Tight control of glycaemia in critically ill patients

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Purpose of review

This manuscript attempts to review the effects associated with hyperglycaemia in critically ill patients and the effects of various insulin regimens. The available clinical findings and pertinent experimental data are examined.

Recent findings

Intensive insulin therapy titrated to maintain blood glucose level between 4.4 and 6.1 mmol/l during intensive care unit stay has recently been shown to significantly decrease mortality, septic morbidity, sepsis-related organ failure, transfusion requirements and polyneuropathies. Prior studies have already documented that hyperglycaemia on admission is related to susceptibility to infections and worse outcomes following myocardial and cerebral ischaemic events. Additional effects of insulin, unrelated to the control of glycaemia, have also been reported.

Summary

Intensive insulin therapy is probably warranted in most categories of critically ill patients, although some of the underlying mechanisms of its beneficial effects still need to be elucidated.

Keywords

Insulin, carbohydrate, infection susceptibility, myocardial ischaemia, stroke

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Introduction

Acute hyperglycaemia frequently occurs during critical illness as a result of the metabolic and hormonal changes that accompany the so-called 'stress response'. This physiological response can actually become harmful, as demonstrated in several clinical and experimental conditions [1•–3•]. The risk factors for the development of stress-induced hyperglycaemia are listed in Table 1.

The importance of careful control of glycaemia in critically ill patients was highlighted by a study recently published in the *New England Journal of Medicine* [4••]. In brief, compared with conventional therapy adjusted to maintain glucose level between 10.0 and 11.1 mmol/l, intensive insulin therapy titrated to keep blood glucose between 4.4 and 6.1 mmol/l reduced overall in-hospital mortality by 34%. Most secondary outcome variables were also improved, as demonstrated by a 46% reduction in the incidence of bloodstream infections, a 41% reduction in the frequency of acute renal failure requiring dialysis or haemofiltration, a 50% reduction in the median number of red blood cell transfusions, and a 44% reduction in the incidence of critical illness polyneuropathies. The population studied was heterogeneous, even though 63% of the patients were admitted into the intensive care unit for postoperative care after cardiac surgery. Interestingly, older retrospective, nonrandomized studies in target populations of critically ill patients documented a positive correlation between admission glycaemia and poor outcome following surgery, acute myocardial infarction, stroke and head injury. The effects of glycaemic control below 11 mmol/l were also assessed in one study that was carried out on patients with diabetes after myocardial infarction. The results of this study will be discussed, as well as the putative underlying mechanisms.

Table 1. Predisposing factors for stress-induced hyperglycaemia [2•]

(1)	Pre-existing diabetes mellitus
(2)	Infusion of catecholamine
(3)	Steroid therapy
(4)	Obesity
(5)	Increasing APACHE score
(6)	Elderly patient
(7)	Pancreatitis
(8)	Sepsis
(9)	Hypothermia
(10)	Hypoxaemia
(11)	Uraemia
(12)	Cirrhosis
(13)	Surgery or trauma

APACHE, Acute Physiological and Chronic Health Evaluation

Deleterious effects of hyperglycaemia

The delineation between beneficial effects of insulin and the prevention of deleterious effects of hyperglycaemia can hardly be deduced [4••]. Previous data describe associations between stress-related hyperglycaemia and adverse outcome, as well as beneficial metabolic effects of insulin. For instance, the incidence and severity of septic complications sharply decreased [4••]. Both the deleterious effects of hyperglycaemia and, to a lesser extent, the beneficial effects of insulin on infectious morbidity have already been described, mainly in patients with diabetes after undergoing surgery.

Increased susceptibility to infections

An increased susceptibility to infections in the presence of hyperglycaemia has long been known in patients with diabetes [1•,2•,5], and was the most often studied short-term consequence of hyperglycaemia (see [6] for a review). In the aforementioned trial of critically ill patients, mostly without diabetes [4••], septic morbidity was found to be decreased in the group randomized to intensive insulin therapy and tight (below 6.1 mmol/l) glycaemic control. In two retrospective studies on burn patients, the incidences of bacteraemia, fungaemia, wound infection and mortality were found to be decreased following insulin therapy titrated to keep blood glucose below 7.8 mmol/l [7•,8]. In the latter retrospective study on the outcome of 74 burn patients without diabetes, skin grafts were less successful in hyperglycaemic patients (62.5%), and in patients with wound infection (63%) or both (54%) than in normoglycaemic, noninfected patients (93%).

Similarly, other recent studies after open-heart surgical procedures in patients with diabetes indicated that, compared with standard therapy, the titration of intravenous insulin therapy to maintain blood glucose between 8 and 11 mmol/l was associated with a significant decrease in the rate of deep sternal wound infections [9,10]. In the first study [9], 2467 patients with diabetes, admitted for open-heart surgical procedures, received insulin titrated to keep blood sugar levels below 11.1 mmol/l either with subcutaneous insulin injections every 4 h or continous intravenous insulin. The intravenous group experienced a reduced incidence of deep sternal wound infection. The second study [10] retrospectively confirmed the beneficial effects of intravenous insulin therapy titrated to maintain blood glucose level below 11.1 mmol/l on the incidence of deep sternal wound infection in 1585 patients with diabetes after cardiac surgery. A multivariate logistic regression also showed that mean blood glucose level for the first 2 days after surgery was an independent predictor of deep wound infection.

Interestingly, in a similar population, intensive insulin therapy adjusted to keep blood glucose between 5.6 and 8.3 mmol/l partially prevented the postoperative decrease in the phagocytosis by polymorphonuclear neutrophils [11]. The function of neutrophils is commonly impaired in patients with diabetes, proportionally according to the degree of hyperglycaemia. In this study [11], the effects of two regimens of peri-operative insulin infusion on neutrophil function were compared in 26 patients with diabetes scheduled for coronary artery bypass. Phagocytosis activity was decreased by 25% in the intensive therapy group compared with 54% in the conventional therapy group. Importantly, even in the absence of diabetes mellitus, the oxidative burst of murine [12] and human leukocytes is blunted following exposure to high concentrations of glucose [13]. Specifically, in normal rats, a 3 h hyperglycaemia significantly depresses the oxidative function of the alveolar macrophage [12], while there is significant reduction in the respiratory burst of human polymorphonuclear neutrophils after 30 min of in-vitro cell exposure to high glucose concentrations, suggesting a potential role for protein glycosylation [13].

Other functional impairments documented in the leukocytes of patients with diabetes include a decrease in the intracellular bactericidal activity and in the opsonic activity. Importantly, these latter dysfunctions can be reversed by a tightening of the insulin therapy [11,14]. In a retrospective review of 241 patients with diabetes [15], a striking correlation was found between the overall prevalence of infection and the mean plasma glucose levels, with a significant diminution in intracellular bactericidal activity of leukocytes and in serum opsonic activity.

Besides the impairment of leukocyte function, some microorganisms can adhere more easily to the immune cells of patients with diabetes compared with those without the condition. For instance, the carbohydrate composition of cell surface receptors and the inhibition of the complement-mediated phagocytosis or a hyperglycaemia-related competitive binding to complement factors have been advocated to explain the increased susceptibility of patients with diabetes to *Candida albicans* [14,16]. The nonenzymatic glycosylation of immunoglobulins, induced by hyperglycaemia, is another potential mechanism of immune depression [17]. Finally, bacterial growth can be further increased by the presence of oedema related to hyperglycaemia [15].

The commonly observed impairment of wound healing in patients with diabetes is also related to an accelerated glycosylation of newly synthesized collagen, and with increased collagenase activity and decreased wound collagen content [9]. Importantly, insulin therapy might

increase protein and collagen synthesis, as a result of its anabolic properties [18].

Detrimental effects of hyperglycaemia on the cardiovascular system

Common findings in patients with long-term, poorly controlled diabetes include the presence of myocardial and vascular compromise. More recent data suggest that the presence and magnitude of stress-induced hyperglycaemia could contribute to the severity of an ischaemic event, as reported following myocardial ischaemia and cerebral stroke.

Myocardial ischaemia

The presence of stress hyperglycaemia has been associated with a worsened outcome following acute ischaemic events, that is, myocardial infarction and stroke. The mechanisms commonly advocated to explain these findings include impairment of cardiac contractility, increase in the frequency of arrhythmias, impairment of the endothelium-dependent vasorelaxation and a prothrombotic status related to altered platelet function and reduced activity of plasminogen activator inhibitor-1 and thromboxane. The literature from 1966 to 1998 related to stress-induced hyperglycaemia and outcome following myocardial infarction was recently extensively reviewed [19]. Patients who had glucose concentrations higher than 6.1–8.1 mmol/l on admission had a 3.9-fold higher risk of death than patients with lower glucose concentrations. In patients with acute myocardial infarction, glucose level on admission was an independent predictor of cardiac damage and late mortality, even in patients without diabetes [20•]. Conversely, in those with diabetes, the systematic administration of insulin titrated to reach a glycaemia level below 11 mmol/l after acute myocardial infarction was associated with significant improvement in several important outcome variables, including late mortality [21], re-infarction, heart failure and the incidence of major cardiovascular events [22]. In the Diabetes and Insulin–Glucose Infusion in Acute Myocardial Infarction study [21], a randomized trial carried out on patients with diabetes suffering from acute myocardial infarction, 306 patients were assigned to more than 24 h insulin–glucose–potassium infusion followed by a multidose subcutaneous insulin, and 340 patients received conventional antidiabetic therapy. During an average follow-up of 3.4 years, 33% of the patients in the insulin group and 44% of the control group died. Intensive insulin treatment reduced long-term mortality despite higher blood glucose and HbA1c levels on admission. The same team also performed a retrospective study with prospective follow-up of 197 patients without diabetes suffering from acute myocardial infarction in whom the mean admission glucose level was 8.3 ± 3.0 mmol/l [22]. The multivariate regression analysis revealed the plasma glucose level on admission to be an independent predictor of nonfatal reinfarction, hospital admission for heart failure and reoccurrence of a major cardiovascular event.

The underlying mechanisms are partially elucidated, but many still remain mainly speculative. These mechansms include the impairment by hyperglycaemia of endothelium-dependent coronary vascular relaxation, at the microcirculatory as well as the macrocirculatory level [23,24]. The endothelium-dependent vasodilatation of the brachial artery was evaluated with a high-resolution ultrasound scan and acetylcholine ionophoresis in 20 volunteers who had received an oral load of glucose [23]. The endothelial-dependent vasodilatation was impaired in both microcirculation and macrocirculation. Similarly, the endothelium-dependent vasodilatation assessed by a metacholine dose–response study in 10 healthy volunteers was attenuated by acute hyperglycaemia.

Biochemically, hyperglycaemia is associated with increased lipolysis and plasma concentrations of free fatty acids. Free fatty acids are toxic for the ischaemic myocardium and may lead to damaged cardiac cell membranes, calcium overload, and arrhythmias, particularly in the case of insulin deficiency. Finally, uncontrolled hypovolaemia related to an osmotic diuresis may further worsen the haemodynamic status of hyperglycaemic patients.

Cerebral ischaemia

Similar to the observations in patients with myocardial infarction, the presence of hyperglycaemia on admission following focal and global cerebral ischaemia is associated with a two to threefold increased mortality and significant impairment in functional recovery [25••,26•,27,28]. For instance, in a pilot randomized controlled trial of 53 acute stroke patients with mild hyperglycaemia randomized to a 24 h infusion of saline solution or glucose–potassium–insulin solution, the 4 week mortality rate was slightly lower in the latter group (28 versus 32%).

In patients with nonlacunar stroke, high blood glucose levels on admission were associated with worse outcome at 3 months, even after adjustment for age, stroke size on admission and the presence of preexisting diabetes mellitus [29]. Similarly, following severe head injury, admission and postoperative serum glucose levels are correlated with the severity of injury and can serve as early prognostic indicators as they reflect the severity of injury. A blood glucose value of 11.1 mmol/l or higher during the first 24 h was associated with a poor outcome in a prospective study of 267 neurosurgical patients admitted with craniocerebral injury [30].

The possible underlying mechanisms of the detrimental effects of hyperglycaemia on cerebral function have been studied in different animals models [25••,26•,28]. A loss of endothelium-dependent vascular relaxation has been documented in the early stages of experimental brain ischaemia, and associated with the apparition of widespread foci of infarction and eventually neuronal loss. Importantly, uncontrolled hyperglycaemia also induces brain oedema and can lead to disruption of the blood–brain barrier and ultimately to the haemorrhagic transformation of an ischaemic stroke. The increase in lactate concentration and the subsequent metabolic acidosis are also advocated to explain the deleterious effect of hyperglycaemia on cerebral tissue. Indeed, enhanced acidosis may exaggerate ischaemic damage by an increase in the formation of oxygen free radicals, thereby leading to alterations in intracellular signal transduction, and to the activation of endonucleases. Recent studies have also shown that hyperglycaemia is associated with the release of glutamate, an excitatory amino acid. Importantly, a steep decrease in glycaemia may also worsen cerebral ischaemia.

Despite conflicting findings on the role of hyperglycaemia in experimental cerebral ischaemia [26•,31], improvements in survival rate and neurological outcome have been reported following the use of insulin in various models [28,32,33], but data from human controlled studies are still lacking. Whether these beneficial effects of insulin are related to a direct insulin-mediated neuroprotection or to the lowering of glucose levels is still an unresolved issue [31]. In any case, the effects of intensive insulin therapy on the outcome of stroke warrant further clinical studies [27].

Conclusion

Hyperglycaemia is a common finding in critically ill patients. Maintenance of normoglycaemia with intensive insulin therapy during intensive care has recently been shown to decrease mortality and morbidity. Therefore, hyperglycaemia should no longer be considered as merely a surrogate marker of severity of illness, but needs to be controlled aggressively. In addition, other insulin-mediated effects which are reflected by control of the circulating level of glucose may play a role, as discussed in this review. Important additional arguments for the implementation of intensive insulin therapy are its safety, cost-effectiveness and ease of use.

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