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Oxidative stress and inflammation in hyperglycemic crises and resolution with insulin: implications for the acute and chronic complications of hyperglycemia

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Diabetic ketoacidosis (DKA) is a complex metabolic disorder caused by an absolute or relative insulin deficiency characterized by hyperglycemia as the result of increased hepatic glucose production and impaired glucose uptake in peripheral tissues, and increased lipolysis resulting in increased free fatty acid release from adipose tissue and increased hepatic production of ketone bodies that leads to metabolic acidosis. A strong body of evidence indicates that the excessive levels of nutrients, including glucose and fatty acids, are associated with a pro-inflammatory and oxidative state. Previous studies have reported significant elevation of IL-6, -1B and -8, and TNF-α and increased counterregulatory hormones in patients with uncontrolled diabetes and ketoacidosis (Hoffman et al., 2003; Stentz, Umpierrez, Cuervo, & Kitabchi, 2004). These elevations of circulating proinflammatory cytokines are reduced to normal levels promptly in response to insulin therapy and normalization of blood glucose concentration. Of interest, similar high levels of these markers occurred in patients with DKA and non ketotic hyperglycemia indicating that hyperglycemia, independent of the presence of ketoacidosis, induces changes in proinflammatory cytokines (Stentz et al., 2004).

Oxidative stress can be defined as an increase in reactive oxygen species (ROS) generation. ROS are formed from the reduction of molecular oxygen or by oxidation of water to yield products such as superoxide anion (O2), hydrogen peroxide (H2O2), and hydroxyl radical (OH) (Rains & Jain, 2011). In moderate amounts, ROS are involved in a number of physiological processes that produce desired cellular responses. However, large quantities of ROS in a biological system can lead to cellular damage of lipids, membranes, proteins, and DNA. Hyperglycemia causes an increase in oxidative stress markers such as membrane lipid peroxidation (Rains & Jain, 2011). The degree of lipid peroxidation is directly proportional to the glucose concentrations in diabetic patients. This is thought to occur via several well-studied mechanisms, including increased polyol pathway flux, increased intracellular formation of advanced glycation end products, activation of protein kinase C, or overproduction of superoxide by the mitochondrial electron transport chain (Brownlee, 2001; Rains & Jain, 2011).

Oxidative stress has been implicated in the development of chronic diabetic complications and also contributes to both the onset and the progression of diabetes. Chronic exposure to high glucose concentration can increase the metabolic flux in mitochondria through the

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hexosamine pathway, leading to excess ROS production; this may perturb insulin secretion and β-cell survival through multiple mechanisms. Oxidative stress decreases the expression and activity of key transcription factors such as PDX-1 and MafA, which regulate multiple genes involved in β-cell function, including proinsulin (Harmon, Stein, & Robertson, 2005). PDX-1 or pancreatic duodenal homeobox factor-1 is a key transcriptional factor that regulates gene transcription in response to glucose (Sharma, Olson, Robertson, & Stein, 1995) and also has antiapoptotic and proliferative activities that help maintain the β-cell mass. Therefore, impaired activity of PDX-1 and most probably other transcription factors in response to hyperglycemia and oxidative stress is detrimental to β-cell function and survival in diabetes.

The report by Shen et al (Shen, Li, & Zou, n.d.) investigated the relationship between oxidative stress and levels of circulating adhesion molecules in 73 patients with hyperglycemic crises, 37 of whom had DKA and 36 severe hyperglycemia. Levels of serum ICAM-1, E-selectin, 8-iso-prostaglandin F2α (8-iso-PGF2α), malondialdehyde (MDA), the activities of superoxide dismutase (SOD) and the total antioxidant capacity (TAC) were measured on admission and 72 h after resolution of hyperglycemia, and in the fasting state in 33 healthy controls. Levels of oxidative stress and adhesion molecules were significantly higher and SOD and TAC were significantly lower in patients with hyperglycemic crises, both on admission (mean BG 360 mg/dl in DKA and 486 mg/dl in nonketotic hyperglycemia) and at resolution (mean BG 136 mg/dl) compared to normal control subjects. These levels improved rapidly following insulin administration and correction of hyperglycemia and acid–base status, but still remained above those of non-diabetic controls. These findings are in agreement with previous studies reporting similar abnormalities on oxidative stress, inflammatory cytokines and circulating adhesion molecules in patients with hyperglycemia crisis (Hoffman et al., 2003; Stentz et al., 2004; Vantyghem et al., 2000).

The study by Shen et al (Shen et al., n.d.) also extends previous observation on the robust and prompt anti-inflammatory and antioxidative effects of insulin (Aljada, Ghanim, Mohanty, Kapur, & Dandona, 2002; Dandona, Chaudhuri, Ghanim, & Mohanty, 2009). Insulin induces expression of endothelial NO synthase through the activation of phosphatidylinositol kinase and AkT kinase (protein kinase B), insulin signaling mechanism similar to that which mediates the uptake of glucose through the glucose transporter (Dandona et al., 2009). Human studies have demonstrated that insulin suppresses intracellular adhesion molecule-1, monocyte chemo attractant protein-1 expression, and NF-kB binding in human aortic endothelial cells. Low-dose insulin infusion (2 U/h) suppressed reactive oxygen species generation and p47 phox expression in mononuclear cells and suppressed NF-kB, thereby leading to lower production of ROS (Aljada et al., 2002). In addition, insulin has suppressive effects on toll-like receptors (TLRs), a class of pathogen-recognition receptors that bind to bacterial, fungal, and viral products and induce inflammation through the subsequent activation of proinflammatory transcription factors. Low-dose insulin infusion reduces expression of TLR-1, TLR-2, TLR-4, TLR-7 and TLR-9 mRNA and TLR-2 and TLR-4 protein levels in MNC's (Ghanim et al., 2008).

Hypoglycemia is the most common complication in patients with DKA during insulin infusion and transition to subcutaneous insulin. Despite the use of low-dose insulin protocols, hypoglycemia is still reported in 10%–30% of patients with DKA (Umpierrez et al., 2009). Insulin-induced hypoglycemia has been associated with increased in *C-reactive protein (CRP) and* proinflammatory cytokines (TNF-alpha, IL-1beta, IL-6, and IL-8), markers of lipid peroxidation, ROS, and leukocytosis (Desouza, Bolli, & Fonseca, 2010; Razavi Nematollahi et al., 2009). This increase in inflammatory cytokines could result in endothelial injury and abnormalities in coagulation, resulting in increased risk for cardiovascular events (Desouza et al., 2010). Thus, minimizing the rate of hypoglycemia

events is of major importance in hospitalized patients during insulin treatment because it has been shown to be a associated with poor clinical outcome (Smiley & Umpierrez, 2010).

In summary, the current body of literature indicates that hyperglycemia and ketoacidosis are associated with a pro-inflammatory state and generation of ROS, lipid peroxidation and adhesion molecules, and that these defects can be corrected rapidly with the infusion of insulin. This observation has important therapeutic implications for the development of acute and chronic complications of diabetes. The increased cytokine release during DKA may result in capillary perturbation and to the development of cerebral or pulmonary edema and to the development of vascular disease, possibly by increasing oxidative stress (Karavanaki et al., 2011; Stentz et al., 2004). Increased oxidative stress could also be responsible for the glucotoxic effects of hyperglycemia on insulin secretion and may explain why some subjects with type 2 diabetes present with DKA (Davis & Umpierrez, 2007; Umpierrez, 2006). In addition, the effects of acute hyperglycemia on oxidative stress and inflammation may also explain why hyperglycemia is associated with poor outcomes in patients with acute myocardial infarction, stroke and cardiac surgery (Umpierrez et al., 2002), and provide the rationale for studying the benefits of lowering glucose with insulin in these acute cardiovascular syndromes (Dandona et al., 2009).

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