Insulin Resistance as Prognostic Indicator in Multi Organ Dysfunction Syndrome

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INTRODUCTION

Sepsis, the host response to infection, involves a series of clinical, haematological, inflammatory and metabolic responses that can ultimately lead to organ failure. Insulin resistance generally refers to resistance to the metabolic effects of insulin, including the suppressive effects of insulin on endogenous glucose production, the stimulatory effects of insulin on peripheral (predominantly skeletal muscle) glucose uptake and glycogen synthesis and the inhibitory effects of insulin on adipose tissue lipolysis. Sepsis is an insulin resistance state and degree of insulin resistance is directly proportional to the severity of stress response.

Multi organ dysfunction syndrome (MODS)

As per the definition proposed by a consensus conference committee in 1992, fever or hypothermia, leucocytosis or leucopenia, tachypnea and tachycardia are the cardinal signs of systemic response often called as systemic inflammatory response syndrome (SIRS). SIRS may be due to infections or a non infectious aetiology. Sepsis is defined as SIRS due to known infectious aetiology. When sepsis is associated with dysfunction of organs e.g. distant from the site of infection, the patient has severe sepsis. Severe sepsis may be accompanied with hypotension or evidence of hypoperfusion. When hypotension can not be corrected by infusing fluids, the diagnosis is septic shock. Mild hyperglycaemia in critically ill patients can also be harmful since it acts as procoagulant, induces apoptosis, impairs neutrophil function, increases risk of infection, impairs wound healing and is associated with increased mortality even after adjusting for severity of illness.

Older practice was to treat only marked hyperglycemia (e.g., >200 mg/dl) in acutely sick non-diabetic subjects but more recent evidence suggests that glycemic control should be much more stringent. Recent scientific experiments have clearly shown that strict blood glucose control in the range of 80-110 mg/dl significantly improves morbidity and mortality among critically ill patients. In the landmark prospective
randomized, controlled clinical trial conducted by Van den Berg et al involving adults admitted to surgical intensive care unit (ICU) who were on mechanized ventilation, intensive insulin therapy reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis by 41%, the median number of red blood cell transfusions by 50% and critical care neuropathy by 44%, and reduced length of mechanical ventilation and ICU care. 

Insulin resistance is a classic characteristic finding in patient with sepsis. It seems that the balance between insulin and its counter-regulatory hormones (cortisol, glucagon, growth hormone, and catecholamines) is disturbed in the metabolic response to sepsis. Metabolically, there are three major substrates that supply energy, namely free fatty acids (FFA), glucose, and amino acids (AA). It seems that one of the metabolic problems during sepsis is the inability to use FFA as a metabolic substrate and inter-organ substrate exchange is severely disrupted in sepsis. Impaired insulin sensitivity (insulin resistance) in the peripheral tissues results with increased availability of AA and FFA as a result of a shift toward lipolysis and proteolysis.

(a) Insulin
In the early phase of sepsis, there are low, circulating concentrations of insulin in serum, although this does not seem to be caused by decreased secretion but rather increased clearance. In the chronic phase, there seems to be a non pulsatile and insufficient secretion of insulin, as well as reduced biologic response peripherally and in the liver, a condition resembling Type 2 DM.

(b) Cortisol
The hypothalamus-pituitary-adrenal-axis response to acute illness is through an increase in the release of adrenocorticotropic hormone (ACTH) and inflammatory mediators(TNF-alpha). ACTH and an activated renin-angiotensin system give rise to an increased secretion of aldosterone and cortisol which shifts the metabolism, by increasing the blood levels of glucose, FFA, and AA so as to ensure availability of substrates to vital organs such as the brain by inducing insulin resistance. In prolonged critical illness, serum ACTH is found to be low due to ensuing secondary failure of the pituitary but cortisol concentrations remain elevated, indicating that here this phase, cortisol release may be driven through an alternative pathway possibly involving endothelin.

(c) Growth hormone (GH)
During acute, critical illness, high baseline levels and more frequent peaks are seen, and as is the case for insulin, the pulsatility is thought to be important for the biologic effects. GH carries out most of its anabolic effects through insulin-like growth factor 1 (IGF-1), and the levels are low in critical illness. The alterations have been interpreted as peripheral resistance to GH and have been observed in human and animal models of acute stress. As acute, critical illness becomes chronic, GH continues to be released in a pulsatile manner. The amount of GH released in each pulse is much smaller, and the level of circulating GH between pulses is higher. This response has been described in humans and was recently confirmed in an animal model of prolonged, critical illness.

(d) Glucagon
As a classical counter-regulatory hormone, glucagon possesses an important role in maintaining euglycemia by stimulating hepatic glucose output during fasting and acute illness. The levels during infection or stress are high. Glucagon increases hepatic glucose output primarily by inducing glycogenolysis.

(e) Catecholamines
The levels of endogenous catecholamines are generally high during sepsis. Furthermore, many patients are treated with exogenous vasopressors in pharmacological doses as a result of hypotension, peripherally, epinephrine and beta adrenergic stimulation rapidly inhibit insulin-mediated glucose uptake (IMGU) by induction of insulin resistance, mainly in the skeletal muscle. The insulin-signalling pathway may be altered by alpha adrenergic stimulation by cyclic adenosine monophosphate (cAMP) and cAMP-independent mechanisms.

(f) Amino Acid metabolism in sepsis
The quantitatively significant AA like alanine and glutamine released into the bloodstream as a consequence to net proteolysis in skeletal muscle are taken up by the liver and used for acute-phase protein synthesis and GNG. The catabolic response in skeletal muscle is mediated by a number of regulators the most important being glucocorticoids and cytokines(TNF-α).

(g) Lipid metabolism in sepsis
During sepsis, the liver increases its uptake of FFA and glucose as a result of increased levels in plasma. The glucose is metabolized in the hepatocyte to malonyl-CoA, which is known to inhibit the action of carnitine-palmitoyl transferase (CPT), the mitochondrial-membrane enzyme
responsible for transport of long-chained FFA into the mitochondria for oxidation. The accumulation of malonyl-CoA also increases the hepatic FFA, triglycerides (Tg), and very low density lipoprotein (VLDL) synthesis leading to further increase in the plasma FFA, Tg, and VLDL. As FFA and glucose blood levels increase, they interact, and FFA is suggested to impair glucose metabolism at various sites, one being inhibition of glucose oxidation and another being stimulation of protein kinase C (PKC).

(h) Glucose Metabolism In Sepsis

It is well known that any type of acute illness or injury results in insulin resistance, glucose intolerance, and hyperglycemia, a constellation termed “diabetes of injury”. Sepsis induces hepatic insulin resistance by increasing hepatic glucose production with ongoing gluconeogenesis despite hyperglycemia. This increases insulin release which is characterized by elevated circulating levels of IGF-binding protein-1 (IGFBP-1). The counter regulatory hormonal responses (catecholamines, cortisol, glucagon, and growth hormone), cytokine release, and signals from the nervous system, all affecting glucose metabolic pathways, bring about the diabetes of injury. Proinflammatory cytokines affect glucose homeostasis indirectly, by stimulating counter regulatory hormone secretion, and directly, by altering insulin receptor signalling.

MECHANISM OF ACCELERATED GLUCOTOXICITY IN MODS

There are two possible explanations for hyperglycemia to be more acutely toxic in patients with MODS than in healthy individuals or patients with diabetes mellitus. The first is accentuated cellular glucose overload, and the second is more pronounced toxic side effects of glycolysis and oxidative phosphorylation.

(a) Cellular glucose overload in the critically ill

The central and peripheral nervous system, hepatocytes, and endothelial, epithelial, and immune cells are cellular compartments that take up glucose independently of insulin. Three glucose transporters, GLUT-1, GLUT-2, and GLUT-3, facilitate insulin-independent glucose transport in these tissues.

(b) More pronounced toxic side effects of oxidative phosphorylation in the critically ill

Besides cellular glucose overload, vulnerability to glucose toxicity may be due to increased generation of and/or deficient scavenging systems for ROS produced by activated glycolysis and oxidative phosphorylation (Fig. 1). Excessive glycolysis and oxidative phosphorylation may result in more peroxynitrite generation in the critically ill. The ensuing nitration of mitochondrial complexes I and IV, MnSOD (manganese superoxide dismutase), GAPDH (Glyceraldehyde 3-phosphate dehydrogenase), and VDAC (voltage-dependent anion channel) may suppress the activity of the mitochondrial electron transfer chain, impair detoxification of superoxide, shuttle glucose into toxic pathways, and increase apoptosis, respectively. These toxic effects may explain organ and cellular system failure related to adverse outcome in the critically ill.

(c) Interaction between leukocytes and endothelium

The metabolic derangements in sepsis have multiple consequences on inflammatory signalling. Disturbed interaction between leukocytes and endothelium plays a pivotal role in sepsis pathogenesis. Hyperglycaemia increases the rolling, adhesion, and transmigration of leukocytes by up regulating the adhesion molecules such as the endothelium, neurons, astrocytes, alveolar epithelial cells, and vascular smooth muscle cells. This “stress response” may overrule the normal protection of the cells against hyperglycaemia, thus allowing cellular glucose overload. Hence, particularly in critical illness, characterized by high circulating levels of all these regulators, all organ systems that take up glucose passively may theoretically be at high risk for direct glucose toxicity. In contrast, skeletal muscle and the myocardium, which normally take up glucose predominantly via the insulin-dependent GLUT-4 transporter, may be relatively protected against toxic effects of circulating glucose.
Fig.1: A diagrammatic representation of energy production in mitochondria and the mechanism of peroxynitrite generation

Once the PMNs have transmigrated the endothelial barrier, their ability to deal with invading microorganisms is crucially dependent on chemotaxis, fagocytic capability, and oxygen dependent superoxide production (respiratory burst). Hyperglycemia and insulin resistance affect the basic functions of PMNs, and this could bear consequence on the PMN dysfunction observed during sepsis.

(d) Macrophage migration inhibitory factor (MIF)
MIF is known to be a regulatory cytokine with a stimulatory effect on macrophage function and counteracting the effects of glucocorticoids on these cells. MIF is secreted constitutively by the anterior pituitary gland, by immune cells in response to proinflammatory stimuli, and by pancreatic β cells in response to glucose stimulation. Further, MIF acts in an autocrine manner to stimulate insulin secretion. This result suggests that an improvement in insulin resistance will lead to MIF release. From this mechanism, it may be speculated that insulin therapy during sepsis could result in increased MIF release, although as yet, no other data exist supporting this hypothesis.

(e) Mannose-binding lectin (MBL)
Deficiency of MBL is associated with an increased susceptibility to infections. The study on intensive insulin therapy in ICU patients by Van den Berghe et al recently measured MBL levels in a subgroup of patients who needed prolonged intensive care (5 days) and were the ones...
benefiting from the intensive insulin therapy. In the group treated with the conventional insulin regimen, MBL levels were overall higher. Patients dying during ICU stay had lower MBL compared with ICU survivors in this group, but this was not the case for patients in the intensive insulin-treated group. The result suggests that insulin has an inhibitory effect on the systemic release of this marker of innate immunity and at the same time, attenuates the adverse effects of low-serum MBL.

(f) Cytokine production
Hyperglycemia has been found to influence the production of proinflammatory cytokines acutely and chronically. Binding of the lipopolysacharide of gram negative bacilli during sepsis releases nuclear factor-kB (NF-kB), which stimulates transcription of immuno regulatory cytokines TNF-α, interleukin -1β and IL-10 and induces insulin resistance. This mutually stimulatory property of glucose and proinflammatory cytokines could potentially aggravate inflammation in a physiologic setting characterized by cytokemia and hyperglycemia, such as sepsis.

STUDY ON INSULIN RESISTANCE IN MODS (MEDICAL I.C.U.)

The most recent publication by Das S et al., consisted of critically ill patients with multi-organ dysfunction syndrome (MODS), diagnosed as per modified Acute Physiology and Chronic Health Evaluation II (modified APACHE II) score criteria and admitted to the medical ward, were assessed for IR and beta cell function by using the homeostasis model assessment A (HOMA-A) and HOMA-B models respectively. Of the 80 consecutive patients enrolled, 60 were followed up to day 7. 16 patients died and 4 did not agree to follow up. Various cases of MODS were taken in the study. Hepatic failure (92.5%) was the most common organ system failure to be followed by renal (75%), neurological (75%), respiratory (72.5%) and hematological (5%) system involvement respectively. Those who died during follow up had respiratory (100%) and CNS (100%) involvement, followed by renal (62.5%) and hepatic failure (50%). Mortality rate was highest with four and more than four organ failure cases (21.05%).

There was significantly high insulin resistance (P<0.05) in patients with stress hyperglycaemia than those who were euglycaemic as shown in Table I. There was significant reduction in serum insulin (P<0.02) and insulin resistance (P<0.02) when these hyperglycaemic patients recovered from critical illness (Table II).

Of those who died (Table III), the first day mean insulin levels were high (13.80 +/- 14.72 micro/ml as well as IR 5.14 +/- 6.76 values), but they had statistically low beta cell function (46.45 +/- 433.64%) as compared to those who recovered (227.60 +/- 430.36%; p < 0.05). This suggests that, beta cell over exhaustion occurs in critically ill patients, because it was required to overcome the prevailing state of IR and has more bearing in patients having less than 4 organ failures, beta cell failure ensued from the onset in those who were more moribund and had more than four organs failing or those who died.

IR is a good and easily estimated method for assessing the severity of morbidity in critically ill patients, but it is not the appropriate indicator of mortality in patients with MODS having more than four organ failure as the degree

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<th>Table I. Comparison of insulin resistance and beta cell function in patients having stress hyperglycaemia with normal on the day of admission</th>
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<td><strong>Hyperglycaemia (n=36)</strong></td>
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<td>FBG (mg/dL)</td>
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<td>Insulin (µL/L)</td>
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<th>Table II. Comparison of mean values of insulin resistance and beta cell function in patients having stress hyperglycaemia on day 1 with their levels on day 7 (n=26)</th>
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<td><strong>Day 1</strong></td>
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of IR decreases with increase in organ failure and cause of death in these patients is multiple and not related to IR or beta cell function.

**SUMMARY AND CONCLUSION**

The metabolic response to MODS causes rapid breakdown of the body’s reserves of protein, carbohydrate, and fat leading to shift in the balance between insulin and its counter-regulatory hormones. Upsurge of counter regulatory hormones as the body’s defence mechanism to acute stress, circulating proinflammatory cytokines and prominent metabolic derangements envisage the state of insulin resistance in patients with sepsis and MODS. Further, increased release of amino acids and free fatty acids, resulting in increased blood levels of alternative substrates for metabolic fuel and decreased use of glucose for metabolic need of tissues which depend on insulin for glucose uptake produces this state of global catabolism. Insulin has the inherent capability to counteract the metabolic changes observed in patients with sepsis. Studies over a decade has shown that preventing acute hyperglycaemia with insulin therapy substantially improves the outcome in critically ill patients with MODS. The response of the body, with regards to insulin sensitivity and enhanced secretion of insulin from pancreatic β cells, in such situation behaves like a parabolic curve. With increase in IR there occurs accelerated β cells response till a zenith but with ensue of more and more organ damage (four or more) due to MODS there is β cells exhaustion and no further improvement in IR in these subset of patients. Therefore, Estimation of IR can be used as an objective tool, in patients with MODS with lesser number of organ failures, to monitor the progress from day one till recovery.

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