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Commentary

Insulin: a wonder drug in the critically ill?

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Abstract

Stress hyperglycaemia is a common event in acute critical illness. There is increasing evidence that maintaining normoglycaemia and treatment with insulin (or with glucose–insulin–potassium [GIK]), even in non-diabetic persons, is helpful in limiting organ damage after myocardial infarction, stroke, traumatic brain injury and other conditions, even though the conditions may be accompanied by insulin resistance. A landmark study now suggests that maintaining normoglycaemia with intensive insulin treatment in a heterogeneous population of critically ill patients decreases morbidity and mortality. The potential mechanisms that underlie such a beneficial effect are discussed.

Keywords apoptosis pathways, critically ill, insulin, ischaemia/reperfusion, stress hyperglycaemia

Intensive care unit patients often have complex disorders. For instance, bouts of inflammation, trauma and ischaemia/reperfusion may occur sequentially or synchronously in patients following surgery, sepsis or shock, thereby upregulating inflammatory and metabolic responses, including cytokine release, protein breakdown and insulin resistance [1–4]. In spite of elevated insulin levels, insulin resistance at the receptor and postreceptor levels may contribute to hyperglycaemia, even in non-diabetic persons, particularly when stress hormones that promote glycogenolysis are released, including catecholamines and cortisol [2,3,5]. 'Stress' hyperglycaemia can be reproduced after administration of minute amounts of endotoxin to healthy volunteers or by injecting several stress hormones at the same time [5]. Stress hyperglycaemia may occur during the acute phase of illness in 5–30% of patients with stroke, myocardial infarction, sepsis, burns, trauma, surgery and other conditions.

Hyperglycaemia

Recent evidence suggests that even mild hyperglycaemia is harmful in animals and humans, and aggravates ischaemia/reperfusion damage to heart and brain. Myocardial infact size in humans, with or without diabetes, is greater in the presence of hyperglycaemia [6]. That the former results from the latter (i.e. more severe stress hyperglycaemia causes greater infarct size) rather than *vice versa* is supported by animal studies [7]. Similarly, hyperglycaemia is associated with poor neurological outcome after traumatic brain injury and stroke [8]. In rodents hyperglycaemia aggravates endotoxin shock, and insulin treatment may decrease mortality [9,10]. Hyperglycaemia may contribute to morbidity and mortality after burns or surgery in humans [3,11]. Therefore, during the course of diabetes mellitus but also during the course of stress hyperglycaemia, untreated or insufficiently controlled hyperglycaemia may adversely impact on organ function after inflammation, trauma or ischaemia/reperfusion, and consequently may have a detrimental impact on morbidity and mortality.

Apart from the detrimental effect of even mild hyperglycaemia on bacterial defences, and wound healing and repair after ischaemia/reperfusion [11], there are various other potential mechanisms to explain the harmful effect of hyperglycaemia. They include the effect of hyperglycaemia on metabolic mitochondrial pathways, which results in oxidative stress and increased superoxide production [12]. Cytosolic oxygen radical production as a result of hyperglycaemia may arise

GIK=glucose–insulin–potassium; IGF=insulin-like growth factor.

from non-enzymatic glycation, auto-oxidation of glucose and the polyol pathway [13]. Hyperglycaemia-induced oxygen radicals may scavenge endogenous nitric oxide, thereby increasing electrical instability of the heart and peripheral vascular tone [14]. Also, in humans acute hyperglycaemia attenuates endothelial nitric oxide-dependent dilatation of the brachial artery [13]. Hyperglycaemia may increase neutrophil activation and interaction with endothelium following ischaemia/reperfusion [15]. Diabetes/hyperglycaemia may attenuate ischaemic preconditioning of the heart, possibly by inhibiting activation of ATP-sensitive potassium channels that may afford protection by activating glycolysis in the cytosol [7,16]. This may also explain why ATP-sensitive potassium channel blockers (e.g. sulfonylurea drugs) may abolish, whereas insulin may not abolish and may even enhance protection afforded by ischaemic preconditioning of the human myocardium [7]. Finally, hyperglycaemia enhances proteolysis in healthy volunteers, even during hyperinsulinaemia.

Insulin treatment

For decades it has been advocated that fasting diabetic persons be treated with a combined glucose and insulin infusion before invasive procedures or surgery [17]. The basis for this recommendation was improved diabetic control and thereby fewer wound infections and better wound healing. However, we now know that this view may be too simplistic. The effects of GIK infusion may extend beyond control of hyperglycaemia alone [4]. Indeed, the use of GIK in patients with myocardial infarction and shock was originally studied decades ago, but has recently undergone a revival. In both diabetic and non-diabetic patients with myocardial infarction, GIK infusion may salvage myocardium, improve heart function without an increase in myocardial oxygen demand, and decrease mortality by an absolute 10%, particularly in those receiving prior reperfusion therapy, provided that hyperglycaemia is prevented. This was demonstrated in a recent landmark trial [18,19]. Animal studies [20] suggest that this effect may partly be independent of glucose. Also, bolus infusion of hyperosmolar GIK improved cardiac output and heart function in canine endotoxin and human septic shock, but this may relate to the positive inotropic effect of hyperosmolarity or insulin rather than to a metabolic effect, in spite of myocardial insulin resistance [21,22]. In diabetic and non-diabetic persons, GIK infusion after cardiac surgery may improve heart function and expedite recovery [23]. Treatment with GIK may also improve outcome in stroke patients [24].

Those studies have now been supplemented by a large trial conducted in a heterogeneous group of 1548 critically ill patients [25]. That trial demonstrated that intensive insulin treatment to avoid hyperglycaemia in diabetic and non-diabetic persons is associated with a decrease in mortality, from 8% in the less intensively treated (blood glucose maintained between 10.0 and 11.1 mmol/l) to 4.6% in the intensively treated patients (blood glucose maintained below 6.1 mmol/l). The reduction in mortality was even greater in sicker patients with a duration of stay longer than 5 days. In that single-centre, landmark trial, patients with sepsis appeared to benefit the most. The effect of insulin apparently occurred even in the assumed presence of insulin resistance. Hypoglycaemia occurred somewhat more frequently in the intensive insulin group, but appeared well controlled and relatively harmless. What could underlie these beneficial effects and what are the potential mechanisms involved?

Mechanisms of the action of insulin

The basis of the beneficial effect of insulin treatment, despite potential insulin resistance in conditions associated with trauma, inflammation and ischaemia/reperfusion, may be multifactorial. On the one hand correction of hyperglycaemia may prevent its adverse effects. On the other hand insulin, whether or not combined with glucose to compensate for increased skeletal muscle glucose uptake, and even in the critically ill with insulin resistance [2], may also benefit non-diabetic or normoglycaemic patients (Table 1).

Glucose or insulin started preoperatively may decrease postoperative insulin resistance [3]. Bolus infusion of insulin combined with glucose may have vasodilatory properties, may inhibit fatty acid, and may increase glucose uptake in ischaemic tissues for anaerobic ATP production following augmented glycolysis. Thus, insulin may limit the fall in tissue high-energy phosphates that may occur during ischaemia, despite its potential to increase lactate concentrations. Insulin may also stimulate pyruvate dehydrogenase during ischaemia, and thereby exerts a beneficial effect associated with an improved energy state and less lactate production, at least in cultures of cardiomyocytes taken from patients during cardiac surgery [26]. Similarly, pyruvate infusions and enhanced uptake thereof in the tricarboxylic acid cycle may decrease the cytosolic redox state and oxygen radical production, maintain phosphorylation potential and thus limit energy depletion during ischaemia [27]. Insulin may have anti-inflammatory properties by inhibiting production of tumour necrosis factor-α, superoxide radicals and intercellular adhesion molecule-1 in macrophages, leucocytes and endothelium; it may inhibit harmful macrophage-inhibitory factor; and it may potentiate release of endothelial nitric oxide synthase and endothelin [4].

Insulin may increase levels of insulin-like growth factor (IGF)-I, a mediator of growth hormone action, and may suppress hepatic synthesis of IGF-1-binding protein, which binds and limits free circulating IGF-I; thus, during critical illness circulating levels of IGF-I are low and those of IGF-1-binding protein are high [28,29]. Insulin may therefore increase the bioavailability of IGF-I [28].

IGF-I may mimick some of the actions of insulin and may have various beneficial actions, but the anabolic properties may not exceed those of insulin, at least in endotoxaemic rats

Table 1

Potentially beneficial actions of insulin in critical illness

Less (stress) hyperglycaemia by 'overcoming' insulin resistance, and therefore better antimicrobial defence and wound healing
Stimulation of glucose uptake/glycolysis, pyruvate dehydrogenase and energy production
Anti-inflammatory properties, such as less oxygen radical formation
Suppression of insulin-like growth factor (IGF)-I-binding protein, increased IGF-I
Increased muscle protein synthesis
Inhibition of apoptosis and promoting repair of damaged tissue
Promotion of ischaemic preconditioning
Less ischaemia/reperfusion damage

[10]. Otherwise, muscle protein synthesis would also become relatively resistant to insulin during sepsis [30]. There have been some small trials on the value of IGF-I administration in the critically ill, but results have been disappointing thus far. Insulin may have anabolic properties in the critically ill, burned and catabolic patient [31]. It stimulates protein synthesis in skeletal muscle [31]. Both IGF-I and insulin may inhibit postischaemic apoptosis, energetic failure and damage of cardiac tissue, both *in vitro* and in animals [20,26]. Insulin may also potentiate ischaemic preconditioning, as described above.

Therefore, there are multiple pathways through which insulin treatment may decrease morbidity and mortality in a variety of critical conditions. Some caution is warranted, however, because hyperinsulinaemia *per se* may have some adverse effects, including endothelial oxygen radical production [13,32].

Conclusion

The finding of the beneficial effect of intensive insulin therapy in critically ill patients to maintain blood glucose levels below 6.1 mmol/l, as reported by Van den Berghe *et al*. [25], has a relatively firm albeit multifactorial basis. Those findings should prompt intensivists to institute strict (perhaps stricter than is commonly advocated [17]) control of blood glucose, with the help of the 'wonder drug' insulin. However, a survival benefit has also recently been shown for administration of hydrocortisone [33]. Hydrocortisone infusion may increase blood glucose levels and thereby necessitate concomitant infusion of insulin. Hence, the interaction between these hormones may be a subject for further therapeutic study. Nevertheless, the study reported by Van den Berghe *et al*. [25] is certainly a major step forward in the treatment of critically ill patients, particularly in the context of failure of most large trials on the value of immunomodulatory treatment of sepsis and shock to show a beneficial impact. Clearly, a limitation of intensive insulin treatment in critically ill patients on sedation is the potential occurrence of hidden hypoglycaemia [31]. Hence, intensive insulin treatment warrants intensive monitoring of blood glucose concentration.

Competing interests

None declared.

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