Research

Open Access

Hyperglycaemic index as a tool to assess glucose control: a retrospective study

Mathijs Vogelzang[1], Iwan CC van der Horst[2] and Maarten WN Nijsten[3]

[1]Department of Surgery, Groningen University Hospital, Groningen, The Netherlands
[2]Department of Internal Medicine, Groningen University Hospital, Groningen, The Netherlands
[3]Department of Surgery, Groningen University Hospital, Groningen, The Netherlands

Corresponding author: Maarten WN Nijsten, m.w.n.nijsten@chir.azg.nl

Received: 30 November 2003

Revisions requested: 22 January 2004

Revisions received: 16 February 2004

Accepted: 25 February 2004

Published: 15 March 2004

Critical Care 2004, **8**:R122-R127 (DOI 10.1186/cc2840)

This article is online at http://ccforum.com/content/8/3/R122

Abstract

Introduction Critically ill patients may benefit from strict glucose control. An objective measure of hyperglycaemia for assessing glucose control in acutely ill patients should reflect the magnitude and duration of hyperglycaemia, should be independent of the number of measurements, and should not be falsely lowered by hypoglycaemic values. The time average of glucose values above the normal range meets these requirements.

Methods A retrospective, single-centre study was performed in a 12-bed surgical intensive care unit. From 1990 through 2001 all patients over 15 years, staying at least 4 days, were included. Admission type, sex, age, Acute Physiology and Chronic Health Evaluation II score and outcome were recorded. The hyperglycaemic index (HGI) was defined as the area under the curve above the upper limit of normal (glucose level 6.0 mmol/l) divided by the total length of stay. HGI, admission glucose, mean morning glucose, mean glucose and maximal glucose were calculated for each patient. The relations between these measures and 30-day mortality were determined.

Results In 1779 patients with a median stay in the intensive care unit of 10 days, the 30-day mortality was 17%. A total of 65,528 glucose values were analyzed. Median HGI was 0.9 mmol/l (interquartile range 0.3–2.1 mmol/l) in survivors versus 1.8 mmol/l (interquartile range 0.7–3.4 mmol/l) in nonsurvivors ($P < 0.001$). The area under the receiver operator characteristic curve was 0.64 for HGI, as compared with 0.61 and 0.62 for mean morning glucose and mean glucose. HGI was the only significant glucose measure in binary logistic regression.

Conclusion HGI exhibited a better relation with outcome than other glucose indices. HGI is a useful measure of glucose control in critically ill patients.

Keywords critically ill patients, hyperglycaemia, normoglycaemia, outcome, prognosis

Introduction

Acute hyperglycaemia is a prognostic factor for mortality in critically ill patients either in the presence or in the absence of diabetes mellitus [1–3]. The benefit of strict glucose control in the intensive care unit (ICU) was demonstrated by the Leuven study [4,5]. Remarkable reduction in morbidity and mortality was achieved in patients who were treated according to a protocol that aimed to achieve normoglycaemia. Thus, the logical aims of glucose control are to eliminate hyperglycaemia as rapidly as possible and to maintain normoglycaemia from then onward, while avoiding hypoglycaemia [6,7]. Although this represents a clear goal for algorithms,

APACHE = Acute Physiology and Chronic Health Evaluation; HGI = hyperglycaemic index; ICU = intensive care unit; IQR = interquartile range; ROC = receiver operator characteristic.

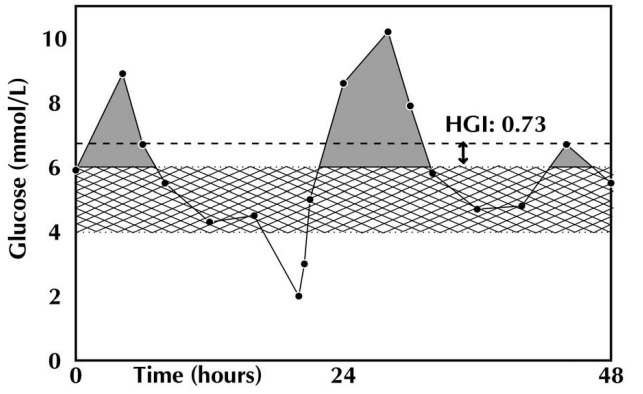
there is no clear way to assess the performance of such algorithms [8].

In ICU patients we do not possess a measure such as glycosylated haemoglobin A_{1c}, which has proven to be an important predictor of long-term complications and to be useful for evaluating the quality of glucose control [9–11]. Therefore, glucose itself must be measured during the ICU stay in order to determine whether hyperglycaemia is present. In studies of acutely ill patients, regular indices of glucose regulation that have been used are admission glucose, maximum glucose, mean morning glucose and mean glucose [5,12–15]. All of these indices have specific drawbacks. Admission glucose, maximum glucose and mean morning glucose are all based on either a single measurement or a subset of measurements, and therefore they are not indicative of overall hyperglycaemia. A single mean glucose that uses all measurements can be strongly biased by unequal time distribution between measurements, as commonly occurs in practice [16–18]. Calculating time-averaged glucose compensates for an unequal time distribution of glucose measurements. However, hypoglycaemic episodes may still lower such an index, thus falsely suggesting normoglycaemia when in reality hyperglycaemia is present.

We hypothesized that an index that takes into account the unequal time distribution of glucose sampling and which is not falsely lowered by low glucose values would be a better index of glucose regulation. We defined the hyperglycaemic index (HGI; Fig. 1) as the area under the glucose curve above the normal range divided by the length of stay.

We evaluated the association of HGI and conventional glucose indices of regulation with mortality in a large group of ICU patients with a prolonged ICU stay.

Figure 1



Calculation of the hyperglycaemic index (HGI). All measured glucose values (black dots) and their corresponding sampling times are taken into account. The average over time is calculated for the area (shaded) under the glucose curve for hyperglycaemic values only. The normal glucose range is indicated by the hatched area, with 6.0 mmol/l (dotted line) the cutoff. HGI is the shaded area divided by the total length of stay. In this case HGI is 0.73 mmol/l, as indicated by the dashed line. Note that normal or hypoglycaemic measurements do not affect HGI, and thus they do not falsely lower this index.

Methods

In a retrospective analysis we included all patients older than 15 years of age admitted to the surgical ICU of our tertiary teaching hospital from 1990 to the end of 2001. Because glucose control appears to be particularly important in patients with prolonged stay in the ICU, we studied only those patients who stayed for 4 days or longer in the ICU [4,5]. Age, sex, admission type and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were obtained from case records and electronic databases of all admitted patients to our hospital. Blood glucose values were obtained from the central laboratory database.

Therapeutic protocol

Patients were fed enterally as soon as possible. Total parenteral nutrition was only given when enteral nutrition failed. Concentrated glucose infusion was not routinely used. Insulin was administrated only to patients with diabetes mellitus or patients with glucose levels exceeding 10.0 mmol/l, and was never administered at rates of infusion greater than 10 IU/hour. Whole blood samples were taken from arterial or central lines and sent to the central laboratory for glucose measurement.

Glucose indices

Admission glucose was defined as the first measurement after ICU admission. Morning glucose was calculated as the arithmetic mean of all measurements done between 06:00 hours and 08:00 hours [4,5]. Mean glucose was calculated as the arithmetic mean of all measurements. Maximum glucose was the highest glucose determined for the entire ICU stay.

To determine the HGI of a patient, all glucose measurements performed during the ICU stay were analyzed. As indicated in Fig. 1, the first step was to interpolate all glucose values. Then, the area between this glucose curve and the upper normal range was calculated. HGI was defined as this area under the curve divided by the total length of stay, thus making HGI independent of length of stay.

Because the Leuven study [4,5] demonstrated improved outcome by lowering glucose levels to under 6.0 mmol/l, we chose this value as our upper range of normal in all tests unless otherwise noted. Since the Leuven study was reported, others have hypothesized that 6.0 mmol/l might not be the best target [19]. Therefore, we also performed an analysis of the performance of HGI at cutoff levels other than 6.0 mmol/l.

As for other measures of glucose regulation, HGI is expressed in millimoles per litre (mmol/l). Thus, a patient in

Table 1

Characteristics for surviving and non-surviving patients and results of univariate analysis of glucose indices

Characteristic	Survivors	Nonsurvivors	*P*
Number of patients (*n* [%])	1484 (83)	295 (17)	
Male sex (*n* [%])	982 (66)	182 (61)	0.18
Age (years; mean ± SD)	53 ± 19	63 ± 16	<0.001
Length of ICU stay (days)	10 (6–20)	10 (6-17)	0.12
Reason for ICU admission (*n* [%])			<0.001
Trauma	372 (25)	30 (10)	
Abdominal surgery	443 (30)	101 (34)	
Liver transplant	219 (15)	38 (13)	
Vascular surgery	164 (11)	51 (17)	
Miscellaneous	286 (19)	75 (25)	
APACHE II score	18 (14–23)	25 (20–28)	<0.001
Number of glucose measurements	20 (10.5–41)	27 (15–45)	<0.001
Mean glucose (mmol/l)	6.9 (6.0–8.4)	7.7 (6.4–9.5)	<0.001
Morning glucose (mmol/l)	6.6 (5.9–7.9)	7.5 (6.2–8.8)	<0.001
Admission glucose (mmol/l)	7.2 (5.8–9.5)	7.9 (6.0–10.9)	0.07
Maximum glucose (mmol/l)	10.2 (8.0–14.2)	12.3 (9.5–16.4)	<0.001
HGI (mmol/l)	0.9 (0.3–2.1)	1.8 (0.7–3.4)	<0.001

Values are expressed as median (interquartile range) unless otherwise stated. APACHE, Acute Physiology and Chronic Health Evaluation; HGI, hyperglycaemic index; ICU, intensive care unit; SD, standard deviation.

whom all glucose values are 8.5 mmol/l will have an HGI of 2.5 mmol/l. A patient who is normoglycaemic, with all measured glucose levels at 6.0 mmol/l or less, will have an HGI of 0.0 mmol/l.

Even though the primary focus of the present study is hyperglycaemia, the importance hypoglycaemia should not be underestimated, and so we determined the incidence of severely hypoglycaemic (glucose <2.7 mmol/l) episodes [6,7].

Statistical analysis

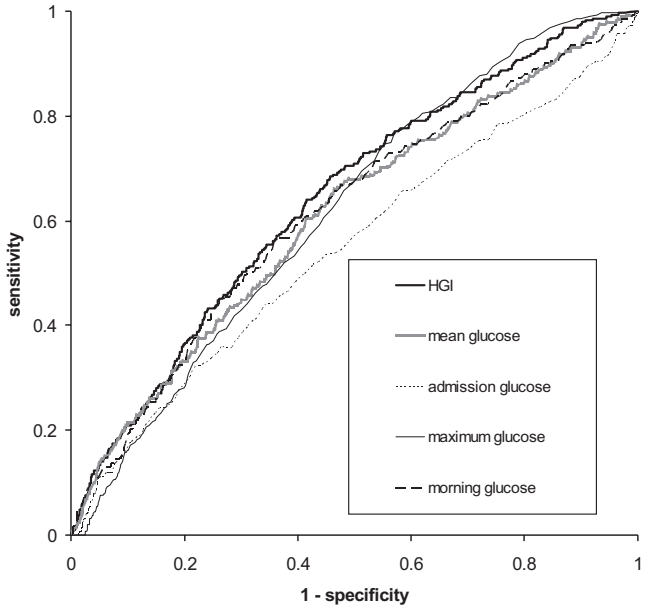
Data were expressed as medians and interquartile ranges (IQRs) unless otherwise indicated. Differences between groups were assessed using the Mann–Whitney U test, and χ^2 analysis was used to test differences between proportions. The primary end-point was 30-day mortality. In univariate analysis we assessed the performance of HGI and other glucose-derived measures in relation to 30-day mortality. Patients were subgrouped into survivors (i.e. patients alive at 30 days) and nonsurvivors. Receiver operator characteristic (ROC) curves were computed. We performed a multivariate binary logistic regression analysis with age, sex, type of admission, APACHE II score and all glucose-derived measures as independent parameters, and 30-day mortality as the dependent parameter. Differences were considered significant for a two-tailed *P* value < 0.05. The Statistical Package for the Social Sciences (version 11.0.1; SPSS Inc, Chicago, IL, USA) was used to conduct statistical analyses.

Results

During the 12-year period of the study, 6885 patients were admitted to the ICU. A total of 1779 patients (26%) stayed for a period of at least 4 days and were included in the present study. The mean age was 55 years (standard deviation 19 years) and 65% were male. Table 1 lists the demographical data and glucose-related measures for survivors and nonsurvivors. APACHE II scores were available for the years 1992–1999; for all other parameters there were no missing data. Abdominal surgery and trauma were the most frequent reasons for ICU admission.

A total of 65,528 glucose measurements were performed in the 1779 included patients, with a median number of glucose measurements of 21 (IQR 11–42). In fewer than 1% of the patients not a single glucose measurement was taken. The median mean glucose concentration of all patients was 7.0 mmol/l (IQR 6.1–8.6 mmol/l), median morning glucose was 6.7 mmol/l (IQR 5.9–8.1 mmol/l), median admission glucose was 7.3 mmol/l (IQR 5.8–9.7 mmol/l), median maximum glucose was 8.7 mmol/l (IQR 6.9–11.6 mmol/l) and median HGI was 1.0 mmol/l (IQR 0.4–2.4 mmol/l). Severe hypoglycaemia (glucose <2.7 mmol/l) occurred in 177

Figure 2



Receiver operator characteristic (ROC) curves for different glucose measures. HGI, hyperglycaemic index.

(6.6%) patients. The median duration of such hypoglycaemic episodes was 1.5 hours (IQR 0.6–3.4 hours).

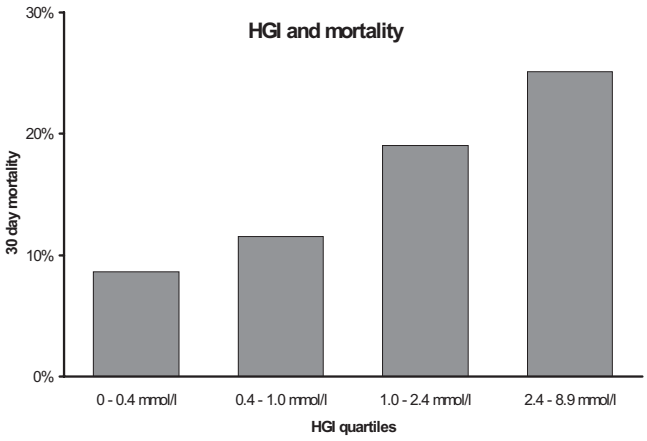
Survivors and nonsurvivors both stayed in the ICU for a median of 10 days (IQR 6–20 days for survivors and 6–17 days for nonsurvivors). A total of 295 patients (17%) died within 30 days after ICU admission.

In the univariate analysis, the median mean glucose level was 7.7 mmol/l in nonsurvivors and 6.8 mmol/l in survivors ($P < 0.001$). Median HGI was 1.8 mmol/l in nonsurvivors, which was twice that in survivors ($P < 0.001$). The ROC curves for all glucose-derived parameters are shown in Fig. 2. HGI had the highest area under the curve (0.64). Fig. 3 shows the relations between HGI quartiles and mortality. Mortality in the lowest HGI quartile was 8.6% as compared with 25.1% in the highest HGI quartile ($P < 0.001$).

Fig. 4 shows the area under the ROC curve for HGI when cutoff values other than 6.0 mmol/l are used.

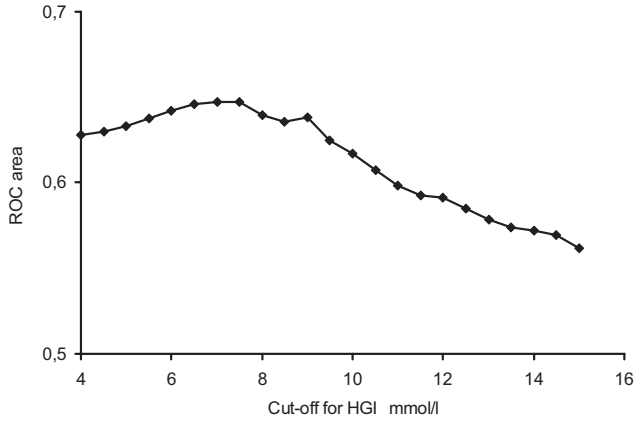
In multivariate analysis with APACHE II score, sex and age, HGI remained the only statistically significant glucose index in the binary logistic model ($P < 0.001$). *P* values for mean glucose, morning glucose, admission glucose and maximum glucose were 0.08, 0.17, 0.43 and 0.49, respectively. With regard to mortality, the results of regression analysis did not differ between the cohort of patients whose APACHE II scores were available and the cohort of patients whose APACHE II scores were not.

Figure 3



Relation between hyperglycaemic index (HGI; divided into quartiles) and mortality. In the highest quartile mortality is nearly three times higher than mortality in the lowest quartile ($P < 0.001$).

Figure 4



Hyperglycaemic index (HGI) for various glucose cutoffs. The cutoff in all other analyses was chosen at 6 mmol/l because it was the upper limit of the intensive treatment group in the Leuven study [4,5]. To see how HGI performs at other cutoff values, the area under the ROC curve was determined for HGI cutoffs from 4.0 to 15.0 mmol/l. In the patients studied, a cutoff between 6.0 and 8.0 mmol/l was associated with the greatest area.

Discussion

Of all measures of hyperglycaemia evaluated, HGI correlated best with 30-day mortality in this population of critically ill patients. This supports our hypothesis that HGI is a useful index for quantifying glucose control. Therefore, assuming that normoglycaemia is the aim, the goal of a glucose–insulin algorithm is clear. The algorithm should obtain an HGI as close to zero as possible.

Both in the univariate analysis and in the multivariate binary logistic regression analysis – in which severity of illness, age

and sex were included – HGI emerged as the best indicator of hyperglycaemia. We assume this reflects the fact that HGI takes better account of the variation in glucose concentrations over time, and avoids the possibility that alternating high and low values will average out to yield a normal value.

The principle of calculating the area under the glucose curve is not new. Brown and Dodek [8] determined the area under the curve above a glucose threshold of 11.5 mmol/l. The area under the curve was used to assess the speed of initial normalization of glucose with an insulin algorithm. Other recent studies have also used glucose thresholds above 10.0 mmol/l to separate good control from poor control [20,21]. However, following the publication of the Leuven study findings [4,5] such thresholds are now considered high, because that study demonstrated improved outcome if normoglycaemia (4.4–6.1 mmol/l) was pursued. Because the vast majority of glucose concentrations in the patients studied here were below 10 mmol/l, crucial information would have been lost if a cutoff of 10.0 mmol/l had been used, as reflected by a decreased area under the ROC curve at a cutoff value for calculation of HGI of 10.0 mmol/l (Fig. 4). The cutoff of 6.0 mmol/l was based on the upper limit of the group of patients with strict regulation in the Leuven study [4,5]. Recently, Finney and colleagues [19] found that glucose regulation below 8.3 mmol/l was not related to a better outcome. This is in accord with our observations; Fig. 4 shows that the optimal cutoff for calculation of HGI lies between 6.0 and 8.0 mmol/l.

Some limitations of the present study should be mentioned. The study is a retrospective, single ICU study that covers a period when strict glucose control was not a major issue. Mortality at 30 days was used as an outcome measure to identify the best glucose index. HGI was the best measure of glucose control, but with a ROC area of 0.64 HGI alone cannot serve as a useful predictor of mortality. The relative contributions of endogenous glucose production, exogenous glucose supply and insulin to HGI and other some other measures could not be identified because our study did not include glucose infusion or (par)enteral feeding, and neither did it include intensive treatment with insulin.

It should be stressed that HGI was designed to quantify hyperglycaemia and not hypoglycaemia. Prevention of hypoglycaemia is a critical requirement of any algorithm for glucose control [5–7]. However, unlike hyperglycaemia, hypoglycaemia is a phenomenon that tends to be relatively short-lived, as our results show, and could be quantified using more straightforward measures such as the lowest glucose concentration.

An elevated admission glucose level is associated with a worse outcome; this has been found by many investigators in various patient categories, and was also found in the present study [1–3,12,13,22–30]. In our study, however, the area under the ROC curves was smaller for conventional measures of glucose control than it was for HGI.

Like other indices of glucose control, HGI is related to outcome. In contrast to admission glucose, however, HGI is also amenable to therapy. HGI involves additional computation (Fig. 1) as compared with more straightforward indices but it does not require more information. Calculating HGI should be feasible in ICUs that possess a patient database management system that can provide automated input for the HGI calculation. The fact that HGI expresses glucose regulation as a single value has methodological advantages. The performance of glucose–insulin algorithms could be compared with HGI, and therefore it is important to measure glucose regularly. A major advantage of HGI is that periods of very frequent sampling (e.g. during hyperglycaemia or hypoglycaemia) are compensated for because HGI is based on an average over time.

HGI must be reassessed in the era of tighter glucose control. Moreover, the value of HGI needs confirmation in other ICUs. Because HGI has not been used by other investigators, it would be of interest to determine how HGI compares with other glucose indices in observational or intervention studies. Existing glucose patient databases could be reanalyzed to determine HGI. The use of glucose measures to predict outcome independently of other parameters such as age and severity scores is interesting but lacks power, as is shown by the area under the ROC. In general, HGI may be more useful for relating hyperglycaemia to organ failure scores such as the Sequential Organ Failure Assessment score [31] or parameters of systemic inflammation.

Continuous measurements of blood glucose will allow us to calculate and compare HGI and the value of other glucose measures to a degree that is not possible with intermittent measurements [32–35]. Currently available glucose sensors are promising but have not yet proven to be sufficiently reliable in critically ill patients and do not allow continuous measurements over prolonged periods [32–35].

Key messages

- Strict glucose control in ICU patients calls for a measure of hyperglycaemia similar to what HbA1c is in diabetic outpatients
- Admission glucose, mean glucose and morning glucose all have drawbacks as indicators of overall hyperglycaemia
- The hyperglycemic index (HGI) was conceived to integrate glucose measurements as they are performed in practice into a single value
- In 1779 surgical ICU patients HGI exhibited a better relation with outcome than other glucose measures
- HGI may be a useful measure of glucose control

Conclusion

In conclusion, HGI quantifies the impact of hyperglycaemia in critically ill patients better than other glucose indices. HGI may thus be a useful measure of glucose control.

Note

On request an annotated computer program with source code that calculates HGI, as well as regular glucose indices, will be provided. The program is written in the multiplatform language Java, and should run on every major platform.

Competing interests

ICC van der Horst is consultant for Medtronic Minimed. M Vogelzang and MWN Nijsten: none declared.

Acknowledgements

Research by ICC van der Horst was supported by a grant of The Netherlands Heart Foundation (99.028).

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* 2000, **355:**773-778.
2. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC: **Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview.** *Stroke* 2001, **32:** 2426-2432.
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* 2002, **87:**978-982.
4. 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.
5. van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P: **Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control.** *Crit Care Med* 2003, **31:**359-366.
6. Fischer KF, Lees JA, Newman JH: **Hypoglycemia in hospitalized patients. Causes and outcomes.** *N Engl J Med* 1986, **315:** 1245-1250.
7. Stagnaro-Green A, Barton MK, Linekin PL, Corkery E, deBeer K, Roman SH: **Mortality in hospitalized patients with hypoglycemia and severe hyperglycemia.** *Mt Sinai J Med* 1995, **62:** 422-426.
8. Brown G, Dodek P: **Intravenous insulin nomogram improves blood glucose control in the critically ill.** *Crit Care Med* 2001, **29:**1714-1719.
9. Tenerz A, Lonnberg I, Berne C, Nilsson G, Leppert J: **Myocardial infarction and prevalence of diabetes mellitus. Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes?** *Eur Heart J* 2001, **22:**1102-1110.
10. Tenerz A, Norhammar A, Silveira A, Hamsten A, Nilsson G, Ryden L, Malmberg K: **Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes.** *Diabetes Care* 2003, **26:**2770-2776.
11. Woo J, Lam CW, Kay R, Wong AH, Teoh R, Nicholls MG: **The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke.** *Arch Neurol* 1990, **47:**1174-1177.
12. Bolk J, van der PT, Cornel JH, Arnold AE, Sepers J, Umans VA: **Impaired glucose metabolism predicts mortality after a myocardial infarction.** *Int J Cardiol* 2001, **79:**207-214.
13. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M: **Association of hyperglycemia with increased mortality after severe burn injury.** *J Trauma* 2001, **51:**540-544.
14. Krinsley JS: **Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients.** *Mayo Clin Proc* 2003, **78:**1471-1478.
15. Yendamuri S, Fulda GJ, Tinkoff GH: **Admission hyperglycemia as a prognostic indicator in trauma.** *J Trauma* 2003, **55:**33-38.
16. Bonnier M, Lonnroth P, Gudbjornsdottir S, Attvall S, Jansson PA: **Validation of a glucose-insulin-potassium infusion algorithm in hospitalized diabetic patients.** *J Intern Med* 2003, **253:**189-193.
17. van der Horst IC, Gans RO, Nijsten MW, Ligtenberg JJ: **Beneficial effect of glucose-insulin-potassium infusion in noncritically ill patients has to be proven [letter].** *J Intern Med* 2003, **254:**513.
18. Bonnier M, Lonnroth P, Gudbjornsdottir S, Attvall S, Jansson PA: **Beneficial effect of glucose–insulin–potassium infusion in noncritically ill patients has to be proven: reply [letter].** *J Intern Med* 2003, **254:**514.
19. Finney SJ, Zekveld C, Elia A, Evans TW: **Glucose control and mortality in critically ill patients.** *JAMA* 2003, **290:**2041-2047.
20. Pomposelli JJ, Baxter JK, III, Babineau TJ, Pomfret EA, Driscoll DF, Forse RA, Bistrian BR: **Early postoperative glucose control predicts nosocomial infection rate in diabetic patients.** *JPEN J Parenter Enteral Nutr* 1998, **22:**77-81.
21. 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.
22. Bruno A, Biller J, Adams HP Jr, Clarke WR, Woolson RF, Williams LS, Hansen MD: **Acute blood glucose level and outcome from ischemic stroke. Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators.** *Neurology* 1999, **52:**280-284.
23. Dorhout Mees SM, Van Dijk GW, Algra A, Kempink DR, Rinkel GJ: **Glucose levels and outcome after subarachnoid hemorrhage.** *Neurology* 2003, **61:**1132-1133.
24. Foo K, Cooper J, Deaner A, Knight C, Suliman A, Ranjadayalan K, Timmis AD: **A single serum glucose measurement predicts adverse outcomes across the whole range of acute coronary syndromes.** *Heart* 2003, **89:**512-516.
25. Lam AM, Winn HR, Cullen BF, Sundling N: **Hyperglycemia and neurological outcome in patients with head injury.** *J Neurosurg* 1991, **75:**545-551.
26. Paret G, Barzilai A, Lahat E, Feldman Z, Ohad G, Vardi A, Ben Abraham R, Barzilay Z: **Gunshot wounds in brains of children: prognostic variables in mortality, course, and outcome.** *J Neurotrauma* 1998, **15:**967-972.
27. Penney DG: **Hyperglycemia exacerbates brain damage in acute severe carbon monoxide poisoning.** *Med Hypotheses* 1988, **27:**241-244.
28. Rovlias A, Kotsou S: **The influence of hyperglycemia on neurological outcome in patients with severe head injury.** *Neurosurgery* 2000, **46:**335-342.
29. Young B, Ott L, Dempsey R, Haack D, Tibbs P: **Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients.** *Ann Surg* 1989, **210:**466-472.
30. Goldberg PA, Siegel MD, Sherwin RS, Halickman JI, Lee M, Bailey VA, Lee SL, Dziura JD, Inzucchi SE: **Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit**. *Diabetes Care* 2004, **27:**461-467.
31. Vincent JL, Moreno R, Takala J, Willatts S, de Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: **The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.** *Intensive Care Med* 1996, **22:**707-710.
32. Chee F, Fernando T, van Heerden PV: **Closed-loop control of blood glucose levels in critically ill patients.** *Anaesth Intensive Care* 2002, **30:**295-307.
33. Chee F, Fernando T, van Heerden PV: **Closed-loop glucose control in critically ill patients using continuous glucose monitoring system (CGMS) in real time.** *IEEE Trans Inf Technol Biomed* 2003, **7:**43-53.
34. Jungheim K, Wientjes KJ, Heinemann L, Lodwig V, Koschinsky T, Schoonen AJ: **Subcutaneous continuous glucose monitoring: feasibility of a new microdialysis-based glucose sensor system.** *Diabetes Care* 2001, **24:**1696-1697.
35. Kapitza C, Lodwig V, Obermaier K, Wientjes KJ, Hoogenberg K, Jungheim K, Heinemann L: **Continuous glucose monitoring: reliable measurements for up to 4 days with the SCGM1 system.** *Diabetes Technol Ther* 2003, **5:**609-614.