



The Role of Insulin in The Critically Ill Patients

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ABSTRACT

Hyperglycemia and insulin resistance are common in critically ill patients, even if there is no previous history of diabetes. Landmark study of Van den Berghe et al showed that intensive insulin therapy (maintenance of blood glucose between 80-110mg/dl) significantly reduced the mortality. The greatest reduction in mortality involved death due to multiple-organ failure with a proven septic focus. Beneficial action of insulin is not only due to its hypoglycemic action but by several other mechanism.(e.g. anti-inflammatory, antioxidant and vasodilatation action.)

INTRODUCTION

Emerging information from different basic and clinical arenas has centered attention on the crucial role of insulin during stress and in particular in the critically ill patients. Hyperglycemia is a relatively common condition among critically ill patients, even in those who have not previously had diabetes mellitus. The cause of this stress-induced hyperglycemia are multifactorial, however, they are mainly related to insulin resistance, insulin deficiency and overfeeding.

Critically ill patients who require intensive care for more than five days have a 20% risk of death and substantial morbidity. Critical-illness polyneuropathy and skeletal-muscle wasting prolong the need for mechanical ventilation. Moreover, increased susceptibility to severe infections and failure of vital organs amplify the risk of an adverse outcome. Hyperglycemia or relative insulin deficiency (or both) during critical illness may directly or indirectly confer a predisposition to complication, such as severe infections, polyneuropathy, multiple-organ failure, and death.

Van den Berghe et al¹ performed a prospective, randomized, controlled study involving adults admitted to surgical intensive care unit who were receiving mechanical ventilation. On admission, patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg/dl) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dl and maintenance of glucose at a level between 180 and 200 mg/dl).

At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0% with conventional treatment to 4.6% ($P < 0.04$, with adjustment for sequential analyses). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2% with conventional treatment, as compared with 10.6%

with intensive insulin therapy; $P = 0.005$). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red cell transfusions by 50%, and critical-illness polyneuropathy by 44%, and the patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care.

Krinsley² in his retrospective study of more than 1800 critically ill medical and surgical patients, consecutively admitted to the ICU at the Stamford Hospital, Stamford, Conn, revealed that patients with increasing level of hyperglycemia have progressively greater mortality. This observation by Krinsley reflects a broader patient population than the predominantly cardiac surgical Van den Berghe et al reported.

Cardiothoracic surgical ICU patient were not included in Krinsley's patient database, and his study included almost twice the number of known diabetic patients compared with the Van den Berghe et al study.

BENEFICIAL EFFECTS OF INSULIN IN CRITICALLY ILL PATIENTS

Control of hyperglycemia

Control of blood sugar by exogenous insulin at a level between 80-100 mg/dl significantly improves the prognosis as reported by Van den Berghe et al in his land mark study.

Anti-inflammatory and antioxidant

Insulin suppresses the production and harmful action of tumor necrosis factor A, macrophage, migration inhibitory factor and free radical as reported by Das UN.³

Recent studies provided further evidence for the anti-inflammatory actions of insulin. A significant decrease in the concentration of plasma soluble intracellular adhesion molecule-1, monocyte chemoattractant protein-1, plasminogen activator inhibitor-1 and decreased generations of reactive oxygen species were found after insulin infusion.⁴ On the other hand, high glucose induced acute inflammatory events in rats, as evidenced by increased leukocyte rolling, leukocyte adherence, leukocyte transmigration through mesenteric venules associated with attenuation of endothelial nitric oxide release, and increased expression of P-selection on endothelial surfaces.⁵ Local application of insulin may explain why insulin is more beneficial during infections and after surgery than oral antidiabetic drugs for type 2 diabetes mellitus.

These actions of insulin and glucose on various parameters associated with inflammation are interesting in light of the relationship between human leukocyte antigen (HLA)-DR and CD11b expression, free radical generation, and development and recovery from postoperative or post-trauma sepsis.^{6,7} In-patients with an uneventful recovery from severe trauma or surgery, the level of monocyte HLA-DR expression fell within hours of trauma or surgery, but returned to normal within a week. In those who developed infection but recovered, 3 weeks were required for HLA-DR expression to normal.

Finally, in those who developed infection and sepsis and who died as a result, HLA-DR expression fell and never returned to normal.^{6,7} Similarly, after uncomplicated elective major abdominal surgery, expression of CD11/CD18 (which is necessary for adhesion of neutrophils to endothelium) was unchanged throughout the postoperative period, in patient who developed postoperative sepsis, the expression of CD11b was significantly elevated within 24 hrs of surgery.^{6,8} Production of hydrogen peroxide by neutrophils followed a pattern similar to that of CD11b expression in these two groups of patients. Even production of hypochlorous acid, a marker of neutrophil activation, was decreased in patients who had uncomplicated abdominal surgery as compared with those who develop sepsis 7-10 days later, in whom its production was augmented to supranormal levels on postoperative day 1.⁹ It is interesting to note that these changes in HLA-DR and CD11b expression, hydrogen peroxide, hypochlorous acid production were noted even when there was no evidence of infection.

It is interesting to know that the variation in neutrophil activation and HLA-DR expression between different groups of patients was noted preoperatively but only after surgery or trauma, which is somewhat similar to the development of insulin resistance in patients only when they are ill but not before illness.¹ This suggests that there are some very clear biologic variations in the response in different individual to injury, surgery, infection, or sepsis that determines their ability to recover from the onslaught of the initial event. The variation in neutrophil activation, HLA-DR expression, concentrations of plasma polyunsaturated fatty acids, and or insulin resistance observed could account for some of this biologic variation. Because insulin and glucose influence neutrophil function, free radical generation, cytokine generation and their action and nitric oxide production and modulate essential fatty acid metabolism, it may be worthwhile to measure some of these parameters in critically ill patients.

Such an approach may aid in implementing appropriate measures to improve this survival.

Intensive insulin treatment reduces the number of deaths from multiple-organ failure with sepsis, regardless of whether there was a history of diabetes or hyperglycemia.¹⁴ Since the introduction of mechanical ventilation, few intensive care interventions have improved survival. Treatment of sepsis with activated protein C results in a 20% reduction in mortality at 28 days.¹⁵ Glycemic control is a preventive approach that is more broadly applicable to critically ill patients and that reduced mortality during intensive care by more than 40%.

Vasodilatation and antiplatelet action: Insulin stimulates the activity of the enzymes d-6-desaturase and d-5-desaturase; these enzymes are essential in the formation of γ -linolenic acid (GLA), and dihomo γ -linolenic acid (DGLA) from dietary linoleic acid, and of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from linolenic acid.¹⁰ DGLA and EPA are the precursors of prostaglandin E1 and prostaglandin I2 respectively, and are potent antiplatelet and antiaggregators and vasodilators. Furthermore, GLA, EPA, DHA, and prostaglandin E1 suppress the synthesis and production of tumor necrosis factor- α and interleukin-2 by human T-cells.^{10,11} This could be yet another mechanism by which insulin functions as an endogenous anti-inflammatory molecule. Furthermore, diets that are rich in EPA and DHA and continuous tube feeding or intravenous infusion of these fatty acids improved survival of experimental animals challenged with endotoxin.³ Earlier Das UN and colleagues showed that patients with septicemia have low concentration of GLA, DGLA, arachidonic acid, α -linolenic acid, and EPA in their plasma.^{11,12}

Prevents axonal degeneration: The exact cause of critical-illness polyneuropathy is unknown, but sepsis and the use of neuromuscular blocking agents, corticosteroids, and aminoglycosides are thought to have a role. The reduction in the risk of polyneuropathy with intensive insulin therapy, regardless of concomitant use of these medications, suggests that hyperglycemia, insulin deficiency, or both contribute to axonal dysfunction and degeneration.¹³ The linear relation between blood glucose levels and the risk of polyneuropathy suggests that maintenance of the lowest possible levels is necessary. The reduced need for mechanical ventilation in patients who received intensive insulin therapy is explained in part by the reduced rate of critical illness polyneuropathy, though a direct anabolic effect of insulin on respiratory muscles may also play a part. However, the exact mechanism by which morbidity and mortality were reduced remains largely speculative, since the effect of glycemic control can not be distinguished from those of increased insulin levels.

CONCLUSION

Intensive insulin therapy in critically ill patient reduces the mortality and morbidity. Beneficial effect of insulin is not only due to its hypoglycemic action but by several other mechanisms.

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