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Review

OXIDATIVE STRESS AND GESTATIONAL DIABETES MELLITUS. THE EFFECTS OF SUPPLIMENTS ON OXIDATIVE STRESS

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The prevalence of diabetes in pregnancy has been increasing. GDM is characterized by increased risk of macrosomia and birth complications and an increased risk of maternal type 2 diabetes after pregnancy. Any imbalance between the reactive species (RS) and antioxidants leads to a condition known as "oxidative stress". Antioxidants obtained from nature helps in neutralization of reactive oxygen species and significantly reduce the probability of progression of diabetic complications [2, 3]. The basic aim of this review was to summarize the basics of oxidative stress in geastational diabetes mellitus and to examine the association between different supplements, biomarkers of oxidative stress and GDM and the posibility to improve the pregnacy outcomes.

Keywords: oxidative stress, gestational diabetes, biomarkers, antioxinats, pregnancy outcome.

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is an idiopathic metabolic disease that occurs during pregnancy, and is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy. It affects 7% of all pregnancies worldwide. This status is associated with increased rates of adverse maternal and perinatal outcome [2,8]. The adverse maternal complications include hypertension, preeclampsia, urinary tract infection, hydramnios, and future type 2 diabetes, metabolic syndrome, and cardiovascular disease.The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated that high maternal blood glucose correlates with increasing fetal morbidity and mortality [14]. The offspring of diabetic mothers are also at high risk of metabolic syndrome and diabetes mellitus in childhood and adulthood [13].

2. SCREENING AND DIAGNOSTIC CRITERIA

Is important to diagnose early gestational diabetes in order to initiate the management of hyperglicemia due to the increase risk of complications [2]. After diagnosis, treatment starts with medical nutrition therapy, physical activity, and weight management depending on pregestational weight. Screening for GDM is usually done at 24–28 weeks of gestation because insulin resistance increases during the second trimester. Placental hormones mediate insulin resistance which increases GDM as the pregnancy advances so testing too early may not be helpful in some patients. Similarly, performing tests too late in third trimester limits the time in which metabolic interventions can take place. Because of these reasons, it is advised to perform the tests at 24–28 weeks of gestation. The recommendations given by International Association of Diabetes and Pregnancy Study Group (IADPSG) is to do on the first prenatal visit, fasting plasma glucose, HbA1C or random plasma glucose in all women. If results are not diagnostic of overt diabetes mellitus and fasting plasma glucose ≥ 92 mg/dl diagnosis of GDM is made. If fasting glucose is < 92mg/dl at the first antenatal visit a 2-hour 75g OGTT should be repeated at 24–28 weeks [20]. In first and early second trimester fasting and postprandial glucose concentrations are normally lower than in normal non-pregnant women. Elevated fasting or postprandial plasma glucose levels at this time in pregnancy may well reflect the presence of diabetes

mellitus which has antedated the pregnancy. To determine if GDM, is present a standard OGTT should be performed with 75g anhydrous glucose in 250–300 ml of water after overnight fasting of 8–14 hours. For IADPSG (International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria an OGTT is done in the fasting state using 75 g of glucose at 24–28 weeks and GDM diagnosed if any one of the following cut-off is met i.e. ≥ 92 mg/dl (≥ 5.2 mmol/l) or 1-hour ≥ 180 mg/dl (≥ 10 mmol/l) or 2-hour ≥ 153 mg/dl (≥ 8.5 mmol/l) [38].Because GDM may represent preexisting undiagnosed type 2 or even type 1 diabetes, women with GDM should be tested for persistent diabetes or prediabetes at 4–12 weeks postpartum with a 75 g OGTT. American Diabetes Association (ADA) states that low risk women for developing GDM are those with age less than 25 years, not a member of ethnic group, BMI 25kg/m^2 or less, no previous history of abnormal glucose tolerance or adverse obstetrics outcomes and no known history of diabetes in first degree relatives [43, 44]. Risk factors for GDM include obese women, BMI above 30 kg/m^2, previous macrosomic baby weighting 4.5 kg or above, previous GDM, family history of DM (first degree relative with DM), ethnic family origin with a high prevalence of DM, clinical conditions associated with insulin resistance like acanthosis nigricans, history of hypertension or hypercholesterolaemia. Two methods proposed by ADA for the diagnoses of GDM in women without pre-existing Diabetes,"One Step" Procedure": Performing OGTT in the morning after overnight fast of ≥ 8 hours, 75g OGTT with plasma glucose (PG) measurement fasting, 1-hour and 2-hour at 24–28 weeks in women not having preexisting diabetes, GDM is diagnosed if PG values equals or exceed:

- Fasting serum glucose of 92 mg/dl (5.1 mmol/l)
- 1-hour serum glucose of 180 mg/dl (10.0 mmol/l)
- 2-hour serum glucose of 153 mg/dl (8.5 mmol/l)

Two Step Procedure: Step one performing 50 gram glucose challenge test irrespective of last meal at 24–28 weeks in women not having preexisting diabetes, if PG at 1-hour after load is ≥ 140 mg/dl (7.8 mmol/l) proceeded to 100 g glucose OGTT. Step two performed while patient is fasting GDM diagnosis is made when two or more PG levels equals or exceeds:

- Fasting serum glucose of 95 mg/dl or 105 mg/dl (5.5/5.8 mmol/l)
- 1-hour serum glucose of 180 mg/dl or 190 mg/dl (10.0 / 10.6 mmol/l)
- 2-hour serum glucose of 155 mg/dl or 165mg/dl (8.6 / 9.2 mmol/l)
- 3-hour serum glucose of 140 mg/dl or 145 mg/dl (7.8 /8.0 mmol/l)

3. OXIDATIVE STRESS AND ASSOCIATION WITH GESTATIONAL DIABETES MELLITUS (GDM)

Normal human pregnancy is considered as a state of enhanced oxidative stress, while pathologic pregnancies, including GDM, are associated with a heightened level of oxidative stress. In this review we focused on finding data about the association between GDM and oxidative stress which is defined as an imbalance between pro-oxidants and antioxidant capacity. Free radicals are produced by different exogenous and endogenous substances. The body has different mechanisms to scavenge the deleterious effects of these free radicals. It produce antioxidants that neutralize the elevated amount of free radicals and keep the cells protected against their toxic effects. The increased oxidative stresses during pregnancy is followed by an increase in the total levels of salivary antioxidants to counteract such stresses. Studies showed that determining the salivary antioxidant levels during pregnancy can be an alternative technique for the early diagnosis of diabetes [50].

3.1. OVERVIEW OF REACTIVE OXYGEN SPECIES (ROS)

Reactive oxygen species (ROS) are substances with one or more unpaired electrons which increase the ability to interact with lipids, proteins, or DNA, leading to oxidation and cellular malfunction that may initiate pathological processes. They are generally very unstable and very much reactive [14–15].

3.2. TYPES OF FREE RADICALS

The most commonly produced ROS is superoxide. The depletion of antioxidant capacity may appear whether through a low abundance of nonenzymatic antioxidants (vitamins C and E, and glutathione) or enzymaticantioxidants (superoxide dismutase, glutathione peroxidases, and catalase). This condition makes the cell vulnerable to oxidative

attack, different from the physiologic situations where redox status is maintained through a careful balance of a low level of ROS synthesis and the pathways of cellular defense [14].

3.3. PATHOPHYSIOLOGY OF OXIDATIVE STRESS IN GDM

In GDM, glucose tolerance and insulin resistance are altered, and the pathophysiologic mechanisms suffermultiple and complexe changes that are accompanied by oxidative stress [31]. Insulin resistance is characterized by the inability of tissues to respond to insulin, and pancreatic beta cells compensating for this inability by secreting increased amounts of insulin. GDM results when the increased insulin secretion cannot compensate for the pregnancy-induced insulin resistance [45]. Oxidative stress is the common factor which underlies insulin resistance. Inflammation is a well recognized manifestation of oxidative stress, and the various pathways that generate inflammatory mediators are induced by oxidative stress [58]. It has been suggested that prolonged stimulation of acute and chronic inflammation may be involved in the pathogenesis of insulin resistance [41–50]. In cells, exists a balance between antioxidants elimination and free radical development. The gradual increase in free radicals and diminishing antioxidant defense mechanism potential explain the association between diabetes mellitus with oxidative stress [3]. In the oxidative stress initiated by non-enzymatic sources, free radicals/reactive oxygen species generation is directly increased by hyperglycemic condition. Auto-oxidation of glucose generates hydroxyl radicals. In the non-enzymatic path glucose reacts with proteins which causes improvement in advanced glycation end products and changes protein and cellular/immune function. In diabetic patients there occurs association between lipid peroxidation and impaired glucose level.

3.4. ANTIOXIDANTS

Antioxidants are chemical or biological agents able to neutralize the potentially damaging action of free radicals such unstable molecules as peroxyl radical, hydroxyl radical, and singlet oxygen and peroxynitrate radicals. The oxidation process of other macromolecules is avoided or slows down by antioxidants. In humans everyday activities oxidation plays important role as there is antioxidant defense mechanism present. Examples of antioxidants are lycopene, beta carotene, glutathione, flavonoid, selenium natural vitamin such as vitamin E, vitamin A antioxidant enzymes such as catalase peroxidase [23]. Antioxidants could be obtained from different dietary sources and are used for maintaining the level of free radicals stable and not to develop oxidative stress. In nature, there are various non-enzymatic and enzymatic mechanisms for removal of reactive oxygen species. Examples of nonenzymatic antioxidant system are ascorbic acid, retinol, glutathione, carotenoids, tocopherols, and trace elements like selenium, copper, zinc, coenzyme Q10, uric acid, factors of folic acid, riboflavin and thiamine. Vitamin E is the fat soluble responsible for prevention of lipid peroxidation. Glutathione acts as a scavenger as well as a substrate for glutathione peroxidase. A complex and integrated antioxidant system plays a crucial role in protecting cells or tissues from damage as the result of reactive oxygen species (ROS). The expression and activity of antioxidants are changed during oxidative stress [9].

3.5 . BIOMARKERS OF OXIDATIVE STRESS IN GDM

3.5.1. Proteins

ROS reacts with some amino acid producing modified, denatured and non-functioning proteins that in further may be responsible for oxidative stress [14]. Hyperglycemia, by the process of free radical production, causes protein glycation and oxidative degeneration. The degree of such protein glycation is estimated by using some biomarkers such as glycated hemoglobin and fructosamine levels. Alteration in function and structure of antioxidant protein enzymes may also be due to nonenzymatic glycation such that detoxification of free radicals is effected enhancing oxidative stress in diabetes [17–18]. During pregnancy, the mother is potentially subjected to glucotoxicity as well as oxidative stress (OS) to help the foetus absorb more nutrients. Data suggest that the Trx (thioredoxin)/ TrxBP(thioredoxin-binding protein)-redox-active proteins that control multiple biological functions, in gestational diabetes, may mediate a compensating mechanism. Reduced TrxBP levels and consequent enhanced Trx activity may alleviate OS and protect the foetus from hypoglycaemia. The decrease in TrxBP levels is not a consequence of GDM, but rather is an instance of the active functional role of TrxBP in maternal development, unifying redox regulation and glucose metabolism [19]. AOPPs are the final products of various protein oxidation

formed by oxidative stress and are considered novel markers of oxidative protein damage. Karacay *et al.* reported that circulating levels of AOPPs are increased at 24–36 weeks of gestation in GDM comparing to normal pregnancies [1, 34, 39]. PCO is a sensitive, stable marker of oxidant-mediated protein damage and is the most widely used. Gelisgen et al. determined that plasma AOPPs and PCO levels are positively correlated with OGTT 1 h glucose level at 16–20 weeks in the GDM. the study showed no correlation between PON1, 8-iso-PGF2α and the OGTT glucose level. These data showed that protein oxidation may play a key role in impaired glycemic equilibrium in GDM [9].

3.5.2. Lipids

GDM produces disturbances in the lipid profile and makes the cells more susceptible to lipid peroxidation. Experimental studies show that polyunsaturated fatty acids in cell membrane are extremely prone to be attackes by free radicals due to the presence of multiple bonds [18, 19]. A critical biomarker of oxidative stress is lipid peroxidation [34]. Malondialdehyde (MDA) is formed as a result of lipid peroxidation that can be used to measure lipid peroxides after reacting it with thiobarbituric acid. GDM is associated with reduced δ-aminolevulinate dehydratase (δ-ALA-D) activity and demonstrate the involvement of oxidative stress in this condition. δ-aminolevulinate dehydratase (δ-ALA-D) activity, reflects lipid peroxidation and is estimated as the levels of thiobarbituric acid reactive substances (TBARS), protein (P-SH) and non-protein thiol (NP-SH) content, and concentration of vitamin C (VIT C) [41].

3.5.3. Vitamins

Vitamins are very important part of biological system and among them vitamin A, C and E act as antioxidants by detoxifying the free radicals. Any alteration in their levels is significant biomarker of oxidative stress. Body levels of vitamin E have been reported to be either increased or decreased by hyperglicemic status.

3.5.4. Glutathione

Diabetes induces alterations in activity of enzymes glutathione peroxidase and glutathione reductase. These enzymes are found in cell that metabolizes peroxide to water and converting glutathione disulfide back into glutathione [27]. Any alteration in their levels will make the cells vulnerable to oxidative stress and cell injury.

3.5.6. Superoxide dismutase (SOD)

Superoxide dismutase provides first line defense against ROS mediated cell injury by catalyzing the proportion of superoxide [44].

3.5.7. CRP

Reactive oxygen species (ROS) induce production of inflammatory mediators such as CRP, which plays an important role in the development and progression of GDM [28]. During pregnancy, increased CRP (a classic acute-phase reactant, and a sensitive marker of inflammation) levels are associated with insulin resistance, maternal dysglycemia, and GDM [36, 47]. In pregnant women with GDM were discovered high levels of hs-CRP which express an increased lipid peroxidation capacity and decreased antioxidant defense capacity of the glutathione system [6, 7, 39].

3.5.8. 8-iso-prostaglandin F2α (8-iso-PGF2α)

8-iso-PGF2α is considered to be a sensitive and stable biomarker of lipid peroxidation (either peroxidation of cell-membrane phospholipids or circulating LDL) [16]. 8-iso-PGF2α from placenta, adipose tissue, and skeletal muscle is greater in women with GDM than in healthy pregnant women [9].8-iso-PGF2α, AOPPs levels are significantly increased at 16–20 weeks, before diagnosis of GDM, suggesting that increased oxidative stress may occur before the onset of GDM and increases with the progression of gestation. Data suggest that oxidative stress may contribute to the development and progression of GDM [21, 39].

3.5.9. PON1

PON1 (paraoxonase 1) is an antioxidant enzyme that can protect LDL and HDL from oxidation, but also it plays a key antiatherosclerotic role. Compared to normal pregnant women, the activity of PON1 was decreased in patients with GDM, and it has been shown that reduced PON1 may be due to increased plasma protein oxidative damage [9]. Studies showed that plasma PON1 levels are lower in patients with GDM compared with the non-GDM pregnant women [51].

4. EFFECTS OF SUPPLIMENTS ON OXIDATIVE STRESS IN GDM

Pregnancy is a physiological challenge that may require additional nutritional support. Suboptimal micronutrient intakes and micronutrient deficiencies

during pregnancy are a global problem, often leading to poor maternal and child outcomes [15–16]. Micronutrient supplementation is commonly recommended during pregnancy to support maternal metabolism. Recent studies suggest that the use of multiple micronutrient supplements may be of benefit during a normal pregnancy and may significantly reduce the risk of preeclampsia, preterm delivery, gestational diabetes, and improve pregnancy outcomes. Data showed that micronutrient supplementation mayinfluence placental function and modulate placental oxidative stress and inflammation [21–22].

4.1. VITAMIN C AND VITAMIN E

We searched data about the potential benefit of prophylactic antioxidant supplementation with vitamin E and C in pregnant women with GDM. Parast VM showed in their study that antioxidants can reduce the biomarkers of maternal endothelial dysfunction, with the ratio of plasminogen activator inhibitor (PAI)-1 to PAI-2 (PAI-1/PAI-2) used as the primary outcome. Supplementation with 1 g vitamin C and 400 IU of vitamin E daily, from 16 wk of gestation until delivery, was associated with a significant reduction in the PAI-1/PAI-2 ratio. It is also reported a reduction in the plasma concentration of 8-epi prostaglandin F2α, a marker of lipid peroxidation, in association with elevation of the plasma vitamin C and E concentrations. It is encouraged to administrate antioxidants to improve oxidative stress, and to reduce the occurrence of the disease. Parast VM *et al.,* compared in their study the antioxidant capacity and antioxidant nutrient intake between women with GDM and healthy pregnant women. The total antioxidant capacity (TAC) of serum was assessed by double-antibody sandwich enzyme-linked immune-sorbent assay (ELISA) method. The results showed that TAC concentration of serum in women with GDM was significantly lower than in healthy pregnant women [36].

4.1.2. Synbiotic effects

Karamali M *et al.* evaluated in their study the effects of synbiotic administration on biomarkers of inflammation, oxidative stress, and pregnancy outcomes among gestational diabetic (GDM) women. Data showed that synbiotic supplementation significantly decreased serum high-sensitivity C-reactive protein (hs-CRP) (- 1.9 ± 4.2 *vs.* +1.1 ± 3.5 mg/L, P = 0.004), plasma malondialdehyde (MDA) (- 0.1 ± 0.6 vs. + 0.3 ± 0.7 μmol/L, P = 0.02), and significantly increased total antioxidant capacity (TAC) (+ 70.1 ± 130.9 *vs.* -19.7 ± 124.6 mmol/L, P = 0.009) and total glutathione (GSH) levels (+ 28.7 ± 61.5 *vs.* - 14.9 ± 85.3 μmol/L, P = 0.02). Synbiotic supplementation did not affect plasma nitric oxide (NO) levels and other pregnancy outcomes. Overall, synbiotic supplementation among GDM women for 6 weeks had beneficial effects on serum hs-CRP, plasma TAC, GSH, and MDA; cesarean section; but did not affect plasma NO levels and other pregnancy outcomes [20]. Badehnoosh B. *et al.,* in his study evaluate the effects of probiotic supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes among subjects with gestational diabetes (GDM). Probiotic supplementation among women with GDM for six weeks had beneficial effects, decreased the fasting plasma glucose (FPG) serum hs-CRP, plasma TAC, MDA and oxidative stress index, but did not affect pregnancy outcomes [11, 46]. The role of gut microbiota in the management of diabetes is shown, but the data are controverse about the effects of synbiotic supplementation. Nabhani Z in their study investigates the effects of synbiotic supplementation on insulin, lipid profile and antioxidative status among women with gestational diabetes mellitus (GDM) and showed that in women with GDM, synbiotic supplementation had no effect on FPG and insulin resistance/sensitivity indices. Lipid profile and TAC status may be affected by synbiotic supplementation. Synbiotic is effective in reducing of blood pressure in women with GDM [36].

4.1.3. Vitamin D and omega 3 fatty acids co-supplementation on biomarkers of inflammation and oxidative stress

Razavi M *et al.,* in their study determine the effects of vitamin D and omega-3 fatty acids co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in gestational diabetes (GDM) patients [24–25]. Their results showed that vitamin D plus omega-3 fatty acids supplements significantly decreased high-sensitivity C-reactive protein (-2.0 ± 3.3 *vs.* -0.8 ± 4.4, -1.3 ± 2.4 and +0.9 ± 2.7 mg/L, respectively, $P = 0.008$), malondialdehyde (-0.5 ± 0.5 *vs.* -0.2 ± 0.5, -0.3 ± 0.9 and +0.5 ± 1.4 μmol/L, respectively, $P < 0.001$), and increased total antioxidant capacity (+92.1 ± 70.1 *vs.* +55.1 ± 123.6, +88.4 ± 95.2 and +1.0 ± 90.8 mmol/L, respectively, $P = 0.001$) and glutathione (+95.7 ± 86.7 *vs.*+23.0 ± 62.3, +30.0 ±

66.5 and -7.8 ± 126.5 µmol/L, respectively, P = 0.001). In addition, vitamin D and omega-3 fatty acids co-supplementation, compared with vitamin D, omega-3 fatty acids and placebo, resulted in lower incidences of newborns' hyperbilirubinemiain (P = 0.037) and newborns' hospitalization (P = 0.037).

All the data suggest that vitamin D and omega-3 fatty acids co-supplementation for 6 weeks among GDM women had beneficial effects on some biomarkers of inflammation, oxidative stress and pregnancy outcomes [52]. In Jamilian study it was investigated the effects of omega-3 fatty acid supplementation on inflammatory factors, biomarkers of oxidative stress, and pregnancy outcomes among pregnant women with gestational diabetes (GDM). They concluded that omega-3 fatty acid supplementation in GDM women had beneficial effects on maternal serum hs-CRP, plasma MDA levels, incidence of newborn's hyperbilirubinemia, and hospitalization [20].

4.1.4. Effects of Omega-3 Fatty Acids and Vitamin E Co-Supplementation on Biomarkers of Oxidative Stress

Jamilian *et al.,* in their study determine the effects of omega-3 fatty acids and vitamin E co-supplementation on biomarkers of oxidative stress, inflammation and pregnancy outcomes in women with GDM.

After 6 weeks of intervention, omega-3 fatty acids and vitamin E co-supplementation, compared with the placebo, resulted in a significant rise in total antioxidant capacity (TAC) (+187.5±224.9 *vs.* -32.5±136.1 mmol/L; p<0.001); nitric oxide (NO) (+5.0±7.7 *vs.* -12.0±28.0 µmol/L; p=0.002) and a significant decrease in plasma malondialdehyde (MDA) concentrations (-0.1±0.9 *vs.* +0.6±1.4 µmol/L; p=0.03). Co-supplementation with omega-3 fatty acids and vitamin E showed no detectable changes in plasma glutathione and serum high-sensitivity C-reactive protein levels. Joint omega-3 fatty acids and vitamin E supplementation resulted in lower incidences of hyperbilirubinemia in newborns (10.3% *vs.* 33.3%; p=0.03). Omega-3 fatty acids and vitamin E co-supplementation for 6 weeks in women with GDM had beneficial effects on plasma TAC, MDA and NO and on the incidence of the newborns' hyperbilirubinemia [21]. Capobianco et alstudied the effects of supplementation with polyunsaturated fatty acids (PUFAs) in pregnant mild diabetic rats by feeding a 6% safflower-oil-enriched diet from day 1 to 14 followed by a 6% chia-oil-enriched diet from day 14 of pregnancy to term. Although gestational hyperglycemia was not prevented by dietary PUFAs in the placenta of GDM rats, PPARγ levels were reduced and lipoperoxidation was increased [9]. Zhang Q *et al.,* in their study determined the effect of various doses of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation and the levels of oxidative stress of pregnant women with gestational diabetes mellitus (GDM). Using ELISA kits, it was determined that insulin, homeostatic model assessment-insulin resistance and total cholesterol were significantly reduced by high dosage vitamin D supplementation (P<0.05). Total antioxidant capacity and total glutathione levels were significantly elevated as a result of high dosage vitamin D supplementation (P<0.01). Their conclusion was that high-dose vitamin D supplementation (50,000 IU every 2 weeks) significantly improved insulin resistance in pregnant women with GDM [60]. Asemi *et al.,* studied the effects of vitamin D supplementation on metabolic profiles, high-sensitivity C-reactive protein, and biomarkers of oxidative stress in pregnant women with GDM. Intake of vitamin D supplements led to a significant decrease in concentrations of fasting plasma glucose (-17.1 ± 14.8 compared with -0.9 ± 16.6 mg/dL; P < 0.001) and serum insulin (-3.08 ± 6.62 compared with +1.34 ± 6.51 µIU/mL; P = 0.01) and homeostasis model of assessment-insulin resistance (-1.28 ± 1.41 compared with +0.34 ± 1.79; P < 0.001) and a significant increase in the Quantitative Insulin Sensitivity Check Index (+0.03 ± 0.03 compared with -0.001 ± 0.02; P = 0.003) compared with placebo. A significant reduction in concentrations of total (-11.0 ± 23.5 compared with +9.5 ± 36.5 mg/dL; P = 0.01) and low-density lipoprotein (LDL) (-10.8 ± 22.4 compared with +10.4 ± 28.0 mg/dL; P = 0.003) cholesterol was also seen after vitamin D supplementation.Vitamin D supplementation in pregnant women with GDM had beneficial effects on glycemia and total and LDL-cholesterol concentrations but did not affect inflammation and oxidative stress [4].

4.1.5. Zinc Supplementation and the Effects on Pregnancy Outcomes in Gestational Diabetes

Karamali M *et al.,* in their study determine the beneficial effects of zinc intake on biomarkers of inflammation, oxidative stress, and pregnancy outcomes among pregnant women with gestational diabetes (GDM). The change in serum zinc levels

after 6 weeks of supplementation was greater in women consuming zinc than in the placebo group (+8.5±13.5 *vs.* -3.6±16.2 mg/dL, P = 0.006). Changes in serum high sensitivity C-reactive protein (hs-CRP) (-110.1±1 475.5 *vs.* + 1 137.8 ± 2 429.2 ng/mL, P=0.03) and plasma total antioxidant capacity (TAC) concentrations (+60.0±129.0 *vs.* -28.4± 81.4 mmol/L, P=0.006) were significantly different between the supplemented women and placebo group [30]. Taken together, zinc administration among patients with GDM was associated with decreased hs-CRP and increased TAC concentrations; however, it did not influence maternal plasma nitric oxide (NO), glutathione (GSH), malondialdehyde (MDA) levels, or pregnancy outcomes [25].

4.1.6. The Effect of Soy Intake on Metabolic Profiles of Women With Gestational Diabetes Mellitus

Jamilian M *et al.,* in their study determine the effects of soy intake on metabolic status of GDM women.Soy protein consumption in women with GDM significantly improved the glucose homeostasis parameters, triglycerides, and biomarkers of oxidative stress, as well as reductions in the incidence of newborn hyperbilirubinemia and hospitalizations [23].

4.1.7. Effects of selenium supplementation on oxidative stress in GDM

We searched the effects of selenium supplementation on metabolic status in pregnant women with GDM who were not on oral hypoglycemic agents.

Selenium supplementation, compared with placebo, resulted in a significant reduction in fasting plasma glucose (-10.5 ± 11.9 *vs.* +4.5 ± 12.9 mg/dL; P < 0.001), serum insulin levels (-1.98 ± 11.25 *vs.* +5.26 ± 9.33 μIU/mL; P = 0.005), homeostasis model of assessment (HOMA)-insulin resistance (-0.84 ± 2.76 *vs.* +1.47 ± 2.46; P < 0.001) and a significant increase in quantitative insulin sensitivity check index (+0.008 ± 0.03 *vs.* -0.01 ± 0.01; P = 0.009). Additionally, a significant decrease in serum high-sensitivity C-reactive protein (hs-CRP) levels (-791.8 ± 2271.8 *vs.* +500.5 ± 2563.3 ng/mL; P = 0.02) was seen after the administration of selenium supplements compared with placebo. Additionally, we observed a significant elevation in plasma glutathione (+52.14 ± 58.31 *vs.* -39.93 ± 153.52 μmol/L; P = 0.002) and a significant reduction in plasma malondialdehyde levels (-0.01 ± 0.36 *vs.*+0.67 ± 1.90 μmol/L; P = 0.04) after consumption of selenium supplements compared with placebo. Data did not showed any significant effect of selenium supplements on HOMA β-cell function, lipid profiles, plasma nitric oxide, or total antioxidant capacity concentrations. Selenium supplementation in pregnant women with GDM demonstrated beneficial effects on glucose metabolism, hs-CRP levels, and biomarkers of oxidative stress [4].

4.1.8. Magnesium supplementation affects metabolic status and pregnancy outcomes in gestational diabetes

Magnesium is known to exert several beneficial effects, including antiglycemic and antilipidemic properties. Data showed that magnesium supplementation administered to women with GDM resulted in a significant decrease in levels of fasting plasma glucose (FPG) (-9.7 ± 5.6 *vs.* -0.1 ± 8.5 mg/dL, P<0.001). Quantitative results of RT-PCR demonstrated that compared with the placebo, magnesium supplementation upregulated gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) (P = 0.003) and glucose transporter 1 (GLUT-1) (P = 0.004) and downregulated gene expression of oxidized low-density lipoprotein receptor (LDLR) (P = 0.001) in PBMCs of women with GDM. In addition, a trend toward a greater decrease in gene expression of lipoprotein (a) [LP(a)] was observed in the patients belonging to magnesium group compared to placebo group (P = 0.08). Overall, magnesium supplementation for 6 weeks in women with GDM significantly improved FPG levels, and gene expression of PPAR-γ, GLUT-1, and LDLR [25]. This study was designed to assess the effects of magnesium supplementation on metabolic status and pregnancy outcomes in magnesium-deficient pregnant women with GDM.The change in serum magnesium concentration was greater in women consuming magnesium than in the placebo group (+0.06 ± 0.3 *vs.* -0.1 ± 0.3 mg/dL, P = 0.02). Changes in fasting plasma glucose (-9.7 ± 10.1 *vs.* +1.8 ± 8.1 mg/dL, P < 0.001), serum insulin concentration (-2.1 ± 6.5 *vs.* +5.7 ± 10.7 μIU/mL, P = 0.001), homeostasis model of assessment-estimated insulin resistance (-0.5 ± 1.3 *vs.* +1.4 ± 2.3, P < 0.001), homeostasis model of assessment-estimated β-cell function (-4.0 ± 28.7 *vs.* +22.0 ± 43.8, P = 0.006), and the quantitative insulin sensitivity check index (+0.004 ± 0.021 *vs.* -0.012 ± 0.015, P = 0.005) in supplemented women were significantly different from those in women in the placebo group. Changes in serum triglycerides

(+2.1 ± 63.0 *vs.* +38.9 ± 37.5 mg/dL, P = 0.005), high sensitivity C-reactive protein (-432.8 ± 2521.0 *vs.* +783.2 ± 2470.1 ng/mL, P = 0.03), and plasma malondialdehyde concentrations (-0.5 ± 1.6 *vs.* +0.3 ± 1.2 μmol/L, P = 0.01) were significantly different between the supplemented women and placebo group [27]. Magnesium supplementation resulted in a lower incidence of newborn hyperbilirubinemia (8.8% *vs.* 29.4%, P = 0.03) and newborn hospitalization (5.9% *vs.* 26.5%, P = 0.02). Magnesium supplementation among women with GDM had beneficial effects on metabolic status and pregnancy outcomes [5].

4.1.9. Effects of calcium-vitamin D co-supplementation on glycaemic control, inflammation and oxidative stress in gestational diabetes

Studies showed that after the administration of calcium plus vitamin D supplements, it was observed a significant reduction in fasting plasma glucose (-0.89 ± 0.69 *vs.* +0.26 ± 0.92 mmol/l, p < 0.001), serum insulin levels (-13.55 ± 35.25 *vs.* +9.17 ± 38.50 pmol/l, p = 0.02) and HOMA-IR (-0.91 ± 1.18 *vs.* +0.63 ± 2.01, p = 0.001) and a significant increase in QUICKI (+0.02 ± 0.03 *vs.* -0.002 ± 0.02, p = 0.003) compared with placebo. In addition, a significant reduction in serum LDL-cholesterol (-0.23 ± 0.79 *vs.* +0.26 ± 0.74 mmol/l, p = 0.02) and total cholesterol: HDL-cholesterol ratio (-0.49 ± 1.09 *vs.* +0.18 ± 0.37, p = 0.003) and a significant elevation in HDL-cholesterol levels (+0.15 ± 0.25 *vs.* -0.02 ± 0.24 mmol/l, p = 0.01) was seen after intervention in the calcium-vitamin D group compared with placebo. In addition, calcium plus vitamin D supplementation resulted in a significant increase in GSH (+51.14 ± 131.64 *vs.* -47.27 ± 203.63 μmol/l, p = 0.03) and prevented a rise in MDA levels (+0.06 ± 0.66 *vs.* +0.93 ± 2.00 μmol/l, p = 0.03) compared with placebo.Calcium plus vitamin D supplementation in women with GDM had beneficial effects on their metabolic profile [6].

6. CONCLUSION

Oxidative stress has been demonstrated in many studies to participate in the progression of diabetes which plays important role during diabetes, including impairment of insulin action and elevation of the complication incidence. Most of the studies reveal the inference of oxidative stress in diabetes pathogenesis by the alteration in enzymatic systems, lipid peroxidation, impaired Glutathione metabolism and decreased Vitamin C levels. Lipids, proteins, DNA damage, Glutathione, catalane and superoxide dismutase are various biomarkers of oxidative stress in diabetes mellitus. [41, 47]Increase in the levels of ROS has been linked with lipid peroxidation, non-enzymatic glycation of proteins and oxidation of glucose which contributes toward diabetes mellitus and its complications. Most of the studies have shown relationship between oxidative stress and gestational diabetes. The oxidative stress status during pregnancy in patients with GDM was analized by determining plasma levels of as a marker of lipid peroxidation, advanced oxidative protein products (AOPPs) as markers of protein oxidation, and plasma glutathione peroxidase-3 (GPX-3) and paraoxonase (PON1) as markers of antioxidative defense, to explore the role of oxidative stress in the development and progression of GDM. In the present study, higher levels of oxidative stress markers were found in patients with GDM than in normal pregnant women. 57, 68, 69]. We found that markers of oxidative stress were increased and antioxidants were decreased with the progress of gestation in GDM, suggesting that there was increased oxidative protein and lipid damage and that the oxidation status was increased with the progression of gestation in GDM. The data showed that the use of antioxidants markedly reverses the oxidative stresses in women with GDM with marked improvement on neonatal outcome [40, 49].

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