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Association of gestational diabetes and proinflammatory cytokines (IL-6, TNF-α and IL-1β)

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Changes to proinflammatory cytokines as a result of gestational diabetes mellitus (GDM), and the pregnancy complications that these changes can cause, are of vital importance to the effective prevention and optimal management. Interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) are cytokines that are associated with gestational diabetes. Therefore, the aim of this review is to draw attention to the relationship between gestational diabetes and these diseases

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Gestational diabetes and proinflamatuar cytokines

GDM is the most prevalent metabolic disorder to occur during pregnancy and is defined as any type of glucose intolerance that starts or is first diagnosed during pregnancy. GDM typically develops in the second or third trimester of pregnancy and can cause hyperglycemia of varying severity. Due to recent increases in pregnancy age and the rate of obesity, the incidence of GDM has risen worldwide (1, 2). GDM can lead to severe pregnancy complications, such as macrosomia, cesarean delivery, shoulder dystocia, and neonatal hypoglycemia (3). Furthermore, the offspring of women with GDM frequently develop defects, injuries, or illnesses, such as birth trauma, prematurity, and respiratory distress syndrome (4). In addition, women with GDM are more likely to develop type 2 diabetes mellitus (DM) and cardiovascular disorders (CVD) after gestation (5, 6). The children of women with GDM are also more likely to develop type 2 DM, in addition to obesity, during their early days of life (7).

It has been determined that the incidence of GDM in pregnant women is related to the prevalence of type 2 DM in that population (2). Overeating and sedentary lifestyles are the most considerable factors to have caused the pandemic spread of type 2 DM worldwide (1). This spread of type 2 DM has contributed significantly to recent increases in the incidence of GDM (2). The prevalence of GDM varies drastically from country to county and from region to region within the same countries (2). Current studies have illustrated that the incidence of GDM is close to 10% in America, varies from 3% to 21.2% in Asian countries, and affects 5% to 8% of the pregnant population in Australia (8, 9). Furthermore, GDM has been more frequently observed in the winter than in the summer (10).

GDM can impact an organism in several different ways. For instance, it can increase the risk of CVD and type 2 DM (by as much as 7 times the normal rate) in expecting mothers (5). Women with GDM have markedly higher rates of obesity, hypertension, and metabolic syndrome than other populations. They also undergo various changes to the levels of their blood inflammatory cytokines (11, 12). Cytokines, such as IL-6, IL-8, and TNF-α, can prevent insulin signaling and have been associated with insulin resistance during cases of type 2 DM. IL-1β is a proinflammatory cytokine that is an effector molecule of inflammatory beta-cell destruction (13, 14). In addition, IL-1β has frequently been observed in the pancreatic sections of patients with type 2 DM (15).

IL-6 (interleukin-6)

IL-6, which is encoded by the IL6 gene in humans, is both a pro-inflammatory cytokine and an interleukin that acts as an anti-inflammatory myokine (16). IL-6 is secreted by T cells and macrophages to stimulate immunity, and it plays an important role in the fight against infection (17). Furthermore, osteoblasts secrete IL-6 during the stimulation of osteoclast formation. IL-6 is produced as a pro-inflammatory cytokine in muscle cells within the tunica media layers of several blood vessels. While the role of IL-6 as an anti-inflammatory cytokine is mediated through the activation of IL-10 by inhibitory effects on TNF-α, and IL-6 is the first stimulator of acute-phase protein production, other cytokines affect the subgroups of acute-phase proteins, as well (18).

Several cytokines, particularly IL-6, stimulate the production of acute-phase proteins in response to a variety of stimuli. In addition, IL-6 stimulates the production of the IL-1 receptor antagonist, which is an anti-inflammatory mediator (19). IL-6 may therefore have a protective effect. Increases in IL-6 during pregnancy have been linked to gestational insulin resistance, particularly due to placental production (20). IL-6 is also upregulated in women with GDM during labor (21). Previous investigations have determined a positive correlation between the concentration of IL-6, insulin sensitivity and plasma glucose levels, and gestational and postpartum body fat percentages (22-25). In case-control studies, plasma IL-6 levels are a significant predictor of GDM (26). The association of IL-6 with gestational diabetes is described as follows: the inflammation of macrophages in the pancreas and adipocytes that cause an increase in the production of IL-6. Other immunocytes also contribute to infiltration (27). Therefore, the destruction of pancreatic β-cells results in low insulin synthesis and apoptosis, which leads to high levels of blood glucose (28, 29).

TNF-α (Tumor necrosis factor alpha)

TNF-α, which is also known as cachectin, plays an important role in the many inflammatory and immune responses that are generated by T lymphocytes and macrophages. It is also a cytokine that is secreted by NK cells, monocytes, endotoxins, macrophages, T and B lymphocytes, and other cells that have been stimulated by microbial products (30). It has been reported that TNF-overexpression is responsible for the development of obesity, insulin resistance, and even TNF-α in rodents. Antagonism also increases insulin sensitivity and the activity of the insulin receptor tyrosine kinase (31-33). As one of the most common metabolic diseases, GDM is characterized by carbohydrate intolerance and insulin resistance during pregnancy (34-36). It has recently been suggested that TNF, one of the proinflammatory cytokines, plays an important role in the development of insulin resistance that has developed due to pregnancy (37, 38).

Although the role of TNF-α in the pathophysiology of insulin resistance is not fully understood, opinions have concentrated on at least two of its mechanisms. Researchers have suggested that TNF-α may either be inhibited during the phosphorylation of the insulin receptor or may result in a decrease in the glucose transporter-4 expression (39, 40). Winkler et. al. declared that TNF-α concentration in patients with GDM significantly increased with surges in C-peptide and BMI during the third trimester of physiological gestation (41). Moreover, Rao et. al. indicated that gestational diabetes, pre-eclampsia, and intra-uterine infection during pregnancy had profound effects, such as the development of endothelial dysfunction, on both the mother and the fetus (42). When endothelial cells are exposed to long-term hyperglycemia and proinflammatory cytokines, they can cause increases to the production of ROS in cells (43, 44). Under these conditions, increased vascular permeability, and ultimately, endothelial dysfunction have been reported (45).

IL-1β (Interleukin-1Beta)

IL-1β is a member of the IL-1 family that presents agonistic activity (46). IL-1β is produced by hematopoietic cells, such as monocytes, tissue macrophages, skin dendritic cells, and brain microglia that develop in response to Toll-like receptors (47). In healthy subjects, 6 ng of IL-1β are produced every day (48). This amount increases with the development of autoinflammatory diseases and can become 5- to 10-times higher than it is in healthy subjects (49). IL-1β stimulates the synthesis of IL-6, chemokines, nitric oxide, cyclooxygenase-2, and adhesion molecules (50). IL-1β exerts its biological function by binding to the IL-1 type I receptor and activating the inhibitor-κB kinase/ nuclear factor-κB pathway and three types of MAPKs: ERK, JNK, and p38 MAPK.

Due to the increased rates of IL-1β concentration in the nondiabetic children of diabetic individuals, recent studies have suggested that IL-1β could be added among the cytokines associated with insulin resistance (51). While chronic overproduction of IL-1β has been associated with many immune system disorders, it has primarily been linked to type I diabetes (52). It has been expressed that the incidence of IL-1β in genetically predisposed individuals furthers the impairment of insulin sensitivity through the secretion of insulin and thus contributes to the development of type II diabetes and macrovascular complications (53). In addition, it has been indicated that proinflammatory cytokine IL-1β levels are higher in patients with type 2 diabetes than in non-diabetic individuals (54). It has also been suggested that increased levels of IL-1β are associated with impaired pancreatic β-cells and decreased secretion of insulin (55). Oztop et al. reported that individuals with DM had significantly higher levels of IL-1β levels than normal pregnant women (56).

Conclusion

In summary, GDM is a significant problem throughout the world. Therefore, knowledge about the roles of certain cytokines in GDM, such as varying levels of IL-6, TNF-α, and IL-1β, may provide insight into future research about the condition.

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