Diabetes, Obesity, COVID-19, Insulin, and Other Antidiabetes Drugs

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COVID-19, INFLAMMATION, OBESITY, AND DIABETES

Coronavirus disease 2019 (COVID-19) viral infection, like other infections, triggers an inflammatory response that is usually confined to the respiratory system. However, there is evidence that in a full-blown case, almost all systems of the body may be involved. In addition, there is the syndrome of cytokine storm, characterized by severe systemic inflammation and a massive release of proinflammatory cytokines (1). It is well established that obesity and diabetes are major risk factors for COVID-19 infections and that the morbidity and mortality in association with these conditions is markedly increased. Since both obesity and diabetes are associated with chronic inflammation, it is likely that the inflammatory response to COVID-19 in such patients is affected by the background of chronic inflammation. This review aims to elucidate some of these processes and potential strategies to combat them.

CHRONIC INFLAMMATORY STATES OF OBESITY AND DIABETES

The concept that obesity is associated with inflammation was initiated with the cardinal work of Hotamisligil et al. (2), which demonstrated that the proinflammatory cytokine tumor necrosis factor-α (TNF-α) was expressed in the adipose tissue and that its expression was markedly elevated in the *ob/ob* mouse. In addition, this increase was associated with insulin resistance. Neutralization of TNF-α with the infusion of soluble TNF-α receptor resulted in the reversal of insulin resistance in the *ob/ob* mouse. These remarkable observations resulted in the understanding that obesity is a state of chronic inflammation and that inflammatory mediators may contribute to the pathogenesis of insulin resistance. The same group then demonstrated that human adipose tissue also expresses TNF-α and that its expression is increased in obesity (3). Another research group simultaneously confirmed this observation (4). This observation was followed by the demonstration that plasma concentration of TNF-α was significantly elevated in obese humans and that TNF-α fell after weight loss (5). A more comprehensive description of inflammation in obesity and its relationship to insulin resistance was demonstrated by the work of Ghanim et al. (6,7). These features were then linked to the metabolic syndrome (8).

These observations were further supported by the fact that human obesity was associated with chronic oxidative stress and that dietary restriction and weight loss led to a marked reduction in the indices of oxidative stress even over a short period of 4 weeks (9). These observations were confirmed by an article from Japan (10). Oxidative stress is known to trigger inflammatory processes and often occurs concomitantly with inflammation.

The occurrence of inflammation in association with type 2 diabetes was first demonstrated by Pickup and Crook (11,12). These articles emphasize the increase in acute phase reactants to inflammation in patients with type 2 diabetes, including sialic acid and cytokines IL-6 and TNF-α in particular.

MACRONUTRIENTS INDUCE INFLAMMATION

The fact that obesity was associated with oxidative stress and inflammation and the fact that dietary restriction and weight loss led to a reduction in inflammation and oxidative stress led to the concept that macronutrient intake may be a mediator of oxidative and inflammatory stress. Glucose and cream (saturated fat) intake has been shown to induce an increase in reactive oxygen species (ROS) generation in mononuclear cells (MNCs) and polymorph nuclear leucocytes as well as an increase in lipid peroxidation (13,14). The intake of a fast-food high-fat, high-calorie meal has been shown to induce comprehensive oxidative stress and inflammation (15,16), as has the intravenous infusion of a saturated fatty acid, palmitic acid (17). In all these experiments, indices of oxidative stress and inflammation, including an increase in intranuclear nuclear factor-κB (NF-κB) and a decrease in inhibitor of κBα (IκBα), were induced within 60 min of macronutrient intake. Plasma concentration of endotoxin increased. Cytokines, including TNF-α and IL-1β (18), and

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chemokines, including MCP-1 and Toll-like receptor 2 (TLR-2) and TLR-4, were induced (16). While TLR-2 is the receptor for gram-positive bacterial products, TLR-4 is the receptor for endotoxin. Suppressor of cytokine signaling 3 (SOCS-3) and p38 mitogen-activated protein kinase were also induced (16,19). Both of these proteins interfere with insulin signaling at the insulin receptor substrate 1 level and, thus, may contribute to the induction of insulin resistance. In contrast, an American Heart Association–based high-fruit and high-fiber meal did not induce endotoxemia, inflammation, or oxidative stress (16). In addition, the consumption of fresh orange juice (19) or dietary fiber (20) with the high-fat, high-calorie meal prevented endotoxemia, inflammation, and oxidative stress. On the basis of these data, macronutrient intake, especially rich in fats and carbohydrates and lacking in fruit and dietary fiber, would contribute to chronic oxidative and inflammatory stress in obesity.

CHRONIC INFLAMMATION, OBESITY, DIABETES, AND IMMUNE RESPONSES

Chronic inflammation, as described above, in obesity and diabetes may contribute to impaired immunological responses to specific pathogens and to vaccinations. The immunological response to hepatitis B, hepatitis A, tetanus, and influenza A vaccinations in obese humans is impaired (21). In addition, the response to influenza vaccine is not as durable in obese individuals as it is in normal-weight subjects without diabetes. These observations have clear implications for both the magnitude and the duration of immunity induced by vaccination in this population. It is possible that vaccination-based protection may not be as effective in this population as in normal subjects. A total of 55.7% of the subjects tested negative for protective antibodies against hepatitis B surface antigen (anti-HBs) titers (21) after nearly a year of vaccination. A BMI $\geq$32.88 kg/m^2 was identified as one of the major risk factors for hepatitis B virus vaccine nonresponse. Only 29.5% of individuals with a BMI greater than or equal to the 75th percentile developed protective anti-HBs titers, compared with 63.3% of individuals below the 75th percentile that achieved protective seroconversion (22). Recombinant vaccines were associated with similar differences in the responses between obese and nonobese individuals.

Obesity was associated with an inadequate immunological response to the vaccine following vaccination for hepatitis A virus (23). In addition, there was an early decline in antibody titers after immunization (24).

Obesity was also associated with diminished immunological response to influenza vaccines and an inability to sustain the magnitude of the immunological response over a prolonged period (25). These defects were associated with diminished expression of CD69, interferon-γ, and granzyme B on $CD8^+$ T cells in obese individuals.

One study demonstrated that children (8–17 years of age) with a BMI above the 85th percentile (BMI 29.1 ± 1.6 kg/m^2) had significantly reduced and inadequate tetanus-specific IgG levels (26). A recent study of veterinary students (27) identified that overweight individuals had an increased likelihood for inadequate rabies-specific antibody titers 2 years after vaccination.

In a study focused on type 2 diabetes, it was shown that monocytes prepared from such patients when challenged with endotoxin (lipopolysaccharide) secreted less TNF-α than monocytes from normal subjects. In addition, the expression of TNF-α, CD11b, and CD163 were diminished following lipopolysaccharide challenge (28). However, the secretion of the anti-inflammatory cytokine IL-10 was not diminished. Thus, it is clear that the magnitude of specific immune responses is diminished in both obesity and type 2 diabetes, in association with the background of chronic inflammation.

ANTI-INFLAMMATORY EFFECTS OF CORTICOSTEROIDS

Although corticosteroids have been used as anti-inflammatory agents since the 1950s, their molecular mode of action was first described in 1995. Two research groups simultaneously described that dexamethasone enhanced the expression of IκBα and, thus, suppressed the intranuclear transfer of the proinflammatory transcription factor NF-κB in immune cells in vitro (29,30). Since these observations were made with high concentrations of dexamethasone in vitro, our group took the initiative of investigating the effect of physiologically and therapeutically relevant doses of hydrocortisone. An intravenous injection of 100 mg of hydrocortisone resulted in the suppression of intranuclear NF-κB and an increase in IκBα expression in the cytosol of MNCs (31), consistent with the previous observations with dexamethasone in vitro. In addition, this dose of hydrocortisone resulted in the suppression of ROS generation by MNCs and polymorph nuclear leucocytes (32). This dose of hydrocortisone also suppressed activator protein 1 (AP-1), another proinflammatory transcription factor modulating the expression of matrix metalloproteinase 2 (MMP-2) and MMP-9 (33). When an intravenous dose of 300 mg hydrocortisone was administered, these actions were observed, but, in addition, an increase in the expression of high-mobility group box 1 (HMG-B1), TLR-2, TLR-5, and TLR-9 was noted in MNCs (34). There was also an increase in plasma concentrations of HMG-B1 and MMP-9. These are all proinflammatory mediators, and, hence, the higher doses of corticosteroids have mixed anti- and proinflammatory effects. In addition, this dose of hydrocortisone results in hyperglycemia and an increase in plasma free fatty acid concentrations, both of which are proinflammatory. These actions may contribute to absence of benefits when high doses of corticosteroids are administered to patients with septicemia. However, a dose of 6 mg of dexamethasone (equivalent to 150 mg of hydrocortisone) has been shown to be beneficial to inflammation, especially in the context of COVID-19 (35). In fact, this dose of dexamethasone is currently being used routinely in all hospital admissions with COVID-19.

ANTI-INFLAMMATORY ACTIONS OF INSULIN

The two major risk factors determining morbidity and mortality that have emerged consistently from the patterns of clinical manifestations in COVID-19 infection are obesity and diabetes with and without hyperglycemia (36). Both diabetes and obesity are characterized by chronic inflammation that impairs the ability to generate specific immunological responses to infections and antigenic challenges. Hyperglycemia also induces inflammation and impairs the defense mechanisms necessary for combating infection. Our work over the years has

demonstrated that glucose administration and hyperglycemia induce oxidative and inflammatory stress (13,37), while intravenously administered insulin exerts a rapid and comprehensive anti-inflammatory action (37,38). This insulin infusion regimen (2.5 units/h with 5% dextrose 100 mL/h) leads to the suppression of ROS generation, NADPH oxidase subunit ($p47^{phox}$) expression, NF-κB binding activity, and intracellular adhesion molecule 1 and MCP-1 expression. These changes commence at 2 h and continue for as long as the infusion is administered. It also results in the suppression of transcription factors AP-1 and early growth response protein 1 (Egr-1) and levels of MMP-2, MMP-9, tissue factor, and plasminogen activator inhibitor 1 (39,40). In addition, this insulin regimen suppresses several chemokines (MCP-1, RANTES [regulated on activation, normal T-cell–expressed and secreted (CCL5)], macrophage inflammatory protein-1β [MIP-1β]) and chemokine receptors 2 and 5 (41). In addition to the general effects on oxidative and inflammatory stress, glucose induces prothrombotic factors like tissue factor and platelet proaggregatory actions while insulin inhibits thrombotic processes, inhibits platelet aggregation, and promotes thrombolysis (42). In addition, insulin is a vasodilator at the arterial, venous, and the microvascular level potentially improving blood flow and perfusion into various organ systems mediated by an increase in endothelial nitric oxide secretion and nitric oxide synthase (43). Hyperglycemia also induces the expression of TLR-2 and TLR-4, which are the receptors for the products of gram-positive and gram-negative (including endotoxin) bacteria and HMG-B1, a marker of mortality in animal sepsis models (37). Thus, hyperglycemia promotes vulnerability to infection. In contrast, insulin suppresses HMG-B1 levels and the expression of TLR-1, TLR-2, TLR-4, TLR-7, and TLR-9 in addition to suppressing PU.1, the major transcription factor responsible for the transcription of TLRs (37,44). TLR-7 and TLR-9 are responsible for mediating inflammation induced by RNA and DNA viruses, respectively. COVID-19 is an RNA virus. In this context, it is also noteworthy that we have shown that the acute effects of endotoxin injection into normal subjects inducing several indices of oxidative and inflammatory indices as well as the systemic febrile response were suppressed by an intravenous insulin infusion (45). Genes related to bronchial asthma are also suppressed by insulin infusion: IL-4, LIGHT (homologous to lymphotoxin, TNF superfamily member 14), LTBR (lymphotoxin β-receptor), ADAM-33 (disintegrin and metalloproteinase domain-containing protein 33), and TSLP (thymic stromal lymphoprotein) are the key genes involved in the pathogenesis of bronchial asthma. They are all suppressed by insulin within 2 h (46), and remain suppressed for as long as insulin is infused. These genes may also be involved with the pulmonary syndrome associated with COVID-19.

The prognostic significance of hyperglycemia has also been demonstrated in the context of acute myocardial infarction (47,48) and acute ischemic stroke (49). Insulin infusion has been shown to provide benefit in acute myocardial infarction inthree separate studies, one from our center (50), the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiologicos Latino America Study Group (CREATE-ECLA) study (47) and the Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) study (51). Hyperglycemia (>140 mg/dL) at admission and its change after admission determine the clinical outcomes of both acute myocardial infarction and ischemic stroke. These issues are relevant to COVID-19 since its infection involves both the heart and the brain and the vasculature serving them.

COVID-19 infection initially affects the lungs and the respiratory system and then, through its effects on vasculature, it can lead to thrombotic changes. When this process involves cerebral vasculature, it can induce the stroke syndrome. In children, it induces features similar to Takayasu arteritis. Respiratory system manifestations are the most prominent and lead to hypoxia and respiratory failure and thus to the need for mechanical ventilation. There are profound inflammatory changes with the release of proinflammatory cytokines, chemokines, and thrombotic factors. A cytokine storm has also been described, characterized by intense release of proinflammatory mediators. The major cytokines increased in COVID-19–related cytokine storm are IL-1β, IL-6, TNF-α, interferon-γ, MIP-1α, MIP-1β, and vascular endothelial growth factor (1). In all these clinical settings, the use of an anti-inflammatory therapy that also has antithrombotic and profibrinolytic effects would be the ideal. Since hyperglycemia promotes these features, reduction of glucose would have beneficial clinical effects. However, as described above, the intravenous infusion of insulin at anti-inflammatory doses would have profound additional beneficial effects since insulin has previously been shown suppress a number of these cytokines.

Recently, a marked increase in mortality in COVID-19 patients with diabetes and hyperglycemia has been shown in a retrospective analysis (52). Patients infused with insulin to control glucose concentrations had a markedly reduced rate of mortality (20% vs. 80%). While diabetes and hyperglycemia were associated with an increase in IL-6 and D-dimer concentrations, patients infused with insulin had significantly lower levels. Since IL-6 is marker for inflammation and D-dimer is a marker for thrombosis, these data are consistent with what has previously been shown in our work described above.

Dexamethasone, which has anti-inflammatory effects, has been shown to improve clinical outcomes in subjects with COVID-19 infection who receive mechanical ventilation or supplemental oxygen (53). However, there was a potential harmful effect in patients who did not require any respiratory support. We have shown that while glucocorticoids have a clear anti-inflammatory effect at physiologically relevant doses (hydrocortisone 100 mg) (31,33), they cause hyperglycemia and an increase in plasma free fatty acid concentrations, and thus may also have a potential proinflammatory effect, at higher doses (300 mg hydrocortisone is equivalent to 60 mg prednisolone) through an increase in expression of TLR-2, TLR-5, TLR-9, and HMG-B1 in MNCs and an increase in plasma HMG-B1 and MMP-9 (34). Our preliminary studies have also shown an additional anti-inflammatory effect and neutralization of the potential proinflammatory effect of steroids when an insulin infusion is coadministered with high-dose glucocorticoids (54). This provides an additional rationale for the use of insulin infusion in hospitalized subjects with COVID-19 infection, as we expect that a majority of our patients

with severe COVID-19 infection may be treated with glucocorticoids.

Clearly, therefore, strategies based on neutralizing hyperglycemia and providing insulin would be beneficial in COVID-19 infection through comprehensive inhibitory actions on oxidative and inflammatory stress, the inhibition of prothrombotic processes, the promotion of fibrinolysis, and the maintenance of organ perfusion. The arrival of COVID-19 has caused a global calamity since January 2020. All sections of the population have suffered, and while some anti-inflammatory therapies have been associated with improved outcomes, there is still a high residual risk of mortality in these patients. The use of intravenous insulin in combination with dexamethasone in all patients in intensive care units could potentially improve clinical outcomes and, thus, needs to be investigated further.

ANTI-INFLAMMATORY ACTIONS OF THIAZOLIDINEDIONES AND GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS

Both thiazolidinediones and glucagon-like peptide 1 receptor agonists have anti-inflammatory properties (55–57) and, therefore, can potentially be tried in COVID-19 infections. However, there are currently no data available on their effect on the inflammation caused by this infection.

CONCLUSIONS

It is clear that both obesity and type 2 diabetes are characterized by chronic inflammation. A major contributor to this state is chronic overfeeding and increased caloric intake. This state of chronic inflammation results in an inability to generate adequate immunological responses to specific infections, including COVID-19. In spite of the insulin resistance associated with these states, an intravenous infusion of insulin induces an anti-inflammatory effect within 2 h. Insulin is also able exert an additive anti-inflammatory action with corticosteroids while simultaneously neutralizing the paradoxical proinflammatory action of the high doses of corticosteroids. In addition, insulin has an antiaggregatory effect on platelets and an antithrombotic and a profibrinolytic action. This combination of actions could provide a potentially potent inhibition of the effects of COVID-19.

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