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EDITORIAL

Update on Inpatient Diabetes Management: Call for Action

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Introduction

During the past two decades, there has been increasing interest in determining the impact of inpatient hyperglycemia on clinical outcomes[1–5] and in conducting clinical trials to determine the best treatment regimens for the management of hyperglycemia and diabetes in hospitalized patients.[6,7] The results of these studies have shown that hyperglycemia, in patients with and without diabetes, is associated with increased risk of hospital complications and mortality.[8–10] We have also learned that avoidance of hyperglycemia (glucose level of >180–200 mg/dL) reduces the risk of hospital infections, length of stay, and mortality.[11] In recent years, we have learned that hypoglycemia, as the result of intensive insulin therapy, is associated with increased risk of complications and mortality.[12–14] Based on these results, clinical guidelines are recommending a glucose target between 140 and 180 mg/dL in the intensive care unit (ICU)[15,16] and a glucose target of <140 mg/dL before meals and a random glucose level of <180 mg/dL in non-ICU settings.[17]

There are numerous areas of controversy and unanswered questions regarding inpatient management of hyperglycemia and diabetes to be addressed in future studies. We list a few interrogates in the area of stress hyperglycemia, hospital management of hyperglycemia and diabetes, and the use of continuous glucose monitoring (CGM) in the hospital setting.

Stress hyperglycemia, defined as the development of high glucose values during an acute medical or surgical illness, is reported in 32–38% of community hospitals,[4,18,19] 40–50% of cardiac patients with acute coronary syndromes and heart failure,[20] and in up to 80% of ICU patients after cardiac surgery.[21,22] Several studies have reported a higher in-hospital death rate and complications compared with patients with a known history of diabetes.[1,3,4,23] Beside these important findings, there are many questions regarding stress hyperglycemia—what glucose level should be used to define hyperglycemia during acute illness, what is the pathogenesis and who is at risk of developing stress hyperglycemia, if the association between stress hyperglycemia and poor clinical outcomes is causal or merely an underlying paraphenomena of the severity of illness, and what is the best treatment regimen and glucose level that should be targeted in patients with stress hyperglycemia. Finally, what are the long-term ramifications in terms of future diabetes risk?

The results from observational and randomized controlled trials indicate that correction of hyperglycemia, in patients with and without diabetes, is associated with reduced risk of hospital complications and mortality.[24–26] In the 1990s clinical trials of insulin–glucose infusion in diabetes patients with acute myocardial infarction or after coronary artery bypass surgery reported that a blood glucose level reduction from approximately 250 mg/dL to approximately 170 mg/dL resulted in a significant reduction in mortality and hospital complications.[24,25] With one exception,[22] several recent clinical trials in critically ill patients have failed to demonstrate improvement in mortality with the use of intensive insulin treatment (target glucose level of <110 mg/dL).[6,27] It is not known, however, if a target glucose level between 110 and 140 mg/dL may result in a lower rate of complications compared with the higher recommended target of 140–180 mg/dL. This important clinical question needs to be answered in large randomized control trials. Furthermore, the appropriate target may differ among patient populations, such as surgical versus medical patients.

In general medical and surgical patients, despite numerous observational studies reporting an increased rate of complications and mortality, only one randomized study has been conducted to determine if improved glucose control reduces the rate of infections and hospital complications in general surgery patients.[28] Today no large studies have been conducted to determine if improved control in non-ICU patients may result in reduced morbidity and mortality in general medicine patients. In addition, clinical trials aiming to determine if a target glucose level of <140 mg/dL is better than a more conservative target of <180 mg/dL must be conducted.

Current clinical guidelines recommend the use of intravenous insulin in most hospitalized critically ill patients and subcutaneous basal bolus insulin in most patients outside of the ICU.[14–16] In general, it is advised that most non-insulin therapies be discontinued at hospital admission. However, this can encourage the ineffective use of sliding-scale monotherapy,

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may disrupt glucose control, and may complicate the discharge process. Therefore, an investigation of other strategies is of interest.

A preliminary clinical trial with the use of sitagliptin in general medicine and surgery patients recently reported that the use of dipeptidyl peptide-4 inhibitors may be safe and efficacious in diabetes patients with mild to moderate hyperglycemia.[29] Two large multicenter studies in general medicine patients are currently investigating the safety and efficacy of dipeptidyl peptidase-4 inhibitors in non-ICU settings. The sitagliptin inpatient trial (NCT 01845831) will compare the combination of sitagliptin plus low-dose basal insulin versus a standard basal bolus regimen in medicine and surgery patients. The linagliptin surgery trial (NCT 02004366) will compare the use of linagliptin once daily plus correction doses of rapid-acting insulin analogs versus basal bolus insulin therapy in general non-cardiac surgery patients. Dipeptidyl peptidase-4 inhibitors are safe in the hospital,[29] but the results of these trials are needed to determine the efficacy of these agents in the inpatient setting and appropriate candidates for therapy.

Other oral agents are commonly used in the hospital; however, their use could be associated with increased risk of complications such as worsening heart failure with the use of thiazolidinediones, hypoglycemia with insulin secretagogues, hypotension and urinary tract infections with sodium–glucose cotransporter 2 inhibitors, and lactic acidosis with metformin therapy.[30–32] Glucagon-like peptide-1 receptor agonists have received increasing attention as effective agents that do not cause hypoglycemia, but their use may be limited by gastrointestinal side effects.[33]

Effective treatment algorithms are needed to guide diabetes care at hospital discharge in general medicine and surgery patients with type 2 diabetes. There is extensive evidence of clinical inertia, defined as failure to initiate or intensify therapy when it is clinically indicated, in the inpatient management and at the time of hospital discharge.[34,35] A recent pilot, prospective, multicenter clinical trial reported that admission levels of hemoglobin A1c (HbA1c) are helpful, not only in assessing glycemic control prior to admission but also in tailoring the treatment regimen at the time of hospital discharge.[36] In this study, patients admitted with a HbA1c level of <7% were discharged on the same pre-admission diabetes therapy (oral agents or insulin), those with an HbA1c level between 7% and 9% were discharged on the combination of oral agents plus half of the inpatient basal insulin dose, and patients with an HbA1c level >9% were discharged on the combination of oral agents and 80% of the inpatient basal insulin dose or on a basal bolus insulin regimen. In that study, the HbA1c level in the entire cohort was reduced after 12 weeks of discharge by 0.1%, 0.8%, and 3.2% in patients with an HbA1c level of <7%, 7–9%, and >9%, respectively. Additional studies with longer duration of follow-up are needed to determine the best treatment regimens for managing patients with hyperglycemia and diabetes after hospital discharge. Additional studies are needed to determine the role of diabetes education and of processes of care at discharge, such as medication reconciliation, identification and case management of patients at high risk for re-admission, communication of discharge regimens to patients and providers, and hospital follow-up.

The third large area that requires attention is the need for improved point-of-care meters and role of new CGM devices (intravenous, subcutaneous) in critical care and noncritical care units. Bedside capillary point-of-care testing is currently recommended as the preferred method for glucose monitoring and to guide glycemic management of individual patients in the hospital setting.[37] The accuracy of most hand-held glucose meters, however, is far from optimal, with a variance of up to 20% for meter measurements compared with the true blood glucose level.[38–43] This has major implications for the capacity to implement tighter glucose control strategies. The results of small, mostly nonrandomized studies are promising, indicating benefits of using real-time CGM in the hospital in detecting hypoglycemia in a more timely fashion compared with point-of-care testing. CGM may also reduce nursing workload and hospital costs.[42] However, it is not known if the use of CGM over the short course of a routine hospitalization will improve clinical outcomes.

This editorial is a call to action inviting clinical researchers to improve the care of millions of inpatients with hyperglycemia and diabetes to seek solid evidence in well-designed clinical trials. We hope that the answer to the numerous clinical questions highlighted in this editorial will improve the care of patients with diabetes admitted to the hospital.

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References

1. Kwon S, Thompson R, Dellinger P, et al.: Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. Ann Surg 2013;257:8–14.
2. Kosiborod M, Inzucchi SE, Krumholz HM, et al.: Glucose normalization and outcomes in patients with acute myocardial infarction. Arch Intern Med 2009;169:438–446.
3. Falciglia M, Freyberg RW, Almenoff PL, et al.: Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 2009;37: 3001–3009.
4. Umpierrez GE, Isaacs SD, Bazargan N, et al.: Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978–982.

5. Draznin B, Gilden J, Golden SH, et al.: Pathways to quality inpatient management of hyperglycemia and diabetes: a call to action. Diabetes Care 2013;36:1807–1814.
6. Finfer S, Chittock DR, Su SY, et al.: Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297.
7. Griesdale DE, de Souza RJ, van Dam RM, et al.: Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180:821–827.
8. Krinsley JS: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003;78:1471–1478.
9. Egi M, Bellomo R, Stachowski E, et al.: The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. Crit Care Med 2011;39:314–321.
10. Korytkowski MT, Salata RJ, Koerbel GL, et al.: Insulin therapy and glycemic control in hospitalized patients with diabetes during enteral nutrition therapy: a randomized controlled clinical trial. Diabetes Care 2009;32:594–596.
11. Murad MH, Coburn JA, Coto-Yglesias F, et al.: Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:49–58.
12. Finfer S, Liu B, Chittock DR, et al.: Hypoglycemia and risk of death in critically ill patients. N Engl J Med 2012;367:1108–1118.
13. Krinsley JS, Grover A: Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007;35:2262–2267.
14. Kosiborod M, Inzucchi SE, Goyal A, et al.: Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA 2009;301:1556–1564.
15. Moghissi ES, Korytkowski MT, DiNardo M, et al.: American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract 2009;15:353–369.
16. Jacobi J, Bircher N, Krinsley J, et al.: Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 2012;40:3251–3276.
17. Umpierrez GE, Hellman R, Korytkowski MT, et al.: Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2012;97:16–38.
18. Cook CB, Kongable GL, Potter DJ, et al.: Inpatient glucose control: a glycemic survey of 126 U.S. hospitals. J Hosp Med 2009;4:E7–E14.
19. Levetan CS, Passaro M, Jablonski K, et al.: Unrecognized diabetes among hospitalized patients. Diabetes Care 1998;21:246–249.
20. Kosiborod M, Inzucchi SE, Spertus JA, et al.: Elevated admission glucose and mortality in elderly patients hospitalized with heart failure. Circulation 2009;119:1899–1907.
21. Schmeltz LR, DeSantis AJ, Thiyagarajan V, et al.: Reduction of surgical mortality and morbidity in diabetic patients undergoing cardiac surgery with a combined intravenous and subcutaneous insulin glucose management strategy. Diabetes Care 2007;30:823–828.
22. van den Berghe G, Wouters P, Weekers F, et al.: Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359–1367.
23. Kotagal M, Symons RG, Hirsch IB, et al.: Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 2015;261:97–103.
24. Malmberg K, Ryden L, Efendic S, et al.: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65.
25. Furnary AP, Gao G, Grunkemeier GL, et al.: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125:1007–1021.
26. Lazar HL, Chipkin SR, Fitzgerald CA, et al.: Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 2004;109:1497–1502.
27. De La Rosa Gdel C, Donado JH, Restrepo AH, et al.: Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. Crit Care 2008;12:R120.
28. Umpierrez GE, Smiley D, Jacobs S, et al.: Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011;34:256–261.
29. Umpierrez GE, Gianchandani R, Smiley D, et al.: Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. Diabetes Care 2013;36:3430–3435.
30. Pasquel FJ, Klein R, Adigweme A, et al.: Metformin-associated lactic acidosis. Am J Med Sci 2013 December 10 [Epub ahead of print].
31. Clement S, Braithwaite SS, Magee MF, et al.: Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004;27:553–597.
32. Smiley D, Umpierrez GE: Management of hyperglycemia in hospitalized patients. Ann N Y Acad Sci 2011;1212:1–11.
33. Schwartz S, DeFronzo RA: Is incretin-based therapy ready for the care of hospitalized patients with type 2 diabetes?: The time has come for GLP-1 receptor agonists! Diabetes Care 2013;36:2107–2111.
34. Griffith ML, Boord JB, Eden SK, et al.: Clinical inertia of discharge planning among patients with poorly controlled diabetes mellitus. J Clin Endocrinol Metab 2012;97:2019–2026.
35. Cook CB, Seifert KM, Hull BP, et al.: Inpatient to outpatient transfer of diabetes care: planning for an effective hospital discharge. Endocr Pract 2009;15:263–269.
36. Umpierrez GE, Reyes D, Smiley D, et al.: Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes. Diabetes Care 2014;37:2934–2939.
37. Klonoff DC, Buckingham B, Christiansen JS, et al.: Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011;96:2968–2979.
38. Gomez AM, Umpierrez GE: Continuous glucose monitoring in insulin-treated patients in non-ICU settings. J Diabetes Sci Technol 2014;8:930–936.
39. Gomez AM, Umpierrez GE, Aschner P, et al.: Comparison of inpatient glycaemic control by continuous glucose

monitoring (CGM) and capillary point-of-care (POC) testing in general medicine patients with type 2 diabetes [abstract 57]. Diabetologia 2013;56(Suppl 1):S30.
40. Ryan MT, Savarese VW, Hipszer B, et al.: Continuous glucose monitor shows potential for early hypoglycemia detection in hospitalized patients. Diabetes Technol Ther 2009;11:745–747.
41. Corstjens AM, Ligtenberg JJ, van der Horst IC, et al.: Accuracy and feasibility of point-of-care and continuous blood glucose analysis in critically ill ICU patients. Crit Care 2006;10:R135.
42. Scott MG, Bruns DE, Boyd JC, et al.: Tight glucose control in the intensive care unit: are glucose meters up to the task? Clin Chem 2009;55:18–20.
43. Yamashita K, Okabayashi T, Yokoyama T, et al.: Accuracy and reliability of continuous blood glucose monitor in post-surgical patients. Acta Anaesth Scand 2009;53: 66–71.
42. Boom DT, Sechterberger MK, Rijkenberg S, et al.: Insulin treatment guided by subcutaneous continuous glucose monitoring compared to frequent point-of-care measurement in critically ill patients: a randomized controlled trial. Crit Care 2014;18:453.

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