Best Practice & Research Clinical Anaesthesiology 23 (2009) 449–459

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

8

Molecular mechanisms behind clinical benefits of intensive insulin therapy during critical illness: Glucose versus insulin

Ilse Vanhorebeek, PhD, Associate Professor *, Lies Langouche, PhD, Post-doctoral Fellow [1]

Department of Intensive Care Medicine, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Keywords:
critical illness
intensive insulin therapy
glucose toxicity
insulin resistance

High blood glucose levels have been associated with morbidity and poor outcome in critically ill patients, irrespective of underlying pathology. In a large, randomised, controlled study the use of insulin therapy to maintain normoglycaemia for at least a few days improved survival and reduced morbidity of patients who are in a surgical intensive care unit (ICU). Since the publication of this landmark study, several other investigators have provided support for, whereas others have questioned, the beneficial effects of intensive insulin therapy.

In this review, we discuss the investigated potential molecular mechanisms behind the clinical benefits of intensive insulin therapy. We first describe the molecular origin of hyperglycaemia and the impact of the therapy on insulin sensitivity. Next, the molecular basis of glucose toxicity in critical illness and the impact of intensive insulin therapy hereon are described, as well as other non-glucose-toxicity-related metabolic effects of intensive insulin therapy.

Clinical benefits of intensive insulin therapy

Critical illness is hallmarked by numerous endocrine and metabolic disturbances, including the development of hyperglycaemia consequent to insulin resistance and increased hepatic glucose production, which is referred to as ‘stress diabetes’ or ‘diabetes of injury’.[1] High blood glucose levels

* Corresponding author. Tel.: +32 16 330242; Fax +32 16 330932.
E-mail addresses: ilse.vanhorebeek@med.kuleuven.be (I. Vanhorebeek), lies.langouche@med.kuleuven.be (L. Langouche).
[1] Tel.: +32 16 330242; Fax: +32 16 330932.

1521-6896/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bpa.2009.08.008

have been associated with morbidity and poor outcome in critically ill patients, irrespective of underlying pathology.[2] This association may merely reflect that the degree of hyperglycaemia is a marker of the severity of illness. Alternatively, it may indicate that hyperglycaemia itself contributes to the disease and that there is a causal relationship between hyperglycaemia and clinical complications.

For a long time, it was believed that a mild degree of hyperglycaemia would be beneficial for organs that largely rely on glucose for energy provision, but do not depend on insulin for glucose uptake. With the publication of the first, landmark Leuven randomised clinical study on intensive insulin therapy in adult surgical critically ill patients this concept was challenged.[3] At the time of the study, standard care consisted of treating only excessive hyperglycaemia above the renal threshold (>220 mg dl^{-1}, known to induce osmotic diuresis and infectious complications) with infusion of exogenous insulin, which was discontinued when levels fell below 180 mg dl^{-1}. This approach was compared with strict glycaemic control to normal fasting blood glucose levels (80–110 mg dl^{-1}) with insulin infusion, labelled 'intensive insulin therapy'. Intensive insulin therapy strikingly lowered mortality in-ICU and in-hospital, most pronounced for long-stay patients, and improved long-term outcome.[3,4] Furthermore, it reduced the incidence of several common critical illness-associated clinical complications. These included the prevention of bloodstream infections, acute renal failure, critical illness polyneuropathy and hyperbilirubinaemia and reduced need for red blood cell transfusions and prolonged mechanical ventilation, all culminating in a reduced need for prolonged intensive care.[3] The therapy also protected the central and peripheral nervous system from secondary insults and improved long-term rehabilitation of patients with isolated brain injury.[5] Subsequently, two large randomised clinical studies were performed by the same investigators in a strictly medical population of critically ill adults[6] and in critically ill children[7], again comparing standard care versus fasting glucose levels targeted to age-adjusted normal levels. These studies largely reproduced the previously observed clinical benefits of intensive insulin therapy.[3,5–9] Since the publication of the first Leuven study, several other investigators have provided support for the beneficial effects of intensive insulin therapy[10–15], whereas in other studies no clinical benefits were seen.[16,17] Due to these apparently conflicting results, the optimal level and modality of glucose control remain an area of heavy debate.[2,18–20] In general, however, studies that were unable to detect clinical benefit already started with lower glucose levels in the standard care group than did the Leuven studies.[21,22] This may suggest that prevention of excessive hyperglycaemia is what evokes the benefit, although the combination with inadequate glucose monitoring and poor achievement of the glycaemic targets may have played a role.[18–20]

Hence, whether strict normoglycaemia should be maintained, as in the Leuven studies, or whether an intermediate glucose range should be targeted needs to be studied further using appropriate glucose monitoring tools. An indication for the answer to this question has been provided by multivariate analyses on the two adult randomised controlled trials performed in Leuven.[8,23] Compared with the intermediate blood glucose levels of 110–150 mg dl^{-1}, mortality was higher with blood glucose >150 mg dl^{-1} and lower with glucose <110 mg dl^{-1}. The largest benefit was gained by prevention of the excessive hyperglycaemia. However, the reduction of blood glucose levels below 110 mg dl^{-1} seemed to be crucial for the prevention of events that cause morbidity such as bacteraemia, anaemia and acute renal failure.

Mechanism of stress hyperglycaemia and blood glucose control

Insulin resistance and glucose uptake

The stress imposed by any type of acute illness or injury results in insulin resistance, glucose intolerance and hyperglycaemia. Despite high blood glucose levels and abundantly released insulin, hepatic glucose production is up-regulated in the acute phase of critical illness. Hepatic insulin resistance is further characterised by elevated circulating levels of IGF-binding protein-1 (IGFBP-1).[24–26] Elevated levels of cytokines, growth hormone, glucagon and cortisol might play a role in this increased gluconeogenesis. Several effects of these hormones oppose the normal action of insulin, resulting in an increased lipolysis and proteolysis and providing substrates for gluconeogenesis. Catecholamines, which are released in response to acute injury, also enhance hepatic glycogenolysis and inhibit