Commentary

Hyperglycemia may alter cytokine production and phagocytosis by means other than hyperosmotic stress

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Abstract

In the previous issue of *Critical Care*, Otto and colleagues used *in vitro* studies to explore the theory that immunomodulation, by correction of hyperglycemia, may be a contributing factor to the reported efficacy of intensive insulin therapy (IIT) in critically ill patients. They suggested that hyperglycemia via hyperosmolarity at supra-physiological levels potentiates the production of cytokines by peripheral blood mononuclear cells in response to lipopolysaccharide (LPS) stimulation and that it also reduces the responses of phagocytosis and oxidative burst in human granulocytes. The efficacy of IIT, they concluded, may be partially due to the correction of hyperosmolality. Other studies, however, have suggested that immunological responses to LPS in the presence of hyperglycemia are mediated by a mechanism other than hyperosmolality.

In the previous issue of *Critical Care*, Otto and colleagues [1] used *in vitro* studies to explore the theory that immunological activation induced by hyperglycemia is the result of hyperosmololaity. There is, in fact, a growing body of literature on osmotic regulation of cell function with possible implications on clinical outcomes [2]. At the forefront of this research is the use of hypertonic solutions to attenuate inflammation and immunosuppression following traumatic injury or sepsis [3-5]. It is widely known that administration of hypertonic solutions promotes a more balanced inflammatory response that may improve outcomes.

Otto and colleagues [1] suggest that immunomodulation, by correction of hyperglycemia, is a contributing factor to the efficacy of intensive insulin therapy (IIT) in critically ill patients, as proposed by Van den Berghe and colleagues [6]. Their *ex vivo* studies suggested that hyperglycemia, via hyperosmolarity, potentiates the production of cytokines by peripheral blood mononuclear cells (PBMCs) in response to lipopolysaccharide (LPS) stimulation. Furthermore, they examined the effect of hyperglycemia on phagocytosis and oxidative burst in human granulocytes and found the responses reduced with hyperglycemia. They postulated that the efficacy of IIT may be due, at least in part, to the correction of hyperosmolality induced by the lowering of blood glucose in response to insulin administration.

When assessing the effect of various solutions, there must be a clear distinction between the osmolality and tonicity. Osmolality and osmolarity refer to the property of a solution in the absence of reference to a membrane. Tonicity, on the other hand, is in reference to a membrane and is equal to the molecular concentrations of the solutes that exert an osmotic force across the membrane. Tonicity is dependent on the permeability of the solutes across the membrane. Thus, a highly permeable solute, such as glucose, does not exert a high tonicity. The majority of solutes that have been demonstrated to attenuate immunological response to injury or infection have been hypertonic, specifically, sodium chloride.

Otto and colleagues tried to address the issue of osmolality and tonicity by contrasting responses to hyperglycemia to those of an equally hyperosmotic solution, mannitol. Mannitol is a hypertonic solution, whereas glucose is usually considered isotonic. In response to LPS stimulation, hyperglycemia enhanced the production of interleukin (IL)-6 and IL-1β; however, mannitol produced no significant difference (compared with control). Otto and colleagues further investigated the hypertonicity of hyperglycemia by supplementing the incubation media with insulin to facilitate cellular uptake of glucose, resulting in a reduction in tonicity. The authors claimed that the inclusion of insulin partially reversed the production of cytokines; however, the only significant decrease was for IL-1β at the highest dose of insulin and glucose. The inability of mannitol to induce an increased

IIT = intensive insulin therapy; IL = interleukin; LPS = lipopolysaccharide; PBMC = peripheral blood mononuclear cell.

cytokine response and the absence of a consistent attenuation of the response with insulin suggest that factors other than hyperosmolality and hypertonicity are involved in the potentiation of cytokine responses by hyperglycemia.

Plasma osmolality is the sum of concentrations of the various solutes in a solution. Normal plasma osmolality ranges from 280 to 305 mOsm/kg. Otto and colleagues increased the glucose concentrations from 100 mg/dL to 250, 500, and 1,000 mg/dL. Theoretically, this would increase plasma osmolality by 8, 22, and 50 mOsm/kg, respectively. But as noted above, changes in cytokines were mostly observed at only the highest glucose level, representing a supra-physiological plasma glucose concentration and thus osmolality. Alterations in phagocytosis and oxidative burst in human granulocytes were determined at only the 500 mg/dL glucose level, an upper clinical limit. Similar supra-physiological increases in hyperosmolality have been used in the evaluation of other solutes. Thus, while these *ex vivo* findings are interesting, when the dose levels are considered clinical application may be limited.

The profound effect of hypertonic saline on immunological responses both *in vitro* and *in vivo* is extensively explored in the literature [2]. Exposure to hypertonic saline reduces PBMC function in response to activation of the p38 MAPK (mitogen-activated protein kinase). This reduction in function correlates with a decrease in inflammation and tissue damage *in vivo*. In contrast, Otto and colleagues demonstrated an increase in activity of PBMC function with exposure to hyperglycemia, suggesting an alternate function other than hyperosmolality.

In addition, Otto and colleagues found hyperglycemia to reduce phagocytosis and oxidative burst in human granulocytes. This response was similar to that observed acutely with hypertonic mannitol or saline [7]. There are various interpretations as to the advantages or disadvantages of attenuation of these responses. In the acute phase, this reduction may, in fact, attenuate tissue damage. However, it may lead later to increased susceptibility to infection.

Otto and colleagues reported enhancement of immunological responses to LPS in the presence of hyperglycemia. This response does not appear to be mediated by hyperosmolality as postulated by the authors but by another mechanism. Their study emphasizes the absence of information able to explain the underlying mechanisms responsible for the purported improvements in clinical outcomes of critically ill patients following correction of hyperglycemia by IIT.

Competing interests

The author declares that he has no competing interests.

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