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*TOPIC HIGHLIGHT*

**Kazuhiro Hanazaki, MD, Professor and Chairman,** *Series Editor*

# Relationship between perioperative glycemic control and postoperative infections

Kazuhiro Hanazaki, Hiromichi Maeda, Takehiro Okabayashi

Kazuhiro Hanazaki, Hiromichi Maeda, Takehiro Okabayashi, Department of Surgery, Kochi Medical School, Kochi University, Kohasu-Okocho, Nankoku-City, Kochi 783-8505, Japan
Author contributions: All authors made an equal contribution to this review.
Correspondence to: Kazuhiro Hanazaki, MD, PhD, Professor and Chairman, Department of Surgery, Kochi Medical School, Kochi University, Kohasu-Okocho, Nankoku-City, Kochi 783-8505, Japan. hanazaki@kochi-u.ac.jp
Telephone: +81-88-8802370 Fax: +81-88-8802371
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## Abstract

Perioperative hyperglycemia in critically ill surgery patients increases the risk of postoperative infection (POI), which is a common, and often costly, surgical complication. Hyperglycemia is associated with abnormalities in leukocyte function, including granulocyte adherence, impaired phagocytosis, delayed chemotaxis, and depressed bactericidal capacity. These leukocyte deficiencies are the cause of infection and improve with tight glycemic control, which leads to fewer POIs in critically ill surgical patients. Tight glycemic control, such as intensive insulin therapy, has a risk of hypoglycemia. In addition, the optimal targeted blood glucose range to reduce POI remains unknown. Since 2006, we have investigated tight perioperative blood glucose control using a closed-loop artificial endocrine pancreas system, to reduce POI and to avoid hypoglycemia. In this Topic Highlight, we review the relationship between perioperative glycemic control and POI, including the use of the artificial pancreas.

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**Key words:** Glycemic control; Surgical site infection; Artificial pancreas; Insulin therapy; Glucose toxicity

**Peer reviewers:** Dr. Pietro Invernizzi, Division of Internal Medicine, Department of Medicine, Surgery, Dentistry, San Paolo School of Medicine, University of Milan, Via Di Rudinfi 8, 20142 Milan, Italy; Michael A Zimmerman, MD, Assistant Professor, Division of Transplant Surgery, University of Colorado Health Sciences Center, 1635 N. Ursula St, Po Box 6510, 7th floor, Aurora, Colorado 80045, United States

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## INTRODUCTION

Recent evidence suggests that perioperative hyperglycemia is the main risk factor for the development of postoperative infection (POI)[1,2]. Intensive glucose control[3-7] leads to fewer POIs in critically ill surgical patients[1]. However, tight glycemic control[8-12] such as intensive insulin therapy (IIT)[3-7] has a risk of hypoglycemia. In addition, the optimal target range for blood glucose to reduce POI remains unknown[1,2,13-15]. We recently demonstrated that tight perioperative glycemic control can be achieved by using an artificial endocrine pancreas[16,17] for surgical patients, and that it was a safe and effective treatment for decreasing the incidence of POI, without increasing the risk of hypoglycemia[18-22].

In this Topic Highlight, we review the relationship between perioperative glycemic control and POI, including the use of an artificial pancreas.

## RELATIONSHIP BETWEEN PERIOPERATIVE HYPERGLYCEMIA AND POI

Perioperative hyperglycemia in critically ill surgery patients increases the risk of POI, which is a common, and often costly, surgical complication[1,2,18-22]. It is well known that diabetic patients are at higher risk of postoperative complications, including POI, than non-diabetic surgery patients. Indeed, hyperglycemia correlates positively with POI in diabetic surgical patients[23] and with a poor prognosis following stroke or head injury[24,25]. POI is exacerbated by perioperative hyperglycemia in critically ill surgery patients[1].

Strict glycemic control decreases the risk of infection

and improves other outcomes for trauma, cardiac, and critically ill non-diabetic surgery patients. Ramos *et al*[1] associated postoperative hyperglycemia with an increased risk of 30 d postoperative infectious complications and a longer hospital stay, independent of diabetic status. On the basis of these findings, they recommended evaluation of the possible benefits of postoperative glycemic control in general surgical patients[1].

Hyperglycemia is also associated with a sustained decrease in polymorphonuclear leukocyte function[26]. Abnormalities in leukocyte function[27] have been identified that are caused by the hyperglycemic state. These include abnormalities in granulocyte adherence[28], impaired phagocytosis[29], delayed chemotaxis[30], and depressed bactericidal capacity[29,31]. The degree of hyperglycemia that has been shown to impair phagocytic function is as low as 200 mg/dL[32]. These leukocyte deficiencies appear to improve with tight glycemic control[33]. Together with the demonstrated role of perioperative hyperglycemia in POI, it is clear that tight glycemic control should improve the clinical outcome for all surgical patients.

Insulin displays a potent and acute anti-inflammatory effect by inhibiting the tissue factor, plasminogen activator inhibitor-1[34], and the intranuclear nuclear factor κB (NF κB)[35]. Insulin plays a vital role, not only in blood glucose control, but also as an anti-inflammatory and anti-oxidant agent. Insulin suppresses the proinflammatory effects of NF κB, activator protein 1, early growth response 1, and high mobility group box 1[34-36], as well as inhibiting nicotinamide hypoxanthine dinucleotide oxidase action to reduce reactive oxygen species production[34,35].

IIT has been reported to reduce infection rates after neurosurgery; therefore, this approach might be an appropriate blood glucose control method to prevent POI[37]. However, clinical evidence is still needed to confirm the efficacy of IIT for strict blood glucose control in preventing POI. Although improved control of blood glucose fluxes have high potential to improve survival and decrease morbidity in surgical patients, the association between perioperative blood glucose range and the incidence of POI remains unclear in the majority of surgical patients due to lack of evidence. Further studies, including prospective randomized controlled trials, are necessary to clarify this issue.

## THE OPTIMAL TARGET RANGE FOR BLOOD GLUCOSE TO PREVENT POI IN SURGICAL PATIENTS

Good long-term glycemic control is strongly associated with significantly fewer POIs in diverse surgical populations[38]. Zerr *et al*[39] reported that elevated blood glucose levels of more than 200 mg/dL in diabetic patients are associated with a higher incidence of deep sternal wound infection. Use of perioperative glycemic control in the range of 150-200 mg/dL significantly reduced POI in diabetic patients undergoing open heart surgery[40].

Van den Berghe *et al*[3] demonstrated that tight glycemic control (IIT) to maintain blood glucose levels in the target range of 80-110 mg/dL improved morbidity and mortality in the surgical intensive care unit (ICU). However, a recent large study by NICE-SUGAR Study Investigators[15] completely denied the effectiveness of IIT shown by Van den Berghe *et al*[3]. Contrary to Van den Berghe's first trial[3], IIT increased mortality among adults in the ICU and a blood glucose target less than 180 mg/dL (most frequent blood glucose value of 142 mg/dL) resulted in lower mortality than did a target of 81-108 mg/dL (most frequent blood glucose value of 107 mg/dL)[15]. Recent meta-analysis[41] including NICE-SUGAR[15], concluded that IIT significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients; however, this therapy might be beneficial to patients admitted to a surgical ICU. Some patients might benefit from IIT, although the characteristics of such patients remain to be clearly defined, as does the effect of different blood glucose algorithms, the method of measuring blood glucose, and the influence of nutritional strategies[41]. Unfortunately, however, the optimal targeted blood glucose range to prevent POI remains unclear, especially in the intraoperative targeted blood glucose zone. IIT is also a risk factor for hypoglycemia ($\leqslant$ 40 mg/dL)[3,4,12-15], which is linked to serious neurological events. Hypoglycemia is the major potential harm of tight glucose control. Tight glycemic control without hypoglycemia will be required in the future.

## TIGHT PERIOPERATIVE GLYCEMIC CONTROL USING A CLOSED-LOOP ARTIFICIAL ENDOCRINE PANCREAS SYSTEM

Since 2006, we have been developing a closed-loop artificial pancreas system[16-20] (STG-22, Nikkiso Co. Ltd., Tokyo) to achieve perioperative glycemic control and prevent POI in general surgery, without the risk of hypoglycemia associated with tight glycemic control.

Firstly, we confirmed that the STG-22[21,22] could reliably and accurately measure blood glucose concentration similarly to the ABL 800FLEX machine (Radiometer Medical Aps, Br0nsh0j, Denmark) recommended by the National Committee for Clinical Laboratory[21,22]. This closed-loop glycemic control system maintained stable blood concentrations by the automatic infusion of regular insulin and/or glucose into the circulation[18].

Secondly, we performed two prospective randomized clinical trials and found that tight perioperative glycemic control using a closed-loop artificial pancreas system (STG-22, Nikkiso Co. Ltd., Tokyo) decreased surgical site infection (SSI) in patients who underwent pancreatectomy[19] or hepatectomy[20]. In our reports, perioperative blood glucose levels were continuously monitored using an artificial endocrine pancreas[16-20] and glucose levels were controlled using either the sliding scale method[42] (SS group: targeted blood glucose zone

of 150-200 mg/dL) or the artificial pancreas (AP group: targeted blood glucose zone of 80-110 mg/dL). In our study of patients who had undergone a pancreatectomy, the AP group, maintained near-normal glycemia, whereas the blood glucose levels of the SS group plateaued at approximately 200 mg/dL between 4 and 6 h after pancreatectomy[19]. In addition, the incidence of SSI in the AP group (0%) was significantly lower than that of the SS group (about 30%). In our study of patients who had undergone a hepatectomy[20], the AP group again maintained near-normal glycemic control and a reduction in the incidence of SSI. As a consequence, the length of stay and cost of hospitalization was reduced. It is worth noting that there were no incidents of hypoglycemia using a closed-loop artificial pancreas system, despite maintaining blood glucose levels similar to those obtained with IIT. Our results support the conclusions of previous reports[1,38-40] that glycemic control could be a simple intervention to decrease the risk of infectious complications resulting from hyperglycemia after surgery.

Thirdly, to date, more than 200 general surgeries (hepatic resection, pancreatic resection, esophageal resection, and emergency operations) have been performed under tight perioperative glycemic control using an artificial pancreas (STG-22) with no incidence of hypoglycemia[20]. To avoid hypoglycemia in tight glycemic control and improve POI in surgery, the closed-loop artificial endocrine pancreas system is an effective and safe means. Furthermore, novel perioperative glycemic control using an artificial pancreas markedly improved the labor burden on nursing staff, and hence reduced concerns about hypoglycemia[43].

Finally, because an ideal comparative study of tight glycemic control should be carried out under conditions without risk of hypoglycemia, blood glucose control using a closed-loop artificial pancreas system might be beneficial for the detection of the optimal target range for blood glucose in surgical patients.

## CONCLUSION

Perioperative hyperglycemia increases the risk of POI. Therefore, perioperative glycemic control in patients undergoing surgery is beneficial to reduce POI. As a closed-loop artificial pancreas system is able to perform tight glycemic control without increasing the risk of hypoglycemia, it might be a safe and useful blood glucose control system in critically ill surgical patients. At present, however, the perioperative optimal target range for blood glucose to reduce POI remains uncertain. Further studies are needed to address this issue.

## REFERENCES


1 **Ramos M**, Khalpey Z, Lipsitz S, Steinberg J, Panizales MT, Zinner M, Rogers SO. Relationship of perioperative hyperglycemia and postoperative infections in patients who undergo general and vascular surgery. *Ann Surg* 2008; **248**: 585-591

2 **Ambiru S**, Kato A, Kimura F, Shimizu H, Yoshidome H, Otsuka M, Miyazaki M. Poor postoperative blood glucose control increases surgical site infections after surgery for hepato-biliary-pancreatic cancer: a prospective study in a high-volume institute in Japan. *J Hosp Infect* 2008; **68**: 230-233

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 the critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367

4 **Van den Berghe G**, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; **354**: 449-461

5 **Krinsley JS**. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; **79**: 992-1000

6 **Klein D**, Schubert T, Horch RE, Jauch KW, Jeschke MG. Insulin treatment improves hepatic morphology and function through modulation of hepatic signals after severe trauma. *Ann Surg* 2004; **240**: 340-349

7 **McMullin J**, Brozek J, Jaeschke R, Hamielec C, Dhingra V, Rocker G, Freitag A, Gibson J, Cook D. Glycemic control in the ICU: a multicenter survey. *Intensive Care Med* 2004; **30**: 798-803

8 **Kanji S**, Buffie J, Hutton B, Bunting PS, Singh A, McDonald K, Fergusson D, McIntyre LA, Hebert PC. Reliability of point-of-care testing for glucose measurement in critically ill adults. *Crit Care Med* 2005; **33**: 2778-2785

9 **Schultz MJ**, Spronk PE, Moeniralam HS. Tight glycaemic control: a survey of intensive care practice in the Netherlands. *Intensive Care Med* 2006; **32**: 618-619; author reply 620-621

10 **Vriesendorp TM**, DeVries JH, van Santen S, Moeniralam HS, de Jonge E, Roos YB, Schultz MJ, Rosendaal FR, Hoekstra JB. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med* 2006; **34**: 2714-2718

11 **Krinsley JS**, Jones RL. Cost analysis of intensive glycemic control in critically ill adult patients. *Chest* 2006; **129**: 644-650

12 **Mitchell I**, Finfer S, Bellomo R, Higlett T. Management of blood glucose in the critically ill in Australia and New Zealand: a practice survey and inception cohort study. *Intensive Care Med* 2006; **32**: 867-874

13 **Brunkhorst FM**, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; **358**: 125-139

14 **Wiener RS**, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008; **300**: 933-944

15 **Finfer S**, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283-1297

16 **Hanazaki K**, Nosé Y, Brunicardi FC. Artificial endocrine pancreas. *J Am Coll Surg* 2001; **193**: 310-322

17 **Kono T**, Hanazaki K, Yazawa K, Ashizawa S, Fisher WE, Wang XP, Nosé Y, Brunicardi FC. Pancreatic polypeptide administration reduces insulin requirements of artificial pancreas in pancreatectomized dogs. *Artif Organs* 2005; **29**: 83-87

18 **Okabayashi T**, Hnazaki K, Nishimori I, Sugimoto T, Maeda H, Yatabe T, Dabanaka K, Kobayashi M, Yamashita K. Continuous post-operative blood glucose monitoring and control using a closed-loop system in patients undergoing hepatic resection. *Dig Dis Sci* 2008; **53**: 1405-1410

19 **Okabayashi T**, Nishimori I, Yamashita K, Sugimoto T, Maeda H, Yatabe T, Hanazaki K. Continuous postoperative

blood glucose monitoring and control by an artificial pancreas in patients undergoing pancreatic resection: a prospective randomized clinical trial. *Arch Surg* 2009; In press
20 **Hanazaki K**, Okabayashi T, Maeda H. Tight glycemic control using an artificial pancreas to control hyperglycemia decreases surgical site infection in pancreatectomized or hepatectomozied patients. *Ann Surg* 2009; In press
21 **Yamashita K**, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, Manabe M, Hanazaki K. The accuracy of a continuous blood glucose monitor during surgery. *Anesth Analg* 2008; **106**: 160-163, table of contents
22 **Yamashita K**, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, Manabe M, Hanazaki K. Accuracy and reliability of continuous blood glucose monitor in post-surgical patients. *Acta Anaesthesiol Scand* 2009; **53**: 66-71
23 **Fietsam R Jr**, Bassett J, Glover JL. Complications of coronary artery surgery in diabetic patients. *Am Surg* 1991; **57**: 551-557
24 **O'Neill PA**, Davies I, Fullerton KJ, Bennett D. Stress hormone and blood glucose response following acute stroke in the elderly. *Stroke* 1991; **22**: 842-847
25 **Scott JF**, Robinson GM, French JM, O'Connell JE, Alberti KG, Gray CS. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST). *Stroke* 1999; **30**: 793-799
26 **McManus LM**, Bloodworth RC, Prihoda TJ, Blodgett JL, Pinckard RN. Agonist-dependent failure of neutrophil function in diabetes correlates with extent of hyperglycemia. *J Leukoc Biol* 2001; **70**: 395-404
27 **Bagdade JD**, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. *Diabetes* 1974; **23**: 9-15
28 **Bagdade JD**, Stewart M, Walters E. Impaired granulocyte adherence. A reversible defect in host defense in patients with poorly controlled diabetes. *Diabetes* 1978; **27**: 677-681
29 **Sima AA**, O'Neill SJ, Naimark D, Yagihashi S, Klass D. Bacterial phagocytosis and intracellular killing by alveolar macrophages in BB rats. *Diabetes* 1988; **37**: 544-549
30 **Mowat A**, Baum J. Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. *N Engl J Med* 1971; **284**: 621-627
31 **Nolan CM**, Beaty HN, Bagdade JD. Further characterization of the impaired bactericidal function of granulocytes in patients with poorly controlled diabetes. *Diabetes* 1978; **27**: 889-894
32 **MacRury SM**, Gemmell CG, Paterson KR, MacCuish AC. Changes in phagocytic function with glycaemic control in diabetic patients. *J Clin Pathol* 1989; **42**: 1143-1147
33 **McMahon MM**, Bistrian BR. Host defenses and susceptibility to infection in patients with diabetes mellitus. *Infect Dis Clin North Am* 1995; **9**: 1-9
34 **Aljada A**, Ghanim H, Mohanty P, Kapur N, Dandona P. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *J Clin Endocrinol Metab* 2002; **87**: 1419-1422
35 **Dandona P**, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 2001; **86**: 3257-3265
36 **Aljada A**, Ghanim H, Mohanty P, Syed T, Bandyopadhyay A, Dandona P. Glucose intake induces an increase in activator protein 1 and early growth response 1 binding activities, in the expression of tissue factor and matrix metalloproteinase in mononuclear cells, and in plasma tissue factor and matrix metalloproteinase concentrations. *Am J Clin Nutr* 2004; **80**: 51-57
37 **Bilotta F**, Spinelli A, Giovannini F, Doronzio A, Delfini R, Rosa G. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. *J Neurosurg Anesthesiol* 2007; **19**: 156-160
38 **Dronge AS**, Perkal MF, Kancir S, Concato J, Aslan M, Rosenthal RA. Long-term glycemic control and postoperative infectious complications. *Arch Surg* 2006; **141**: 375-380; discussion 380
39 **Zerr KJ**, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Ann Thorac Surg* 1997; **63**: 356-361
40 **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 Thorac Surg* 1999; **67**: 352-360; discussion 360-362
41 **Griesdale DE**, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; **180**: 821-827
42 **Rafoth RJ**. Standardizing sliding scale insulin orders. *Am J Med Qual* 2002; **17**: 175-178
43 **Hanazaki K**, Maeda H, Okabayashi T. Tight perioperative glycemic control using artificial endocrine pancreas. *Surg Today* 2009; In press

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