

Is there a role for metformin in the ICU?

Commentary on

Advantage of adjunct metformin and insulin therapy in the management of glycemia in critically ill patients. Evidence for nonoccurrence of lactic acidosis and needing to parenteral metformin

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A severe burn, trauma or critically ill patients is associated with metabolic disturbances, with hyperglycemia and insulin resistance representing one of the major metabolic alterations. During the early phases hyperglycemia is due to an increased rate of glucose appearance along with an impaired tissue extraction of glucose leading to an increase of glucose and lactate [1, 2]. Not only does burn, trauma, or the state of critical illness lead to inefficient insulin mediated glucose [3] and lipid metabolism [4], but also to an impaired anabolic effect on protein metabolism [5]. The clinical relevance of hyperglycemia was shown in recent studies. Patients with poor glucose control had a significantly higher incidence of bacteremia/fungemia and mortality [6-9]. In addition hyperglycemia exaggerates protein degradation, enhancing the catabolic response. These data indicate that hyperglycemia associated with insulin resistance represents a significant clinical problem in burn patients, in critically ill and trauma patients. Van den Berghe and colleagues described the detrimental effects of hyperglycemia in critically ill patients, and they conducted multiple clinical studies investigating the effect of decreased glucose levels on outcome [8-10]. These authors showed that insulin administered to maintain glucose at levels below 110 mg/dl decreased mortality, incidence of infections, sepsis and sepsis-associated multi-organ failure in surgically critically ill patients [9]. In an "intent to treat" study the effects of insulin in medical ICU patients were investigated [8]. Intensive insulin therapy significantly reduced newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital. In a recent study the authors showed that insulin given during the acute phase not only improved acute hospital outcomes but also improved long-term rehabilitation and social reintegration of critically ill patients over a period of 1 year [11, 12], indicating the advantage of insulin therapy. In severely burned patients, insulin given

during acute hospitalization improved muscle protein synthesis, accelerated donor site healing time, and attenuated lean body mass loss and the acute phase response [13-16].

Intensive insulin therapy to maintain tight euglycemic control, however, represents a difficult clinical effort which has been associated with hypoglycemic episodes. Therefore, the use of a continuous hyperinsulinemic, euglycemic clamp throughout ICU stay has been questioned in multiple multicenter trials throughout the world and has resulted in a dramatic increase in serious hypoglycemic episodes [17]. In a recent multi-center trial in Europe [Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP)] the effect of insulin administration on morbidity and mortality in patients with severe infections and sepsis was investigated [18]. The authors found that insulin administration did not affect mortality but the rate of severe hypoglycemia was 4-fold higher in the intensive therapy group when compared to the conventional therapy group [18]. Maintaining a continuous hyperinsulinemic, euglycemic clamp in burn patients is particularly difficult because these patients are being continuously fed large caloric loads through enteral feeding tubes in an attempt to maintain euglycemia. As burn patients require weekly operations and daily dressing changes the enteral nutrition occasionally has to be stopped, which lead to disruption of gastrointestinal motility and the risk of hypoglycemia. Metformin has recently been suggested as an alternative means to correct hyperglycemia in severely injured patients [19, 20]. However, there are only few studies investigating the role of metformin in critically ill and trauma patients. Therefore Mojtahezadeh et al. conducted a study in which they determined whether metformin administration represent a beneficial adjunct in critically ill patients. The authors wanted to investigate the effectiveness and safety of metformin in glycemic control in patients traumatized by critical illness by measuring the blood glucose, lactate, and pH values, in addition to the patients' insulin requirements when insulin was co-administered with metformin. They showed that metformin is a safe adjunct, decreases insulin requirements and propose to add metformin to critically ill patients who have difficult titrations of blood glucose levels [21].

What is metformin? Metformin is an anti-diabetic drug from the biguanide class of oral hypoglycemic agents and is the most widely used, anti-diabetic drug in the United States and one of the most prescribed drugs overall [22-24]. Recently, a large study demonstrated that metformin is also one of the safest anti-diabetic drugs. The exact mechanism by which metformin exerts its effects is unknown despite its known therapeutic benefits

[22-24]. Metformin reduces circulating lipids without affecting insulin secretion [25]. The glucose-lowering effects of metformin are attributable to both an increase in muscle glucose uptake and a decrease in hepatic glucose production [25, 26].

The findings of Mojtahezadeh et al. are remarkable as this is the first evidence that metformin is safe in an ICU setting and that metformin improves insulin sensitivity and requirements without causing hypoglycemia [21]. Do we understand how metformin works from this study? No, however, this is a step in a new direction that will hopefully initiate new studies investigating the effect of metformin in critically ill patients. We therefore like to conclude this editorial with the conclusion by the authors of this study: "Taking collectively, this preliminary study suggests that combination therapy with metformin and insulin is of benefit to hyperglycemic critically ill patients, but that remains to be confirmed by more experimental and clinical investigations with larger sample numbers in different types of patients" [21].

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