

## Letter Insulin and the critically ill

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Septic shock is the most common cause of death in intensive care units. In the USA alone, more than 100,000 deaths occur as a result of septicemia and septic shock per year (for review [1]).

In a prospective, randomized, controlled study involving adults admitted to surgical intensive care units and receiving mechanical ventilation [2], intensive insulin therapy substantially reduced mortality and morbidity. Intensive insulin treatment reduced the number of deaths from multiple organ failure with sepsis. Markers of inflammation were found to be less frequently abnormal in the intensive insulin treatment group than in the conventional treatment group, although the nature of the inflammatory markers measured was not given.

While commenting on this interesting study, Groeneveld and coworkers [3] outlined the possible mechanisms that could be responsible for this beneficial action of insulin in the critically ill. I was the first to suggest that the beneficial action of insulin (administered in the form of a glucose-insulin-potassium regimen) in patients with acute myocardial infarction, especially those who are poor candidates for thrombolytic therapy and in whom the risk of bleeding is high, can be ascribed to its ability to suppress the production and harmful actions of tumor necrosis factor- $\alpha$ , macrophage migration inhibitory factor, and free radicals [1,4,5].

Recent studies have provided further evidence for the anti-inflammatory actions of insulin. For instance, insulin infusion decreased concentrations of intranuclear NF- $\kappa$ B in mononuclear cells, increased levels of its inhibitor, and decreased the generation of reactive oxygen species and levels of p47 (the key protein of nicotinamide dinucleotide phosphate oxidase in obese persons) [6,7]. A significant decrease in the concentrations of plasma soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and plasminogen activator inhibitor-1 was noted in those obese persons after insulin administration. 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-selectin on endothelial surfaces [7,8]. Local application of insulin attenuated these inflammatory actions of glucose. This anti-inflammatory action of insulin may explain why insulin is more beneficial during infections and after surgery than are 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 [1,9,10]. 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 [9,10]. In those who developed infection but recovered, 3 weeks were required for HLA-DR expression to return 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. Similarly, after uncomplicated elective major abdominal surgery, expression of CD11b/CD18 (which is necessary for adhesion of neutrophils to endothelium) was unchanged throughout the postoperative period [9,11]; in patients who developed postoperative sepsis, the expression of CD11b was significantly elevated within 24 hours of surgery. 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 developed sepsis 7–10 days later, in whom its production was augmented to supranormal levels on postoperative day 1 [12]. It is interesting to note that these changes in HLA-DR and CD11b expression, hydrogen

peroxide, and hypochlorous acid production were noted even when there was no evidence of infection.

Insulin stimulates the activity of the enzymes  $\delta$ -6-desaturase and  $\delta$ -5-desaturase; these enzymes are essential in the formation of  $\gamma$ -linolenic acid (GLA) and dihomo- $\gamma$ -linolenic acid (DGLA) from dietary linoleic acid, and of eicosapentaenoic acid (EPA) and docosahexaenoic acid from  $\alpha$ -linolenic acid [13]. DGLA and EPA are precursors of prostaglandin  $E_1$  and prostaglandin  $I_2$ , respectively, and are potent platelet antiaggregators and vasodilators. Furthermore, GLA, EPA, DHA, and prostaglandin  $E_1$  suppress the synthesis and production of tumour necrosis factor- $\alpha$  and interleukin-2 by human T cells (for review [1,5,13]). 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 (for review [1]). Previously, my colleagues and I showed that patients with septicemia have low concentrations of GLA, DGLA, arachidonic acid,  $\alpha$ -linolenic acid, and EPA in their plasma [5,14].

It is interesting to know that the variation in neutrophil activation and HLA-DR expression between different groups of patients was noted not 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. This suggests that there are some very clear biologic variations in the response of different individuals to injury, surgery, infection, or sepsis that determines their ability or inability to recover from the onslaught of the initial event. The variations 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 their survival.

## Competing interests

None declared.

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