Commentary

Insulin and metabolic substrates during human sepsis

Simon J Finney

Unit of Critical Care, National Heart and Lung Institute, Imperial College, London, UK

Corresponding author: Simon J Finney, s.finney@imperial.ac.uk

Published online: 25 May 2004
This article is online at http://ccforum.com/content/8/4/227

Critical Care 2004, **8:**227-228 (DOI 10.1186/cc2883)

Related to *Research* by Rusavy *et al*., see page 292

Abstract

Rusavy and colleagues recently endeavoured to dissect out the metabolic effects of insulin in patients with severe sepsis, in the setting of normoglycaemia. Twenty stable patients were studied 3–7 days after admission using a euglycaemic clamp at two supraphysiological insulin levels. Increased doses of exogenous insulin caused preferential use of glucose as a metabolic substrate, while total energy expenditure remained constant. Consequently, hyperinsulinaemia reduced tissue oxygen demand and catabolism of protein in patients with sepsis; the benefits of these effects are not proven. The effects of insulin at different time points in sepsis were not examined.

Keywords glucose, insulin, metabolic response, severe sepsis

The landmark study of intensive insulin therapy conducted by van den Berghe and colleagues [1] highlighted to critical care physicians the vital importance of the metabolic substrate–insulin axis in critically ill patients. An impressive 3.4% absolute reduction in intensive care unit mortality was achieved in predominantly surgical patients managed with insulin to achieve a blood glucose level of 4.0–6.0 mmol/l (80–110 mg/dl) as compared with a 'control' target range of 10.0–11.1 mmol/l (180–200 mg/dl). Thus, it is clear that blood glucose levels exceeding 10.0 mmol/l (180 mg/dl) are unacceptable in such patients, although the merits of further increasing doses of exogenous insulin by either supplying additional substrate or aiming to achieve tighter glycaemic control have been debated [2]. Thus, the roles of insulin administration, avoidance of hyperglycaemia, and other metabolic substrates have been examined [2–4]. These studies were complicated by the strong associations between variables. Whether the results can be extrapolated to the critically ill patient admitted for nonsurgical reasons has not been defined, although this is the subject of planned investigations [5].

In the present issue of *Critical Care*, Rusavy and colleagues [6] take this intriguing story a stage further. They examined the effects of two very different levels of insulinaemia during a euglycaemic clamp in 20 patients with sepsis. The reasons why the data are particularly interesting are twofold. First, one variable – glucose – was controlled while the effects of insulin were examined. Second, the patients were admitted for nonsurgical reasons.

Those investigators demonstrated that patients with sepsis but not diabetes mellitus are significantly hyperinsulinaemic relative to healthy volunteers before institution of the clamp. Furthermore, increasing levels of insulinaemia during the clamp resulted in increased glucose uptake, oxidation and storage in patients with sepsis. The increases in glucose uptake and storage were significantly less than those in volunteers. Increased insulin significantly reduced plasma alanine levels and tended to reduce free fatty acid levels in patients with sepsis. In the setting of increased glucose oxidation, this suggests that high doses of exogenous insulin can reduce the catabolism of protein and the oxidation of fat stores. Although energy expenditure was higher in patients with sepsis, it remained constant, whereas respiratory quotient fell at the higher level of insulinaemia; this implies that increased insulinaemia can induce a reduction in tissue oxygen demand. One theory for why glucose–insulin–potassium regimens are beneficial after myocardial infarction is that they promote myocardial utilization of glucose rather than free fatty acids, resulting in a greater number of molecules of ATP generated per molecule of oxygen utilized.

The more efficient use of oxygen may benefit ischaemic myocardium at the penumbra of an infarction. However, tissues from patients with sepsis are not hypoxic [7] and are replete in ATP [8]. The potential advantages of an insulin-induced fall in oxygen demand are less obvious.

How robust are these potentially important data? First, the definition of sepsis employed in the study was not standard, although it is broadly similar to the American College of Chest Physicians/Society of Critical Care Medicine Consensus definition of severe sepsis. This makes comparison with other studies difficult. Furthermore, only those patients who no longer required vasoactive agents at a point 3–7 days after admission to the intensive care unit were studied. This implies that the patient population was restricted with respect both to severity and to the time point in the natural course of their illness. It is well established that the metabolic response changes over time in sepsis [9]. Second, patient numbers are relatively low, limiting the power of the study. Finally, as the authors themselves acknowledge, gluconeogenesis may not be entirely suppressed by the clamp in patients with sepsis, resulting in a potential underestimation of glucose storage.

Nevertheless, the findings reported by Rusavy and colleagues [6] expand our knowledge further. They demonstrate clear differences in dose–response to insulin between healthy volunteers and patients with sepsis. In particular, defects in glucose storage were partially overcome by supraphysiological levels of insulin. They also demonstrate that, at the time point studied, increased doses of insulin (and glucose) are able to reduce the catabolism of protein and fat stores. Although limitation in protein catabolism may improve outcome by preserving muscle strength and aiding withdrawal of mechanical ventilation, this is not proven. Finally, it is likely that the effects and relative importance of hyperinsulinaemia will change during the course of a critical illness. The metabolic changes demonstrated in the study were the consequence of large doses of insulin given during the early but not immediate stages of sepsis.

Competing interests

None declared.

References

1. 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.
2. Finney SJ, Zekveld C, Elia A, Evans TW: **Glucose control and mortality in critically ill patients.** *JAMA* 2003, **290:**2041-2047.
3. 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.
4. Mesotten D, Swinnen JV, Vanderhoydonc F, Wouters PJ, van den Berghe G: **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.
5. The ANZICS NICE study [www.nhmrc.gov.au/funding/progra04.pdf].
6. Rusavy Z, Sramek V, Lacigova S, Novak I, Tesinsky P, Macdonald IA: **Influence of insulin on glucose metabolism and energy expenditure in septic patients.** *Crit Care* 2004, **8:**213-220.
7. Boekstegers P, Weidenhofer S, Kapsner T, Werdan K: **Skeletal muscle partial pressure of oxygen in patients with sepsis.** *Crit Care Med* 1994, **22:**640-650.
8. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M: **Association between mitochondrial dysfunction and severity and outcome of septic shock.** *Lancet* 2002, **360:**219-223.
9. Uehara M, Plank LD, Hill GL: **Components of energy expenditure in patients with severe sepsis and major trauma: a basis for clinical care.** *Crit Care Med* 1999, **27:**1295-1302.