Hyperglycemia Is Associated With Adverse Outcomes in Patients Receiving Total Parenteral Nutrition

N. Wah Cheung, phd[1]
Brett Napier, mbbs[1]
Cathy Zaccaria, rn[2]
John P. Fletcher, md[2]

OBJECTIVE — Hyperglycemia is associated with poor clinical outcomes and mortality in myocardial infarction, stroke, and general hospital patients. However, there are few data regarding the effect of hyperglycemia on outcomes in patients receiving total parenteral nutrition (TPN), a therapy that predisposes patients to hyperglycemia. The aim of this study was to determine whether elevated blood glucose levels are associated with adverse outcomes in patients receiving TPN.

RESEARCH DESIGN AND METHODS — A retrospective analysis was undertaken from the medical records of 111 patients (122 treatment episodes) receiving TPN. All patients had blood drawn daily for the measurement of blood glucose levels. Outcome measures were assessed as a function of mean daily blood glucose levels while receiving TPN.

RESULTS — Increased blood glucose levels were associated with an increased risk of cardiac complications (odds ratio 1.61, 95% CI 1.09–2.37, $P = 0.02$), infection (1.4, 1.08–1.82, $P = 0.01$), systemic sepsis (1.36, 1.00–1.86, $P = 0.05$), acute renal failure (1.47, 1.00–2.17, $P = 0.05$), and death (1.77, 1.23–2.52, $P < 0.01$). When the data were examined by quartiles of blood glucose levels, the mortality of subjects in the highest quartile was 10.9 times (95% CI 2.0–60.5, $P < 0.01$) that of subjects in the lowest quartile, and the risk of developing any complication was 4.3 times higher (1.4–13.1, $P < 0.01$). These effects were independent of age, sex, or prior diabetes status.

CONCLUSIONS — Hyperglycemia is a predictor of poor outcomes in patients receiving TPN. The confirmation of a relation between blood glucose levels and adverse outcomes provides support for tight glycemic control in these patients.

Diabetes Care **28:2367–2371, 2005**

Hyperglycemia is associated with adverse outcomes in critically ill patients. A number of studies have demonstrated a relation between blood glucose levels and mortality after myocardial infarction (1) and stroke (2). Among hospitalized patients in general, those with hyperglycemia have a higher mortality rate than those with normal glucose levels (3). Hyperglycemia has been associated with increased infection rates in patients after cardiothoracic (4–6) or general (7) surgery. Recent randomized controlled trials in intensive care settings (8) and myocardial infarction (9) have also demonstrated that glucose control with insulin therapy can reduce mortality.

One group of patients who should be particularly susceptible to hyperglycemia are those who require total parenteral nutrition (TPN). These patients are often critically ill and are administered preparations with a high glucose content. The combination of these two factors leads to a high frequency of hyperglycemia in a particularly vulnerable population. Central vein catheter infections have been observed to be five times more prevalent in diabetic patients than in the general TPN population (10). However, to date, the potential for hyperglycemia to result in other adverse outcomes in patients receiving TPN has not been systematically examined. The purpose of this study was to determine if hyperglycemia in patients receiving TPN is associated with adverse outcomes and, in particular, with increased mortality.

RESEARCH DESIGN AND METHODS

— The medical records of all patients receiving TPN during the calendar year of 2002 at Westmead Hospital, Sydney, were reviewed. The majority of patients receiving TPN at our hospital have a gastrointestinal indication (abdominal surgery or ileus) or require nutritional support in the context of renal/pancreas or bone marrow transplant. Patients receiving TPN are individually assessed on a daily basis by a specialist clinical pharmacist and a clinical nurse consultant in the Nutrition Support Service. One liter of standard TPN formula includes 8.3 g nitrogen, 50 g L-amino acids, and 250 g glucose, giving 3,980 kJ. TPN is usually commenced at 42 ml/h, with remaining fluid requirements made up from 0.9% saline. Vitamin K, a multivitamin solution (Cernevit; Baxter, Mourepas, France), thiamine, and trace elements are added as required. A fat emulsion of Intralipid (Pharmacia, Freseniusabi, Sweden) might also be commenced. After 24 h, the TPN rate is adjusted according to the patient's needs. A special file with daily clinical and biochemical details recorded on a flow sheet is kept for every patient receiving TPN.

All patients have blood drawn daily for measurement of blood glucose levels. If the blood glucose level is >10 mmol/l, the TPN rate would be reduced by 21 ml/h to a minimum of 42 ml/h. The TPN solution would also be adjusted to provide maximal calories and protein, with a lower glucose content where possible. Hyperglycemic patients would also undergo blood glucose testing every 4 h by finger prick. If the blood glucose level remains >10 mmol/l, the protocol calls for the commencement of an insulin infu-

From the [1]Centre for Diabetes & Endocrinology Research, Westmead Hospital, Westmead, Australia; and the [2]Department of Surgery and Nutrition Support Service, Westmead Hospital, Westmead, Australia.

Address correspondence and reprint requests to Dr. N. Wah Cheung, Centre for Diabetes & Endocrinology Research, Westmead Hospital, Westmead, NSW 2145, Australia. E-mail: wah@westgate.wh.usyd.edu.au.

Received for publication 11 May 2005 and accepted in revised form 26 June 2005.

Abbreviations: TPN, total parenteral nutrition.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Risk of complications in relation to mean daily blood glucose level*

	OR (95% CI)	*P*
Any infection	1.40 (1.08–1.82)	0.01
Septicemia	1.36 (1.00–1.86)	0.05
Acute renal failure	1.47 (1.00–2.17)	0.05
Cardiac complications	1.61 (1.09–2.37)	0.02
Death	1.77 (1.23–2.52)	<0.01
Any complication	1.58 (1.20–2.07)	<0.01

Data determined by logistic regression analysis.

sion, which is continued for the duration of TPN therapy.

For each TPN episode, we recorded the daily blood glucose levels and calculated the mean daily blood glucose levels for the duration of TPN therapy. Outcome measures during TPN were recorded from the medical record. These were the development of any infection, septicemia, a cardiac complication, acute renal failure, or death. Any infection was defined as culture-proven infection while receiving TPN and included wound, drain, catheter, respiratory tract, and urinary tract infections. Septicemia was determined on the basis of blood culture–proven infection. Cardiac complications were defined as myocardial infarction, cardiac arrhythmia, or cardiac arrest documented by electrocardiogram and/or cardiac enzyme evidence. Acute renal failure was defined as the clinical diagnosis of acute renal failure with documented new-onset abnormal renal function while receiving TPN. Death was defined as death occurring during admission, either during the time TPN was received or after TPN treatment was completed. Death during admission rather than during the treatment episode, as with other outcome measures, was chosen because many patients who undergo treatment with TPN die within a period of several days after treatment cessation. The aggregate outcome variable of "any complication" was made on the basis of any of the above complications being present. Outcome measures were assessed as a function of mean daily blood glucose levels while receiving TPN.

In addition to mean daily blood glucose levels, other prognostic variables were examined: previous diabetes status (based on clinical history), insulin infusion therapy, and age. Patients were classified as having diabetes if they had a documented history of diabetes.

Statistical evaluation of univariate relations was performed using simple logistic regression analysis. Multivariate analyses and calculation of adjusted odds ratios (ORs) were conducted with stepwise multiple logistic regression. ANOVA was used to compare groups with normally distributed data. Where there was a nonnormal distribution of data, the Mann-Whitney *U* test was used. $P < 5\%$ was considered significant. Except where stated otherwise, all results are expressed as means ± SD.

RESULTS — In the study, 109 patients (mean age 51.9 ± 18.7 years) received TPN in 122 treatment episodes. Of the 122 treatment episodes, 67 (55%) occurred in men and 33 (27%) occurred in patients with known diabetes. Among the 33 episodes in diabetic patients, 20 patients were being treated with insulin, 5 with oral hypoglycemic agents, and 8 with diet alone. TPN was administered for a primary gastrointestinal indication in 63 episodes, as support for transplantation in 43 episodes, and for other reasons in 16 episodes. The mean duration on TPN was 12.1 ± 20.4 days. The overall mean daily blood glucose level during TPN was 8.0 ± 1.5 mmol/l.

Of the 122 treatment episodes, 51 were affected by one or more complications. With logistic regression analysis, the risk of "any complication" occurring while receiving TPN was found to be increased with an elevated blood glucose level (OR 1.58, 95% CI 1.2–2.07, $P = 0.001$). Therefore, for each 1-mmol/l increase in blood glucose, the risk of any complication increased by a factor of 1.58. Similar increases in risk with higher blood glucose levels were also seen with the other outcome parameters (Table 1).

For each outcome measure, data were also analyzed by dividing the TPN episodes into quartiles by mean daily blood glucose levels (≤6.9, 7.0–7.8, 7.9–9.1, and >9.1 mmol/l). The relative risk of complications was analyzed using blood glucose ≤6.9 mmol/l as the reference category. Compared with those in the lowest quartile of mean daily blood glucose levels, patients in the highest quartile had an OR of 4.3 (95% CI 1.4–13.1, $P = 0.01$) for developing any complication and 10.9 (2.0–60.5, $P < 0.01$) for dying. This association persisted even after adjusting for age, sex, and preexisting diabetes (Table 2).

Having known diabetes did not increase the risk of any of the complication outcomes. In fact, there was an independent negative association between having known diabetes and death (OR 0.18, 95% CI 0.04–0.90, $P = 0.04$), despite a higher mean blood glucose level. However, diabetic patients were on TPN for a lesser duration and had a shorter hospital stay (Table 3).

Table 2—*Risk of complication by blood glucose level quartile after adjusting for age, sex, and presence of preexisting diabetes*

	<6.9 mmol/l	6.9–7.8 mmol/l		7.9–9.1 mmol/l		>9.1 mmol/l	
	(OR)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Any infection	1	1.3 (0.4–4.2)	0.71	2.8 (0.9–8.8)	0.08	3.9 (1.2–12.0)	0.02
Septicemia	1	0.8 (0.2–3.6)	0.73	1.0 (0.2–4.5)	1.0	2.5 (0.7–9.3)	0.17
Acute renal failure	—	1	—	14.8 (1.7–129.1)	0.02	10.9 (1.2–98.1)	0.03
Cardiac complications	1	1.1 (0.1–18.7)	1.0	4.9 (0.5–47.4)	0.17	6.2 (0.7–57.8)	0.11
Death	1	1.0 (0.1–8.0)	1.0	3.4 (0.6–19.9)	0.18	10.9 (2.0–60.5)	<0.01
Any complication	1	1.2 (0.4–3.8)	0.76	4.1 (1.4–12.4)	0.01	4.3 (1.4–13.1)	<0.01

Data determined by stepwise logistic regression analysis. ORs are expressed using blood glucose ≤6.9 mmol/l as a reference category. Because there were no cases of acute renal failure in the lowest quartile of blood glucose, the combined blood glucose groups <6.9 and 6.9–7.8 mmol/l were used as the reference category.

Table 3—*Differences between subjects known to have diabetes and those not known to have diabetes*

	Known diabetes	No diabetes	*P*
TPN episodes	33	89	—
Age (years)	49.5 (38–69)	52 (38–67)	NS
Male sex (%)	48	60	NS
Mean blood glucose (mmol/l)	9.0 (7.8–9.6)	7.4 (6.5–8.7)	0.05
TPN duration (days)	5 (4–7)	7 (5–14)	0.06
Length of hospital stay (days)	23 (10–42)	29 (20–45)	0.04

Data are median (range).

Treatment of hyperglycemia with insulin infusion was associated with an increased rate of "any complication" (OR 2.7, 95% CI 1.3–5.6, $P = 0.01$), but this association did not achieve significance for death (2.4, 0.9–6.4, $P = 0.07$). However, the patients requiring insulin infusion had a higher mean blood glucose level compared with those not requiring insulin (8.9 ± 1.3 vs. 7.5 ± 1.4 mmol/l; $P < 0.01$), suggesting that their insulin infusion was inadequately administered. It is also likely that patients who were treated with insulin had a greater severity of illness, as they had a longer TPN treatment duration (12.9 ± 15.2 vs. 11.3 ± 22.7 days; $P = 0.03$) and longer hospital stay (42.9 ± 34.6 vs. 37.1 ± 46.7 days; $P = 0.03$) than those not requiring insulin infusion. No cases of hypoglycemia were documented with insulin infusion therapy.

CONCLUSIONS — This study demonstrated a strong relation between hyperglycemia and morbidity and mortality in patients receiving TPN. Although an association between hyperglycemia and infection in surgical patients is well established, our study indicates that there are other more serious complications from hyperglycemia. The 11-fold increase in mortality among subjects in the highest quartile of mean daily blood glucose level (>9.1 mmol/l) provides stark evidence of the implications of hyperglycemia in this situation. We also found an association between hyperglycemia and the development of cardiac complications and acute renal failure. Moreover, the increase in risk was present at a much lower glucose level than what might be regarded as frankly diabetic. An increase in total complications appeared to develop after the mean daily blood glucose level rose to >7.8 mmol/l, although for individual complications examined this did not reach statistical significance until higher mean glucose levels were reached. This threshold is in agreement with that in recent studies where relatively modest levels of hyperglycemia have been associated with adverse outcomes in patients with critical illness (11).

A number of studies have demonstrated that severity of hyperglycemia rather than background diabetes is a stronger predictor of adverse outcome for patients with acute myocardial infarction (1) and stroke (2) and for hospitalized patients in general (3). We also found that it was primarily hyperglycemia, rather than diabetes per se, that was associated with adverse outcomes. In fact, in our study, diabetic subjects had a lower risk of death despite a higher mean blood glucose level. The longer duration on TPN and length of hospital stay suggests that the nondiabetic patients were sicker, which may explain their worse outcomes. In many ill nondiabetic patients, the hyperglycemic state indicates an extreme level of illness or "stress hyperglycemia." When these patients returned to good health, their glucose levels may have normalized. Therefore, the same level of hyperglycemia in a nondiabetic patient may indicate a greater severity of illness than for a diabetic person. We acknowledge, however, that because the diagnosis of diabetes in our study was based on clinical history, it is possible that some of the nondiabetic subjects had undiagnosed diabetes. Because this was a retrospective study, there was no organized testing for diabetes among the surviving hyperglycemic nondiabetic subjects after discharge.

Although the elevation in blood glucose may reflect the severity of illness, there is evidence that hyperglycemia in itself is directly harmful. Earlier studies have suggested a threshold glucose level of ~11–12 mmol/l for increased risk of infection. One study that examined postoperative diabetic patients found that in patients with at least one glucose measurement >220 mg/dl (12.2 mmol/l) on the first postoperative day, the infection rate was 2.7 times that observed in diabetic patients with all glucose measurements below this cutoff (7) and the relative risk for serious infection was 5.8 (24.6 vs. 4.2%). Golden et al. (6) found an association between infection rates and blood glucose levels in cardiac surgery patients, with a progressive increase after the mean finger prick capillary blood glucose exceeded 200 mg/dl (11.1 mmol/l). Zerr et al. (5) noted that among patients undergoing open heart operations, there was an overall deep wound infection rate of 1.7 vs. 0.4% for diabetic and nondiabetic patients, respectively. During their study period, the implementation of a protocol of postoperative insulin infusion to maintaining capillary blood glucose <200 mg/dl (11.1 mmol/l) decreased the rate of deep wound infections from 2.4 to 1.5% among the diabetic patients. A further study from this group compared the use of insulin infusion to maintain a blood glucose level <200 mg/dl against historical control subjects where sliding scale subcutaneous insulin was used. This resulted in a reduction in the rate of deep sternal wound infection from 2 to 0.8% (4).

The reasons for the increased risk of complications with hyperglycemia may be multifactorial. Different mechanisms have been identified for the various complications. The primary mechanism responsible for the increased risk of infection with hyperglycemia has been characterized as phagocyte dysfunction. Specific abnormalities that have been demonstrated include impaired leukocyte chemotaxis (12), impaired granulocyte adherence (13), agonist-dependent reduced release of lysosomal enzymes and leukotriene B_4 production (14), reduced superoxide formation (15), and reduced respiratory burst activity (16). In addition, short-term hyperglycemia has been demonstrated to reduce lymphocyte counts (17); glycation of immunoglobulins has also been reported (18).

Diabetes has been associated with altered hemostasis, increased levels of clotting factors, increased platelet activation, and elevated levels of plasminogen activator inhibitor 1 (19). Hyperglycemia also increases inflammatory cytokines and oxidative stress (20–21). The hypercoagulability and inflammatory state are likely to contribute to the increased risk of cardiac complications, and an association between hyperglycemia and adverse outcome after myocardial infarction has been

demonstrated in older studies (1) as well as in the reperfusion era (22). Moreover, there is evidence that hyperglycemia promotes apoptosis in some cell systems and that this may contribute to cardiac myocyte loss (23). Acute hyperglycemia has also been associated with proteolysis (24), which may contribute to the catabolic state of critically ill patients.

It seems logical that control of hyperglycemia during critical illness should result in an improved outcome. In one study of TPN patients, hypocaloric feeding failed to improve glycemic control and did not reduce the infection rate (25). However, in other patient groups with critical illnesses, randomized controlled trials of glucose control with insulin therapy has been shown to improve survival and reduce morbidity. Tight glycemic control with insulin infusion in intensive care patients reduces mortality, sepsis, renal failure, critical-illness polyneuropathy, the need for blood transfusion, the duration of mechanical ventilation, and the length of stay (8). The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (9) showed a survival benefit where hyperglycemic or diabetic patients experiencing myocardial infarction were treated with insulin infusion.

Insulin may improve outcomes through the correction of hyperglycemia, but it also has direct anti-inflammatory properties that may provide additional benefits to critically ill patients (26). In myocardial infarction, insulin infusion reduces C-reactive protein, serum amyloid A, and plasminogen activation inhibitor 1 (27,28), all factors that have been associated with adverse outcomes. Insulin's well-known anabolic effect might also be beneficial in times of nutritional stress, such as in patients requiring TPN. Therefore, we were initially surprised that the treatment of hyperglycemia with insulin infusion in our study was associated with poorer clinical outcome in relation to increased risk of infection, renal, and cardiac complications. However, it is possible that the patients receiving insulin had more severe disease and suboptimal treatment of hyperglycemia, as suggested by these patients' higher mean blood glucose level and longer duration of TPN and hospital stay. It is unlikely that the insulin infusion protocol was strictly adhered to. It therefore remains to be determined whether insulin infusion therapy might be beneficial for patients receiving TPN.

The implications of our findings may be profound. Hyperglycemia is a common occurrence in patients receiving TPN, even in patients without known diabetes (29). Although we do not have conclusive data to show that tight glycemic control will improve outcomes, studies from other critically ill patient groups would suggest this to be the case. Administering insulin infusions to all these patients would place additional demands on the patient, nursing staff, and hospital system. Because the risk of hypoglycemia rises with tight control, frequent capillary blood glucose monitoring would be mandatory. This may be particularly difficult for hematology patients. In an intensive care setting, one-on-one nursing allows the adoption of a tight glycemic control/insulin protocol with relative ease. However, many TPN patients may be outside the intensive care unit, where nurse staffing levels are lower. For patients on prolonged durations of TPN, it might be difficult to maintain the level of nursing care required for an intensive insulin protocol. These factors will need to be considered in the adoption of an intensive insulin protocol. However, the marked association between hyperglycemia and adverse outcomes suggests that tight glucose control is an important aspect of the care of patients receiving TPN.

In conclusion, hyperglycemia is associated with adverse outcomes in patients receiving TPN. This suggests that control of hyperglycemia might be of benefit, but formal clinical trials of insulin infusion therapy for TPN patients with hyperglycemia should be conducted to ascertain the glycemic targets required for optimal clinical outcomes.

Acknowledgments— We thank the clinical nurse consultant staff of the Westmead Nutrition Support Service and Sally Piggot and Christina Heazlewood for their diligent record keeping and support for this study. We also thank Karen Byth, statistician, for her assistance with the statistical analyses.

References

1. Capes SE, Hunt D, Malmberg K, Gerstein HC: Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 355:773–778, 2000
2. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC: Stress hyperglycaemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 32:2426–2432, 2001
3. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE: Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 87:978–982, 2002
4. 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* 67:352–362, 1999
5. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A: Glucose control lowers the risk of wound infection in diabetes after open heart operations. *Ann Thorac Surg* 63:356–361, 1997
6. Golden SH, Kao WHL, Peart-Vigilance C, Brancati FL: Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care* 22:1408–1414, 1999
7. Pomposelli J, Baxter J, Babineau T, Pomfret E, Driscoll D, Forse R, Bistram B: Early postoperative glucose control predicts nosocomial infection rate in diabetic patients: *J Parenter Enteral Nutr* 22:77–81, 1998
8. 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 critically ill patients. *N Engl J Med* 345: 1359–1367, 2001
9. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Welin L: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI): effects on mortality at 1 year. *J Am Coll Cardiol* 26: 57–75, 1995
10. Overett TK, Bistrian BR, Lowry SF, Hopkins BS, Miller D, Blackburn GL: Total parenteral nutrition in patients with insulin-requiring diabetes mellitus: *J Am Coll Nutr* 5:79–89, 1998
11. Van den Berghe G, Wouters P, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P: Outcome of intensive insulin therapy in the critically ill: insulin dose versus glycaemic control. *Crit Care Med* 31:359–366, 2003
12. Mowat A, Baum J: Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. *N Engl J Med* 284: 621–627, 1971
13. Bagdade J, Neilson K, Bulger R: Reversible abnormalities in phagocytic function in poorly controlled diabetic patients. *Am J Med Sci* 263:451–456, 1972
14. McManus LM, Bloodworth RC, Prihoda TJ, Blodgett JL, Pinckard N: Agonist-dependent failure of neutrophil function in diabetes correlates with extent of hyperglycemia. *J Leukoc Biol* 70:395–404, 2001
15. Sato N, Kashima K, Ohtani K, Shimizu H, Mori M: Elpalrestat, an aldose reductase

inhibitor, improves an impaired generation of oxygen-derived free radicals by neutrophils from poorly controlled NIDDM patients. *Diabetes Care* 20:995–998, 1997
16. Nielson C, Hindson D: Inhibition of polymorphonuclear leukocyte respiratory burst by elevated glucose concentration in vitro. *Diabetes* 38:1031–1035, 1989
17. Von Kanel R, Mills P, Dimsdale J: Short-term hyperglycemia induces lymphopenia and lymphocyte subset redistribution. *Life Sci* 69:255–262, 2001
18. Black CT, Hennessey PJ, Andrassy RJ: Short-term hyperglycemia depresses immunity through nonenzymatic glycosylation of circulating immunoglobulin. *J Trauma* 30:830–832, 1990
19. Fattah MA, Shaheen MH, Mahfouz MH: Disturbances of haemostasis in diabetes mellitus. *Dis Markers* 19:251–258, 2003–2004
20. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A: Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans. *Circulation* 106: 2067–2072, 2002
21. Marfella R, Nappo F, De Angelis L, Paolisso G, Tagliamonte MR, Giugliano D: Hemodynamic effects of acute hyperglycemia in type 2 diabetic patients. *Diabetes Care* 23:658–663, 2000
22. Wong V, Ross DL, Park K, Boyages S, Cheung NW: Hyperglycemia following acute myocardial infarction is a predictor of poor cardiac outcomes in the reperfusion era. *Diabetes Res Clin Pract* 64:85–91, 2004
23. Ceriello A, Quagliaro L, D'Amico M, Di Filippo C, Marfella R, Nappo F, Berrino L, Rossi F, Giugliano D: Acute hyperglycemia induces nitrotyrosine formation and apoptosis in perfused heart from rat. *Diabetes* 51:1076–1082, 2002
24. Flakoll PJ, Hill JO, Abumrad NN: Acute hyperglycemia enhances proteolysis in normal man. *Am J Physiol* 265:E715–E721, 1993
25. McCowen KC, Friel C, Sternberg J, Chan S, Forse RA, Burke PA, Bistrian BR: Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications: a randomized clinical trial. *Crit Care Med* 28:3606–3611, 2000
26. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S: 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* 86:3257–3265, 2001
27. Wong V, McLean M, Boyages S, Cheung NW: CRP levels following acute myocardial infarction: effect of insulin infusion and tight glycemic control. *Diabetes Care* 27:2971–2973, 2004
28. Chaudhuri A, Janicke D, Wilson MF, Tripathy D, Garg R, Bandyopadhyay A, Calieri J, Hoffmeyer D, Syed T, Ghanim H, Aljada A, Dandona P: Anti-inflammatory and prothrombolytic effect of insulin in acute ST-segment-elevation myocardial infarction. *Circulation* 109:849–854, 2004
29. Rosmarin DK, Wardlaw GM, Mirtallo J: Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. *Nutr Clin Pract* 11: 151–156, 1996