

**Understanding the Mechanisms of Hyperglycemia for the Inpatient with Diabetes:  
A Review of the Basic Science**

**References and Key Readings**

1. Andreelli F, Jacquier D, Troy S. Molecular aspects of insulin therapy in critically ill patients. *Curr Opin Clin Nutr Metab Care*. 2006;9:124-130.
2. Boden G. Free fatty acids and insulin secretion in humans. *Curr Diab Rep*. 2005;5:167-170.
3. Bonnefont-Rousselot D. Glucose and reactive oxygen species. *Curr Opin Clin Nutr Metab Care*. 2002;5:561-568.
4. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *JAMA*. 2006;295:1707-1708.
5. Ceriello A. Oxidative stress and diabetes-associated complications. *Endocr Pract*. 2006;12 Suppl 1:60-62.
6. Chaudhuri A, Janicke D, Wilson MF, et al. Anti-inflammatory and profibrinolytic effect of insulin in acute ST-segment-elevation myocardial infarction. *Circulation*. 2004;109:849-854.
7. Cheung NW, Wong VW, McLean M, et al. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care*. 2006;29:765-770.
8. Choi KM, Lee KW, Kim SG, et al. Inflammation, insulin resistance, and glucose intolerance in acute myocardial infarction patients without a previous diagnosis of diabetes mellitus. *J Clin Endocrinol Metab*. 2005;90:175-180.
9. Dandona P, Aljada A, Mohanty P, et al. 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.
10. Das UN. Is insulin an antiinflammatory molecule? *Nutrition*. 2001;17:409-413.
11. Devaraj S, Venugopal SK, Singh U, et al. Hyperglycemia induces monocytic release of interleukin-6 via induction of protein kinase c- $\alpha$  and - $\beta$ . *Diabetes*. 2005;54:85-91.
12. Devos P, Chioloro R, Van den Berghe G, et al. Glucose, insulin and myocardial ischaemia. *Curr Opin Clin Nutr Metab Care*. 2006 Mar;9(2):131-139.

13. Egan BM, Greenw EL, and Goodfriend TL. Insulin resistance and cardiovascular disease. *Am J Hyperten.* 2001;14 Suppl 1:S116-S125.
14. Esposito K, Nappo F, Marfella R, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation.* 2002;106:2067-2072.
15. Evans JL, Goldfine ID, Maddux BA, et al. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev.* 2002;23:599-622.
16. Golovchenko I, Goalstone ML, Watson P, et al. Hyperinsulinemia enhances transcriptional activity of nuclear factor-kappaB induced by angiotensin II, hyperglycemia, and advanced glycosylation end products in vascular smooth muscle cells. *Circ Res.* 2000;87:746-752.
17. Hink U, Tsilimingas N, Wendt M, et al. Mechanisms underlying endothelial dysfunction in diabetes mellitus: therapeutic implications. *Treat Endocrinol.* 2003;2(5):293-304.
- 18. Hirsch IB. Effect of insulin therapy on nonglycemic variables during acute illness. *Endocr Pract.* 2004;10 Suppl 2:63-70.**
19. Hofmann MA, Schiekofer S, Kanitz M, et al. Insufficient glycemic control increases nuclear factor-kappa B binding activity in peripheral blood mononuclear cells isolated from patients with type 1 diabetes. *Diabetes Care.* 1998;21:1310-1316.
20. Jouven X, Charles MA, Desnos M, et al. Circulating nonesterified fatty acid level as a predictive risk factor for sudden death in the population. *Circulation.* 2001;104:756-761.
21. Kitabchi AE, Stentz FB, Umpierrez GE. Diabetic ketoacidosis induces in vivo activation of human T-lymphocytes. *Biochem Biophys Res Commun.* 2004;315(2):404-407.
22. Krankel N, Adams V, Linke A, et al. Hyperglycemia reduces survival and impairs function of circulating blood-derived progenitor cells. *Arterioscler Thromb Vasc Biol.* 2005;25:698-703.
23. Kremen J, Dolinkova M, Krajickova J, et al. Increased subcutaneous and epicardial adipose tissue production of proinflammatory cytokines in cardiac surgery patients: possible role in postoperative insulin resistance. *J Clin Endocrinol Metab.* 2006;91:4620-4627.
24. Krogh-Madsen R, Moller K, Dela F, et al. Effect of hyperglycemia and hyperinsulinemia on the response of IL-6, TNF-alpha, and FFAs to low-dose endotoxemia in humans. *Am J Physiol Endocrinol Metab.* 2004;286:E766-E772.
- 25. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest.* 2005;115:2277-2286.**

26. Lindmark S, Buren J, Eriksson JW. Insulin resistance, endocrine function and adipokines in type 2 diabetes patients at different glycaemic levels: potential impact for glucotoxicity in vivo. *Clin Endocrinol (Oxf)*. 2006;65:301-309.
27. Mabley JG, Soriano FG. Role of nitrosative stress and poly(ADP-ribose) polymerase activation in diabetic vascular dysfunction. *Curr Vasc Pharmacol*. 2005;3:247-252.
28. Manzella D, Grella R, Marfella R, et al. Elevated post-prandial free fatty acids are associated with cardiac sympathetic overactivity in Type II diabetic patients. *Diabetologia*. 2002;45:1737-1738.
29. Mesotten D, Swinnen JV, 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;89:219-226.
30. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006;295:1681-1687.
31. Monti LD, Landoni C, Setola E, et al. Myocardial insulin resistance associated with chronic hypertriglyceridemia and increased FFA levels in Type 2 diabetic patients. *Am J Physiol Heart Circ Physiol*. 2004;287:H1225-H1231.
32. Nilsson L, Banfi C, Diczfalusy U, et al. Unsaturated fatty acids increase plasminogen activator inhibitor-1 expression in endothelial cells. *Arterioscler Thromb Vasc Biol*. 1998;18:1679-1685.
33. Pickkers P, Hoedemaekers A, Netea MG, et al. Hypothesis: Normalisation of cytokine dysbalance explains the favourable effects of strict glucose regulation in the critically ill. *Neth J Med*. 2004;62:143-150.
34. Piconi L, Quagliaro L, Da Ros R, et al. Intermittent high glucose enhances ICAM-1, VCAM-1, E-selectin and interleukin-6 expression in human umbilical endothelial cells in culture: the role of poly(ADP-ribose) polymerase. *J Thromb Haemost*. 2004;2:1453-1459.
35. Quagliaro L, Piconi L, Assaloni R, et al. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes*. 2003;52:2795-2804.
36. Risso A, Mercuri F, L. Quagliaro L, et al. Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture. *Am J Physiol Endocrinol Metab*. 2001;281:E924-E930.

37. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues*. 2004;15:45-62.
38. Schalkwijk CG, Stehouwer CD. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin Sci (Lond)*. 2005;109:143-159.
39. Schiekofe S, Andrassy M, Chen J, et al. Acute hyperglycemia causes intracellular formation of CML and activation of ras, p42/44 MAPK, and nuclear factor kappaB in PBMCs. *Diabetes* 2003;52:621-633.
40. Simkova R, Kazdova L, Karasova L, et al. Effect of acute hyperglycaemia on sodium handling and excretion of nitric oxide metabolites, bradykinin, and cGMP in Type 1 diabetes mellitus. *Diabet Med*. 2004;21:968-975.
41. Staehr P, Hother-Nielsen O, Landau BR, et al. Effects of free fatty acids per se on glucose production, gluconeogenesis, and glycogenolysis. *Diabetes*. 2003;52:260-267.
42. Steinberg HO, Tarshoby M, Monestel R, et al. Elevated circulating free fatty acid levels impair endothelium-dependent vasodilation. *J Clin Invest*. 1997;100:1230-1239.
43. Stentz FB, Kitabchi AE. Hyperglycemia-induced activation of human T-lymphocytes with de novo emergence of insulin receptors and generation of reactive oxygen species. *Biochem Biophys Res Commun*. 2005;335:491-495.
- 44. Stentz FB, Umpierrez GE, Cuervo R, et al. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. *Diabetes*. 2004;53:2079-2086.**
45. Sudic D, Razmara M, Forslund M, et al. High glucose levels enhance platelet activation: involvement of multiple mechanisms. *Br J Haematol*. 2006;133:315-322.
- 46. Taylor JH, Beilman GJ. Hyperglycemia in the intensive care unit: no longer just a marker of illness severity. *Surg Infect (Larchmt)*. 2005;6:233-245.**
47. Tripathy D, Mohanty P, Dhindsa S, et al. Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. *Diabetes*. 2003;52:2882-2887.
48. Vaidyula VR, Rao AK, Mozzoli M, et al. Effects of hyperglycemia and hyperinsulinemia on circulating tissue factor procoagulant activity and platelet CD40 ligand. *Diabetes*. 2006;55:202-208.
- 49. Vanhorebeek I, Langouche L, Van den Berghe G. Glycemic and nonglycemic effects of insulin: how do they contribute to a better outcome of critical illness? *Curr Opin Crit Care*. 2005;11:304-311.**

- 50. Worthley MI, Holmes AS, Willoughby SR, et al. The deleterious effects of hyperglycemia on platelet function in diabetic patients with acute coronary syndromes mediation by superoxide production, resolution with intensive insulin administration. *J Am Coll Cardiol.* 2007;49:304-310.**
51. Wright E Jr, Scism-Bacon JL, et al. Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. *Int J Clin Pract.* 2006;60:308-314.
52. Xu B, Ji Y, Yao K, et al. Inhibition of human endothelial cell nitric oxide synthesis by advanced glycation end-products but not glucose: relevance to diabetes. *Clin Sci (Lond).* 2005;109:439-446.