Byophys Res Commun* 309: 384–390.

Ceriello, A. and Ihnat, M. (2010) "Glycaemic variability": a new therapeutic challenge in diabetes and the critical care setting. *Diabetes Med* 27: 862–867.

Clement, S., Braithwaite, S.S., Magee, M.F., Ahmann, A., Smith, E.P., Schafer, R.G. *et al.* (2004) Management of diabetes and hyperglycemia in Hospitals. *Diabetes Care* 27: 553–591.

Dotson, S., Freeman, R., Failing, H.J. and Adler, G.K. (2008) Hypoglycemia increases serum IL-6 levels in healthy men and women. *Diabetes Care* 31: 1222–1223.

Finfer, S. *et al.* (2009) NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 360: 1283–1297.

Furnary, A.P. *et al.* (2003) Continuous intravenous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 125: 1007–1021.

Keller-Wood, M.E. *et al.* (1983) Inhibition of the adreno-corticotropin and corticoid responses in hypoglycemia after prior stress. *Endocrinology* 113: 491–496.

Kilpatrick, E.S., Rigby, A.S. and Atkin, S.L. (2010) Glucose variability and diabetes complication risk: we need to know the answer. *Diabetic Med* 27: 868–871.

Knecht, L.A., Gauthier, S.M., Castro, J.C., Schmidt, R.E., Whitaker, M.D., Zimmerman, R.S. *et al.* (2006) Diabetes care in the hospital: is there clinical inertia? *J Hosp Med* 1: 151–160.

Levetan, C.S. *et al.* (1998) Unrecognized diabetes among hospitalized patients. *Diabetes Care* 21: 246–249.

Magee, M. (2007) Hospital protocols for targeted glycemic control: Development, implementation and models for cost justification. *Am J Health-Syst Pharm* 64(Suppl. 6): S15–S20.

Matheny, M.E. *et al.* (2008) Treatment intensification and blood glucose control among hospitalized diabetic patients. *J Gen Inter Med* 23: 184–189.

Moghissi, E.S., Korytkowski, M.T., DiNardo, M., Einhorn, D., Hellman, R., Hirsch, I.B. *et al.* (2009) AACE and ADA consensus statement on inpatient glycemic control. *Diabetes Care* 32; 1119–1131.

Monnier, L., Colette, C. and Owens, D.R. (2009) Integrating glycaemic variability in the glycaemic disorders of type2 diabetes: a move towards a unified glucose tetrad concept. *Diabetes Metab Res Rev* 25: 393–402.

Monnier, L. *et al.* (2006) Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 295: 1681–1687.

Newton, C.A. and Young, S. (2006) Financial implications of glycemic control: results of an inpatient diabetes management program. *Endocrine Practice* 12(Suppl. 3): 43–48.

Piconi, L., Quagliaro, L., Assaloni, R., Da Ros, R., Maier, A., Zuodar, G. *et al.* (2006) Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. *Diabetes Metab Res Rev* 22: 198–203.

Service, F.J., Molnar, G.D., Rosevear, J.W., Ackerman, E., Gatewood, L.C. and Taylor, W.F. (1970) Mean amplitude of glycemic excursions, a measure of diabetes instability. *Diabetes* 19: 644–655.

Siegelar, S., Holleman, F., Hoekstra, J.B. and DeVries, J.H. (2010) Glucose variability; Does it matter? *Endocrine Rev* 31: 171–182.

Sung, J. *et al.* (2005) Admission hyperglycemia is predictive of outcomes in critically ill trauma patients. *J Trauma* 59: 80–83.

Umpierrez, G.E. *et al.* (2002) Hyperglycemia: an independent marker of in-hospital mortality in patient with undiagnosed diabetes. *J Clin Endocrinol Metab* 87: 978–982.

Umpierrez, G.E., Smiley, D., Jacobs, S., Peng, L., Temponi, A., Mulligan, P. *et al.* (2007) Randomized study of basal-bolus insulin therapy in the in-patient management of patients with type2 diabetes (RABBIT 2 trial). *Diabetes Care* 30: 2181–2186.

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M. *et al.* (2001) Intensive insulin therapy in critically ill patients. *N Engl J Med* 345: 1359–1367.