Insulin in Sepsis and Septic Shock

Undurti N Das

Abstract

NF-κB activation, and elevated concentrations of macrophage migration inhibitory factor (MIF), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, free radicals, inducible nitric oxide (iNO), and stress hyperglycemia occurs in sepsis and this leads to systemic inflammatory response and myocardial depression seen in sepsis and septic shock. Conversely, insulin suppresses production of MIF, TNF-α, IL-1, IL-6, and free radicals, enhances endothelial NO generation, and enhances the production of anti-inflammatory cytokines IL-4, and IL-10, corrects stress hyperglycemia and improves myocardial function. This supports my earlier proposal that insulin (with or without glucose and potassium) therapy to maintain euglycemia suppresses the inflammatory response, improves myocardial function, and thus, is of benefit in acute myocardial infarction, sepsis and septic shock.

INTRODUCTION

Serious infections and some noninfectious disorders such as trauma, pancreatitis, and following major abdominal and cardiovascular surgery trigger systemic inflammatory response or sepsis and when this results in hypotension and multiorgan dysfunction, it is referred to as septic shock.1,2 Septic shock is due to inappropriate increase in innate immune response by neutrophils, macrophages, and natural killer (NK) cells.

Pathobiology of sepsis and septic shock

Gram-positive and Gram-negative organisms, malarial parasite, fungi, endotoxin-containing organisms and other microbials proliferate and produce bacteremia and/or release toxins that stimulate the innate immune system, endothelial cells and other cells.1 These cells release interleukin-1 (IL-1), IL-2, IL-6, IL-8, tumor necrosis factor-α (TNF-α), platelet activating factor (PAF), endorphins, eicosanoids, nitric oxide (NO), oxygen free radicals, high mobility group 1 (HMG1), macrophage migration inhibitory factor (MIF), and chemokines. As a result of the action of various cytokines and chemokines, the expression of various adhesion molecules is enhanced. ILs, TNF-α, MIF, eicosanoids, and oxygen free radicals have profound effects on the cardiovascular system, kidneys, lungs, liver, central nervous system, and coagulation cascade (see Fig. 1). As a result renal failure, myocardial dysfunction, acute respiratory distress syndrome (ARDS), hepatic failure, and disseminated intravascular coagulation occur that may result in death.1,2 Both anti-TNF monoclonal antibody and IL-1 receptor antagonist are of no benefit in sepsis (reviewed in1,3). This suggests that new therapeutic strategies are necessary in the management of sepsis and septic shock.

Mediators in sepsis and septic shock

MIF, TNF-α, and ILs stimulate phospholipases inducing the release of AA, the precursor of 2 series prostaglandins (PGs) and 4 series leukotrienes (LTs), and the production of free radicals and inducible nitric oxide (iNO), which have potent pro-inflammatory actions.1 Members of the NF-κB (nuclear factor-(appa B) family are induced by cytokines and free radicals, which have a significant role in sepsis and septic shock. Patients who succumb to sepsis showed increased NF-κB activity that correlated with the APACHE-II score compared to those who recovered from sepsis.4-6 This led to the suggestion that suppression of NF-κB activity may be of benefit in sepsis and septic shock. But, transgenic animals expressing degradation-resistant IκBα in hepatocytes results in obstruction of NF-κB activation and were unable to clear Listeria monocytogenes from the liver and succumbed to sepsis and septic shock.7 On the other hand, adenosine, adenosine receptors and inosine have anti-inflammatory actions and their use improved survival of LPS-challenged animals.8,9 These are independent of the degradation of IκBα and NF-κB activation. Furthermore, NF-κB, IL-6, adenosine, inosine, and adenosine receptor agonists are necessary for the resolution of inflammation.10 In this context, it is important to note that IL-10 and TGF-β are anti-inflammatory cytokines that may mediate resolution of sepsis.11,12 Based on this, it is suggested that normally a delicate balance exists between pro- and anti-inflammatory molecules and when this balance is tilted more in favor of
pro-inflammatory molecules it results in sepsis and septic shock (Fig. 1). If so, restoring this balance is important to resolve and enhance recovery from sepsis and septic shock.

**Insulin Resistance Occurs In Sepsis And Septic Shock**

Insulin resistance is common in septic shock. Early hyperglycemic and later hypoglycemic phases occur in sepsis and septic shock. In sepsis glucose utilization rate in response to insulin infusion is decreased compared to control subjects, suggesting impaired insulin action in sepsis. This is due a decrease in whole-body glucose uptake with lack of response to the elevated insulin levels. Glucose uptake is elevated during the euglycemic and hypoglycemic stages of sepsis and is independent of changes in glucose and insulin.
Insulin resistance in sepsis could be in response to elevated concentrations of TNF-α, IL-1, IL-2, and/or IL-6. In the euglycemic or hypoglycemic phases of sepsis glucose uptake is enhanced secondary to increased glucose transporter protein-1 (GLUT-1) receptor expression that is preferentially metabolized to lactate. The elevated basal serum lactate, glucose, and insulin in the critically ill can be correlated with the APACHE-II score. Further, they show increase in serum glucose, free fatty acids (FFA), glycerol, and triacylglycerol, very low-density lipoprotein, and low-density lipoprotein and a substantial decrease in high-density lipoprotein cholesterol. In those who did not survive due to sepsis also have elevated serum lactate and free glycerol, indicators of lipolysis compared with survivors. This suggests that glucose and lipid metabolism that is influenced by insulin, is altered in sepsis. Hence, these parameters may be used as markers to predict prognosis in those with sepsis. These disturbances in glucose and lipid metabolism are due to the development of insulin receptor autoantibodies, insulin-like effect of endotoxin, perturbation by endotoxin of insulin action at the cellular level, and alterations in insulin secretion pattern. The presence of insulin resistance and altered insulin homeostasis in sepsis is as a result of diminished insulin-stimulated phosphorylation of insulin receptor, insulin-receptor substrate-1, and mitogen-activated protein kinase by endotoxin. Low insulin levels seen in these patients in the early stages of sepsis are caused by increased clearance and not due to decreased production, and alterations in corticosterone levels.

Insulin resistance seen in sepsis can be restored to normalcy by infusing insulin continuously. Studies revealed that in the early phase of sepsis (i.e., first 0.5-1 hour period as studied by using cecal ligation and puncture technique), plasma glucose levels increased, whereas plasma insulin and glucagon levels remained unchanged, but corticosterone levels increased 2.5 fold over control values. At the end of 20 hours, plasma glucose levels returned to normal, whereas insulin, glucagon, and corticosterone levels increased significantly, i.e., 40-fold, 6.5 fold, and 6-fold respectively. Thus the initial rise and subsequent decline in blood glucose levels depends to a large extent on the balance between plasma insulin and corticosterone concentrations. In view of this, continuous infusion of insulin (without inducing hypoglycemia or hypokalemia) might enhance tissue glucose uptake, suppress lactate, FFA, glycerol production, and lipolysis, and overcome corticosterone-induced insulin resistance and improve tissue perfusion and recovery. This is similar to the administration of insulin for diabetic ketoacidosis (DKA). Most patients with DKA are traditionally treated by “low-dose” insulin schedules in which 8 to 10 units of insulin (approximately 0.01 units/kg body weight) are infused continuously each hour. Most subjects with DKA respond adequately to this low-dose insulin regimen. But some patients do not respond to this regimen, presumably due to insulin resistance, and are given 25 to 50 units of insulin as an intravenous bolus, followed by an infusion of insulin in the form of glucose-insulin-potassium (GIK) regimen that improves cardiac performance and that myocardial dysfunction is not due to hypoglycemia of septic or endotoxin shock. These results also suggested that the beneficial actions of insulin on cardiac performance are due to mechanisms other than myocardial glucose transport.

Several animal and clinical studies suggested that GIK regimen preserved systolic and diastolic function in ischemia and reperfusion and protects the myocardium in patients undergoing open-heart surgery, although this is not without controversy. It is not clear why some studies showed positive results whereas others failed to show a benefit from the GIK regimen against myocardial dysfunction in septic shock. On a closer examination of these studies, it was noted that this could be due to the different doses of glucose and insulin used in various protocols.

For instance, Mauritz et al. used glucose 70%, 1g/kg and insulin 1.5 units/kg, whereas Bronsveld et al. employed glucose 50%, 1g/kg and insulin 1.5 units/kg. Mauritz et al. noted that their patients did develop hyperglycemia following GIK regimen since they used a lower dose of insulin relative to the concentration of glucose infused compared to Bronsveld et al. It is evident that studies in which higher concentrations of insulin were used showed better results than did those studies that employed lesser dose. Since stress...
hyperglycemia or even mild hyperglycemia with myocardial infarction is associated with increased mortality \(^{31}\) and that intensive insulin treatment to maintain blood glucose levels between 80 and 110 mg/dl is highly beneficial and reduces morbidity and mortality among critically ill. \(^{32}\) The negative between 80 and 110 mg/dl is highly beneficial and reduces intensive insulin treatment to maintain blood glucose levels transported in by insulin.

It is common knowledge that continuous intravenous infusion of insulin is superior to subcutaneous administration to control hyperglycemia, especially in patients with diabetes mellitus during the preoperative and postoperative periods. \(^{34}\) Improved diabetic control results in fewer wound infections and better wound healing. Earlier, I suggested that the beneficial effects of GIK regimen might extend beyond the control of hyperglycemia alone. \(^{24,30,33,35,36}\) GIK infusion may salvage myocardium, improve cardiac function, and decrease mortality by an absolute 10\%, provided that hyperglycemia is prevented. \(^{37,38}\) This beneficial effect is independent of glucose. A large trial \(^{35}\) conducted in a heterogeneous group of 1548 critically ill patients, in which it was noted that intensive insulin therapy to maintain blood glucose \(< 110\) mg/dl in predominantly nondiabetic patients admitted to surgical intensive care units and receiving mechanical ventilation showed a decrease in morbidity and mortality as compared with less intensively treated patients (blood glucose maintained between 180 and 200 mg/dl). In this study, it was also observed that intensive insulin therapy was associated with a decrease in pro-inflammatory markers compared to the control. This suggests that maintaining blood glucose concentrations \(< 110\) mg/dl is critical to derive the benefits of insulin treatment and reverse the inflammatory process in critically ill. This is supported by the observation that cardiac dysfunction induced by endotoxin administration was not related to arterial blood glucose concentrations, and that infusions of insulin but not glucose reversed cardiac failure and maintained normal performance. \(^{25,26}\) American College of Cardiology and the American Heart Association recommended intravenous GIK be given to patients with acute myocardial infarction (AMI), especially those who are poor candidates for thrombolytic therapy and in whom the risk for bleeding is high, \(^{39}\) because the GIK regimen is beneficial in treating AMI. GIK treatment improves the integrity and function of myocardial cells once glucose and potassium are transported in by insulin.

### Hyperglycemia and Insulin in Inflammation

Hyperglycemia increases the production of reactive oxygen species inside cultured aortic endothelial cells. \(^{40}\) Superoxide anion \((\text{O}_2^-)\) inactivated both eNO and prostacyclin \((\text{PGI}_2)\), which are potent vasodilators and platelet anti-aggregators. \(^{41}\) Free radicals are cytotoxic to myocardial cells and suppress myocardial function. Thus, free radicals induce endothelial and myocardial dysfunction. Glucose challenge stimulated reactive oxygen species generation in polymorphonuclear leukocytes and monocytes, even in otherwise normal subjects. \(^{42}\) High glucose concentrations enhanced leukocyte rolling; adherence, and transmigration with attenuation of eNO release, and increase expression of P-selectin on endothelial surfaces. \(^{43}\) Insulin not only attenuated these pro-inflammatory effects but also inhibited reactive oxygen species generation, and NF-κB in mononuclear cells, and reduced soluble intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 production by augmenting NO generation. \(^{33,35,36,44}\) suggesting that hyperglycemia triggers and accentuates inflammation whereas insulin prevents inflammation. \(^{33,45}\) One potential mechanism by which glucose initiated and perpetuates inflammation include its ability to stimulate the production of TNF-α, a potent pro-inflammatory molecule, which is capable of activating NADPH-dependent oxidase, and enhance NF-κB and ICAM-1 expression. \(^{33,46}\) These pro-inflammatory actions of glucose could be responsible for the increased morbidity and mortality seen in patients with AMI exhibiting hyperglycemia.

On the other hand, insulin suppresses NF-κB expression, free radical generation, MIF production, IL-1, IL-6, and enhances eNO generation \(^{13,33,44,45,47}\) and thus, inhibits inflammatory process. Insulin inhibited TNF-α production, \(^{48}\) and reversed the toxic effects of cachectin (TNF-α) in liver, lungs, kidney and spleen. \(^{49}\) This explains why intensive insulin therapy and GIK regimen are beneficial in critically ill, AMI, and sepsis and septic shock.

### Conclusions and Therapeutic Implications

Activation of NF-κB, and enhanced formation of TNF-α, MIF, and other pro-inflammatory cytokines, free radical generation and iNO occurs in sepsis and septic shock. The failure of monoclonal anti-TNF-α antibody to show any significant benefit in sepsis and septic shock led to the suggestion that there could be a major role for other molecules in this condition. In this context, the anti-inflammatory actions of insulin are note worthy. Many physicians are familiar with the use of insulin. Hence, it is not difficult to extend insulin therapy to sepsis and septic shock. It is also likely that insulin alone may not be of sufficient benefit for sepsis and septic shock, partly because many mediators are involved in this process. For instance, adenosine restores myocardial responsiveness to insulin during acute endotoxin shock, \(^{50}\) suggesting that its co-administration along with insulin need to be considered in sepsis and septic shock. Both adenosine and insulin are not only endogenous natural molecules but are also capable of suppressing NF-κB expression and TNF-α production and thus, antagonize inflammatory events. It is interesting to note that adenosine and insulin enhance wound healing. \(^{51}\) Hence, combined use of insulin and adenosine might be of significant benefit in sepsis and septic shock.

Any one single drug or molecule is unlikely to be of
significant benefit in sepsis due to its complex nature. In view of this, a combination of endogenous anti-inflammatory molecules such as insulin, adenosine, ω-3 fatty acids, and activated protein C need to be tried for their possible use in sepsis and septic shock (see Fig. 1), a condition for which no satisfactory therapy is available at present.

REFERENCES


