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The Role of Oxidative Stress in Gestational Diabetes Mellitus

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ABSTRACT

The most typical pregnancy-related medical problem is gestational diabetes mellitus. The hormones released during pregnancy, particularly human placental lactogen, estrogen, and progesterone, are responsible for this illness because they can hinder the body's ability to metabolize carbohydrates and tolerate insulin. Hyperglycemia during pregnancy is caused by the action of these hormones. Maternal plasma and placental tissues have higher levels of oxidative stress in GDM patients. And antioxidants are reduced in placental tissue and maternal blood. Consequently, a decrease in antioxidant levels may cause rise in the oxidative stress and result in poor pregnancy outcomes. In GDM-affected women, antioxidant, probiotics and nutritional supplements have been used to lower indicators of oxidative stress.

Keywords: oxidative stress, Gestational diabetes mellitus, antioxidant

INTRODUCTION

Gestational diabetes mellitus is a condition in which there is increased blood sugar level (hyperglycemia) which is first diagnosed during pregnancy in the second trimester. One of the most frequent medical issues associated with pregnancy is gestational diabetes mellitus (GDM), and if left untreated, it can have major negative implications on both the mother's and the child's health1.The International Diabetes Federation (IDF) has released updated statistics showing that GDM affects about 14% of pregnancies globally, or about 20 million birth of babies yearly[2]. Diabetes mellitus is becoming more common. A number of factors, such as rising obesity rates, changing diagnostic standards, and aging mothers, are responsible for this increase. A poor pregnancy result and long-term consequences for the mother and the child are linked to gestational diabetes mellitus.The pancreatic β-cell malfunction in women with GDM prevents it from compensating for the pregnancy-induced insulin resistance[3]. These abnormalities are caused by a variety of factors, such as oxidative stress, epigenetic modifications, placental hormones, adipokines - hormones generated from adipose tissue and

inflammatory cytokines[4] [5] [6]. "Oxidative stress" is the result of an imbalance between the generation of reactive oxygen species (ROS) and the activation of antioxidant mechanisms. This demonstrates how the oxidation of macromolecules and the generation of reactive oxygen species cause harm to cells and tissues. It is well recognized that in some situations, the body's antioxidant defences can weaken or even disappear, which increases reactive oxygen species (ROS) and oxidative stress. Uncontrolled ROS generation can cause cell death and changes metabolism. Rapid oxidation of biomolecules (DNA, proteins, lipids, and carbohydrates) by ROS results in irreversible damage, disturbs homeostasis, and causes cell death. The activation of glucotoxicity pathways is triggered by an increase in superoxide anion in the respiratory chain. Oxidative stress has been linked to the physiopathology of a number of diseases, with metabolic diseases (diabetes and metabolic syndrome) being the most prominent examples, however it has also been linked to obesity and pregnancy. Within this environment, ROS generation is encouraged by elevated glucose and lipids, which frequently coexist with metabolic disorders. ROS are also produced by increased NADH and FADH2 levels, the activation of additional metabolic pathways, and the increased electron supply in the mitochondrial respiratory chain. Raised ROS stimulate changes in insulin secretion, damage to pancreatic β-cells, and their eventual death[17]. ROS-induced changes in the mitochondrial membrane potential resulted in a reduction in ATP generation and insulin secretion triggered by glucose[18]. Furthermore, alterations in mitochondrial permeability trigger the release of proapoptotic proteins (such as cytochrome c and apoptosis-inducing factor) and β-cell apoptosis[19].

Antioxidants, which can neutralise and decrease the action of free radicals, are thought to have a significant role in diet[20]. An abnormal glucose tolerance can be improved with a healthy diet. Fruits, vegetables, and low-fat dairy products are among the dietary patterns related to a decreased risk of GDM[21]. Following the fruit-and vegetable-rich Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diet is linked to a lower risk of developing GDM[22]. In a recent systematic review, an inverse association between DTAC and blood glucose concentrations was observed[23] through its effects on glucose metabolism[24]. Fruits are an excellent source of antioxidants, vitamins, minerals, lignans, terpenes, polyphenols, and flavonoids. Due to their low energy density and low glycemic load, fruits also help to increase insulin sensitivity and pancreatic β cell function because of their antioxidant activity, which also reduces oxidative stress[25] [26] [27]. Additionally, whole grains can reduce the absorption of glucose because of their strong antioxidant potential[28]. Diabetes-related biomarkers benefit from dietary fibre sources such as fruits, vegetables, and whole grains[29].

Free radical and antioxidant of modern medicine are believed to be equivalent to the Tahleel Wa Tajfeef (Dissolution & drying) of Unani concept. Although antioxidants and oxidative stress are not discussed in classical Unani literature, and Unani physicians were not well-versed in the effects of antioxidants and the side effects of oxidative stress, philosophical ideas about dissolution, the dryness of innate heat and moisture, the accumulation of morbid moisture and morbid heat, and life and death are similar to the modern understanding of oxidation and oxidative stress. Antioxidants include medications such as Protective, Nutrimental, Rasayan, Aggravator of Innate Heat, Moisturiser, and others that function as antioxidants or assist antioxidants in some way[30] [31].

Association between oxidative stress and GDM:

There is strong evidence that GDM is characterized by increased oxidative stress. Circulating ROS levels are elevated during physiological pregnancy due to increased

oxidative stress. The placenta is the primary source of ROS during pregnancy. An increase in antioxidant production balances an increase in oxidative stress[7]. Compared to placentas from healthy pregnancies, the placentas of women with GDM exhibit a greater production of 8-isoprostane, a hallmark of lipid peroxidation. Similarly, the expression of malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), xanthine oxidase (XO), and protein carbonyl is likewise increased by the GDM placenta. Oxidative damage can extend to distant tissues when oxidative stress exceeds the placenta's antioxidant defense. Maternal circulation levels of oxidative stress indicators are elevated in GDM (compared to healthy pregnancy) and antioxidant defense is compromised. In GDM, there is a considerable increase in the reactive oxygen species (XO), MDA, thiobarbituric acid reactive substances (TBARS), and lipid hydroperoxide (LOOH), while there is a significant decrease in TAC[8]. Insulin resistance and decreased insulin production are caused by elevated ROS and oxidative stress[9]. Because pancreatic β-cells contain low quantities of antioxidant enzymes that quench free radicals, such as superoxide dismutase, glutathione peroxidase, and catalase, they are especially vulnerable to reactive oxygen species (ROS)[10]**.** As a result, oxidative stress causes β-cell failure by causing apoptotic events, blocking transcription factors like Pdx-1 and MafA that are involved in β-cell neogenesis, weakening KATP channels, and causing mitochondrial dysfunction, which reduces the synthesis of insulin[11]. Oxidative stress, on the other hand, can disrupt insulin signaling, resulting in decreased peripheral tissue insulin sensitivity. ROS and oxidative stress trigger several serine kinase pathways to become activated in vitro. The insulin receptor (IR) and its family of substrate proteins are tyrosine phosphorylated less frequently in response to insulin, which attenuates the effects of insulin[12]. Furthermore, in skeletal muscle and adipose tissue, oxidative stress can lower GLUT-4 expression and content, which lowers cellular glucose absorption and leads to insulin resistance[13]. Furthermore, by inducing inflammatory reactions, oxidative stress can interfere with insulin synthesis and insulin signal transduction.

Supplementation for oxidative stress in GDM:

Therapeutic treatment aims to control the hyperglycemia while having no impact on the oxidative stress linked to GDM. As a result, another novel therapeutic approach using probiotics and vitamin supplements has been documented. Recent randomized controlled trials (RCTs) have examined the impact of probiotic supplements and nutritional supplementation, calcium, magnesium, zinc, and their concurrent administration with vitamin D, on oxidative stress biomarkers in patients with GDM.

Studies:

Hajifaraji M et al. (2018) looked into the effects of probiotics containing four bacterial strains on oxidative stress markers in women with newly diagnosed GDM. These strains are Lactobacillus acidophilus LA-5, Bifidobacterium BB-12, Streptococcus thermophilus STY-31, and Lactobacillus delbrueckii bulgaricus LBY-27. After eight weeks of probiotic administration, they observed an increase in glutathione reductase levels and a decrease in blood levels of hs-CRP, TNF-α, erythrocyte GPx, and MDA[14]. Research indicates that probiotics reduce oxidative stress by inhibiting the NF-κB pathway, which has biological benefits[15]**.**

For women with GDM, multinutrient treatment has demonstrated beneficial benefits on oxidative stress. In a randomized, double-blind, placebo-controlled study conducted in 2019 with GDM patients not on oral hypoglycemic medications, Jamilian et al. found that co-supplementing with magnesium, zinc, calcium, and vitamin D for six weeks significantly decreased plasma MDA concentrations and serum hs-CRP levels

while increasing TAC levels in comparison to the placebo[16].

CONCLUSION

When compared to normal glucose-tolerant pregnancies, there is consistent evidence that GDM has higher markers of oxidative stress and altered antioxidant defences in the placenta, skeletal muscle, adipose tissue, and circulation. Furthermore, the results imply that ROS trigger the transcription factor NF-kB, which in turn triggers the transcription of many mediators of inflammation. Women who go on to develop GDM had increased levels of several oxidative stress indicators beginning in the first trimester. This offers the chance to anticipate the onset of GDM prior to the manifestation of glucose intolerance and to encourage prompt measures aimed at averting the development of difficulties for both mother and fetus and lowering the corresponding medical expenses.

Declaration by Authors

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