

Mechanisms of Insulin-Induced Alterations in Metabolism during Critical Illness

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Through the explosion of therapeutic possibilities within the setting of intensive care medicine, patients can nowadays survive previously lethal disease states. Specific endocrine approaches to critical illness have always been limited to sporadic trials and isolated schools advocating rigorous metabolic control. This is in stark contrast with the boom of therapeutic possibilities for diabetes mellitus and coronary artery disease, where tight glycemic and lipemic control are now common practice. The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) [1] showed an improved outcome of diabetic patients with myocardial infarction upon ‘moderate’ blood glucose control. As a further step, a large prospective, randomized, controlled trial was set up to examine the effect of ‘strict’ glycemic control below 6.1 mmol/l (110 mg/dl) with exogenous insulin on the mortality and morbidity of critically ill patients [2], both diabetic and nondiabetic. Over a 1-year period, 1,548 mechanically ventilated patients admitted to the intensive care unit (ICU), predominantly after extensive surgery or trauma, were randomly allocated to either intensive insulin therapy with blood glucose levels kept tightly between 4.5 and 6.1 mmol/l (80–110 mg/dl), or the conventional approach which only recommended insulin therapy when blood glucose levels exceeded 12 mmol/l. Strict blood glucose control reduced the intensive care mortality of critically ill patients by more than 40%. Even patients in the conventional insulin treatment schedule with only moderate hyperglycemia (6.1–11.1 mmol/l), the equivalent of the therapeutic arm in the DIGAMI study, showed higher mortality compared to the patients in the strict glycemic control schedule [3]. Intensive insulin therapy also had a major effect on morbidity. It decreased the duration of ventilatory support and intensive care stay,

reduced the need for blood transfusions, and lowered the incidence of septicemia and excessive inflammation.

Even more striking, intensive insulin therapy caused a highly significant decrease in the development of critical illness polyneuropathy and acute renal failure. The exact mechanisms underlying this dramatic improvement in the outcome of critically ill patients are as yet unknown.

Therefore, we embarked on studies to delineate the effect of intensive insulin therapy on key metabolic pathways such as glucose and lipid homeostasis and, in view of the deleterious effects of exogenous growth hormone (GH), also on the somatotrophic axis.

Glucose Homeostasis

The stress of critical illness evokes insulin resistance and hyperglycemia [4]. A causative factor in this is the immobilization of critically ill patients in whom exercise-stimulated glucose uptake in skeletal muscle disappears. Additionally, insulin-stimulated glucose uptake is hampered through a combined inhibition of glucose transporter-4 (GLUT-4)-dependent insulin-stimulated glucose uptake and glycogen synthase activity. However, the decrease in insulin-stimulated glucose uptake in skeletal muscle and adipose tissue is offset by a massive increase in total body glucose uptake, of which the mononuclear phagocyte system in the liver, spleen and ileum is the main recipient. The overall increased peripheral glucose uptake in light of hyperglycemia only underscores the pivotal role of increased hepatic glucose production during critical illness, which cannot be suppressed by exogenous glucose. Normally, gluconeogenesis and glycogenolysis, the components of hepatic glucose production, are inhibited by insulin. Increased serum insulin levels in combination with impaired peripheral glucose uptake and elevated hepatic glucose production indicate insulin resistance during critical illness.

In diabetes mellitus, the lack of a hepatic insulin effect is indirectly illustrated by elevated insulin-like growth factor (IGF)-binding protein-1 (IGFBP-1) levels, a principally liver-derived protein which is suppressed by insulin at the transcriptional level. Interestingly, in protracted critically ill patients high serum IGFBP-1 levels have been linked to increased mortality [5–7] and catabolism [8].

Hence, the hypothesis was that intensive insulin therapy would overcome hepatic insulin resistance, resulting in a suppression of IGFBP-1 levels and gluconeogenesis, associated with the concomitant improvement in survival under intensive therapy. However, contrary to expectation, intensive insulin therapy did not suppress the elevated serum IGFBP-1 levels, despite its improvement in the intensive care outcome [9]. Nevertheless, the predictive value of a high-serum IGFBP-1 level for mortality remained as serum IGFBP-1 levels were much higher in those patients who ultimately died. In long-stay intensive care

patients, serum IGFBP-1 concentrations increased gradually from 3 weeks before death onwards, while levels decreased over time in patients who recovered. Since insulin treatment decreases serum IGFBP-1 levels in diabetes mellitus [10], these data suggest that another IGFBP-1 regulatory factor has taken over during critical illness. IGFBP-1 levels were higher in patients who died of cardiac or septic shock and sepsis as compared with those who died of severe brain damage. While the former causes of death are accompanied by low tissue perfusion, no such condition is expected in the latter. This explanation is quite plausible as IGFBP-1 gene expression is induced by tissue hypoxia [11]. Like IGFBP-1 mRNA levels, phosphoenolpyruvate carboxykinase gene expression in non-survivors was unaffected by the insulin treatment schedule. Phosphoenolpyruvate carboxykinase is the rate-limiting enzyme of hepatic gluconeogenesis, which is stimulated during critical illness. Its lack of responsiveness to intensive insulin therapy confirms the hepatic insulin resistance during protracted critical illness. In contrast, intensive insulin therapy increased gene expression levels of GLUT-4 and hexokinase-II (HXK-II) in skeletal muscle. The latter genes encompass the rate-limiting step in glucose uptake in skeletal muscle and adipose tissue and both are dominantly regulated by insulin.

In summary, our study indicated that intensive insulin therapy exerted its glucose-lowering effect through stimulation of peripheral glucose uptake rather than through the suppression of hepatic gluconeogenesis.

Lipid Homeostasis

The other important feature of critical illness is a strongly deranged serum lipid profile. The increased serum triglyceride levels together with decreased serum low- (LDL) and high-density lipoprotein (HDL) cholesterol levels resemble the dyslipidemia of the diabetic patient [12, 13]. However, only scant reports have been published on the pathophysiological implications of the altered serum lipid profile during critical illness and therapeutic strategies to reverse this were missing.

For the first time, we have shown that intensive insulin therapy could partially restore the deranged serum lipid profile [14]. The strongest effect of this therapy was on hypertriglyceridemia, which was totally obliterated. Serum levels of HDL and LDL increased, but remained lower than those of healthy subjects (80–150 mg/dl for LDL and 35–60 mg/dl for HDL).

Recently, lipoproteins and chylomicrons have been shown to act as endotoxin scavengers and hence prevent death in animal models [15, 16]. For that reason, intensive insulin therapy may have improved the overall endotoxin scavenging function. Contrary to the proposed infusions of lipoproteins, intensive insulin therapy would be a more integrated approach to correct the deranged serum lipid profile and improve outcome. This was demonstrated by

multivariate logistic regression analysis in which the improvement in the deranged lipidemia explained a significant part of its beneficial effect on mortality and organ failure. Surprisingly this surpasses the effect of glycemic control and insulin dose. Likewise, the effect of intensive insulin therapy on inflammation, reflected by a lowering of the serum C-reactive protein concentrations [17], was no longer independently related to the outcome benefit when the changes in lipid metabolism were taken into account. This may suggest a link between the anti-inflammatory effect of intensive insulin therapy and the amelioration of derangement of the lipid profile.

However, the mechanisms involved in the link between esterified cholesterol, or its carrying particles, and the outcome of prolonged clinical illness remain to be elucidated. Nevertheless, one could speculate on a role for LDL and HDL as scavengers for endotoxin or as transporters for cholesterol as an essential substrate for the integrity of cell membranes.

In addition, unequivocal proof of the benefit of lipemic control in critical illness can only be provided by directly targeting HDL and LDL at levels higher than 15 and 20 mg/dl, respectively, as deduced from the cutoff values from our study. In addition, serum triglyceride levels around 100 mg/dl seem an ample therapeutic option.

The Somatotrophic Axis

Except for hyperglycemia and hypertriglyceridemia, prolonged critical illness is most typically characterized by a 'wasting syndrome'. While muscle mass gradually melts away, adipose tissue mass is maintained, mimicking the change in body mass composition of GH-deficient subjects. This wasting takes place despite adequate nutritional support [18]. Other studies hinted at a link between the catabolic state of critical illness and a suppressed somatotrophic GH-IGF-IGFBP axis [19, 20]. This protein hypercatabolism gives rise to functionally important complications such as prolonged immobilization, delayed weaning from mechanical ventilation, impaired tissue repair and atrophy of the intestinal mucosa, together resulting in prolonged convalescence, conceivably with a higher cost burden. Driven by systemic inflammation in combination with the metabolic derangement, the 'wasting syndrome' boils down to a rerouting of amino acids such as glutamine and alanine from skeletal muscle to the liver for the synthesis of acute phase proteins and the gluconeogenesis. This fits with the redirection of the energy provision during critical illness. This reliance on amino acids as an energy source becomes even more pronounced as organ failure progresses.

In order to reverse the catabolic state, GH therapy in critically ill patients has been suggested and tested. Quite surprisingly, Takala et al. [21] showed a doubling of the mortality upon GH administration in prolonged critically ill patients. This occurred in spite of a GH-induced increase in serum IGF-I and

IGFBP-3 levels, used as markers of its efficacy. In contrast, intensive insulin therapy appeared to exert an anabolic effect during critical illness because the presumed clinical effects of muscle breakdown, such as prolonged mechanical ventilation and hospital stay, were improved [2]. The intriguing disparity between markers of anabolism (IGF-I and IGFBP-3) and the clinically relevant patient outcome, warranted a thorough analysis of the somatotrophic axis during intensive insulin therapy.

In our study of 363 prolonged critically ill patients, mean GH levels were increased on day 1, but decreased again on day 8 and the last day of intensive care stay, both in survivors and non-survivors [22].

This confirms previous findings of elevated GH secretion during the acute phase of critical illness [19] and a relative suppression (low or normal mean GH concentrations) during protracted critical illness [23]. Although insulin treatment in diabetes mellitus is known to inhibit GH secretion, intensive insulin therapy compared to conventional treatment increased serum GH levels in critically ill patients. The detailed effect of intensive insulin therapy on the GH secretory profile could not be appreciated in our study as only single sample GH analysis was performed.

To gauge the peripheral GH response, serum levels of the GH-dependent ternary complex proteins were assessed. This complex of IGF-I, IGFBP-3 and acid-labile subunit (ALS) is decreased under a wide array of catabolic conditions including starvation [24] and critical illness [8, 6]. Contrary to expectation, intensive insulin therapy prevented the recovery over time of the circulating levels of these ternary complex proteins, a time-dependent recovery which did occur in the conventionally treated patients.

The stimulation of GH secretion and the concomitant suppression of IGF-I, IGFBP-3 and ALS suggested an induction of GH resistance by intensive insulin therapy. This conclusion is supported by the finding of suppressed GH-binding protein levels under the latter therapy. While intensive insulin therapy failed to suppress the insulin-regulated IGFBP-1, indicating hepatic insulin resistance, it clearly affected GH sensitivity of these critically ill patients. As patients with a lowered GH response had a better outcome, one could argue that the maintenance of GH resistance is a 'protective' response for survival. The latter hypothesis is supported by the observation that GH-receptor knock-out mice, which are extremely GH-resistant, live longer than wild-type mice [25]. Also, diabetic mice overexpressing GH antagonist or normal mice after GH antagonist G120K-PEG administration were protected from the development of diabetic glomerulosclerosis [26, 27]. This may be related to an increased insulin sensitivity in the GH-receptor knock-out mice [28], pointing to a constellation of reduced GH and increased insulin effects as a mechanism to provide a survival benefit. Alternatively, the suppression of the GH axis by intensive insulin therapy may have no causal link with its effect on outcome and may instead be seen as a detrimental catabolic side effect accompanying its beneficial impact on survival.

Our data provided further evidence that insulin and GH sensitivity are inextricably linked, and indicate that the patient with the best 'anabolic' parameters may not be the most favored to survive the ICU stay.

In summary, intensive insulin therapy lowered blood glucose levels probably through stimulation of peripheral glucose uptake and not through suppression of hepatic gluconeogenesis, and annihilated the rise in serum triglycerides with partially restored LDL and HDL levels. Intensive insulin therapy, while improving ICU survival, suppressed the somatotrophic axis, probably by inducing or prolonging the GH resistance present in the acute phase of severe illness. In a general perspective, a better understanding of the mechanisms of the endocrine therapies during critical illness may lead to custom endocrine management for the critically ill patient with even further survival benefits beckoning.

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