CRITICAL CARE

COMMENTARY

Insulin therapy improves protein metabolism in the critically ill

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See related research by Hsu *et al.*, http://ccforum.com/content/16/2/R56

Abstract

Critical illness, trauma and burns are associated with profound metabolic abnormalities, of which protein catabolism, hyperglycemia and insulin resistance are hallmarks of these conditions. Increased protein breakdown and loss results in muscle wasting, weakness and diminished functioning. Interestingly, hyperglycemia and insulin resistance augment catabolic responses. Insulin, which is routinely administered to critically ill patients to prevent excessive hyperglycemia, also stimulates protein synthesis and prevents whole-body protein loss. The present commentary highlights the results of a recent study published in *Critical Care* and discusses whether moderate insulin therapy is equally as beneficial as conventional insulin therapy in preventing protein catabolism and loss.

In the previous issue of *Critical Care*, Hsu and colleagues compare the effectiveness of moderate insulin therapy with that of conventional insulin therapy on the stimulation of protein synthesis and prevention of protein loss in critically ill patients [1]. This is of clinical relevance since muscle wasting including accelerated protein breakdown and hyperglycemia are metabolic responses frequently observed in critically ill or severely injured patients. These metabolic abnormalities lead to organ failure and loss of strength and function, resulting in increased morbidity and mortality [2-4]. To counteract hyperglycemia in critically ill or severely injured patients, the current gold-standard treatment is insulin administration. Insulin lowers blood glucose levels by stimulating glucose uptake into muscle and fat [5], and overcomes insulin resistance [2]. Insulin also has anabolic actions and stimulates protein and lipid biosynthesis [5]. Of particular interest is whether insulin administration could also counteract the loss of protein seen in critically ill patients.

Hsu and colleagues demonstrate that when critically ill patients in the ICU received moderate insulin therapy to maintain blood glucose levels at 120 to 140 mg/dl, improvements in protein metabolism were observed compared with critically ill patients that received lower doses of insulin to maintain higher blood glucose levels (180 to 200 mg/dl) [1]. Improvements in protein metabolism were indicated by decreases in whole-body protein loss and increases in serum albumin and prealbumin levels. The beneficial effects of moderate insulin therapy on protein metabolism in critically ill patients were most pronounced at the early stages of illness (between days 0 and 3), reaching a plateau after 3 days of therapy with no further stimulation of protein metabolism at the later stages of illness. It is uncertain from this study whether critically ill patients are more responsive to insulin therapy during the early stages of illness compared with the later stages or whether an equilibrium between the insulin dose administered and the stimulation of protein metabolism was reached by the third day of insulin therapy. In addition to the time of insulin administration, the insulin dosing was not well defined. The authors showed that the higher insulin dose was less catabolic compared with the lower dose, indicating that administering increased amounts of insulin would be more anabolic, which was not tested in the present study. Although administering higher doses of insulin could possibly stimulate further increases in protein synthesis and minimize protein loss, administering higher doses of insulin could also lead to hypoglycemia that is associated with increased morbidity and mortality, hence counteracting its beneficial effects. For example, in the study by Hsu and colleagues, both groups of patients showed improvements in protein metabolism that reached a plateau at day 3 of therapy but the patients that received moderate insulin therapy received higher doses of insulin and showed increased levels of protein metabolism [1].

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The study by Hsu and colleagues [1] is in agreement with a recent study by Jeschke and colleagues in which the authors determined the ideal glucose range for intensive insulin therapy in severely burned children [6]. Using statistical modeling, Jeschke and colleagues found that a blood glucose concentration of 130 mg/dl is the most beneficial for this patient population. A blood glucose concentration of 130 mg/dl avoids the side effects associated with hyperglycemia and also prevents hypoglycemia, which is equally detrimental. This glucose concentration is effective and safe in burn patients, and is reflected in the current sepsis guidelines from Dellinger and colleagues in which they recommend that blood glucose levels be maintained at 150 mg/dl [7]. Hsu and colleagues are therefore following this range and have found benefits in terms of muscle metabolism [1], which is encouraging since the levels of insulin necessary to maintain tight glycemic control are most likely sufficient to induce anabolic effects.

In conclusion, the overwhelming research to date indicates that insulin therapy for critically ill patients ameliorates many of the metabolic and systemic abnormalities that occur – for example, insulin counteracts hyperglycemia [8], decreases the inflammatory response in severe injury [9], improves liver function [10] and stimulates protein metabolism [11]. While it has been known for some time that insulin therapy decreases whole-body protein loss [12] and stimulates protein synthesis in muscle [13], the current study by Hsu and colleagues provides important evidence that the insulin dose which maintains the blood glucose level at 130 mg/dl can have anabolic effects [1]. This is particularly beneficial for critically ill patients where these doses of insulin could stimulate protein synthesis and maintain muscle mass while avoiding the risks of hypoglycemia or other adverse events. Based on our own data and other trials, we are in agreement that glucose levels should be targeted around 130 mg/dl in critically ill, burn and trauma patients.

Competing interests

The authors declare that they have no competing interests.

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