Gestational diabetes and oxidative stress

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ABSTRACT

The pathophysiology of gestational diabetes mellitus (GDM) remains unclear. Current consensus indicates that women with GDM have a greater degree of insulin resistance, cell dysfunction, central obesity and hyperlipidaemia, which would imply that GDM is a transient manifestation of an underlying state of metabolic dysfunction. Hyperglycaemia is acknowledged as the principal factor responsible for the complications of DMT2 but, together with oxidative stress, it can also play an important role in GDM and the development of mother-foetus complications. The relationships between GDM and oxidative stress and the importance of the oxidant/antioxidant balance are not clearly understood. Some studies have shown associations between GDM and markers of oxidative stress; an increase in oxidative stress and a decrease in anti-oxidative defence in GDM have been observed. These data suggest that oxidative stress can be implicated in the progression and/or pathogenesis of GDM, and that the reduced antioxidant defences can reflect a protective response to an existing oxidative stress. Markers of oxidative stress and inducible nitric oxide synthase (iNOS) have been described as being overexpressed in GDM placenta, which could be related to cell damage. GDM placenta may be pre-conditioned by transient intracellular oxidative stress to attenuate the responsiveness to further oxidative insult. However, the effects of oxidative as well as nitrosative stress in GDM placenta, and the impact that they could have on perinatal morbidity and risk of future complications, need to be elucidated. This review centres on the importance of oxidative/nitrosative stress in the pathophysiology of GDM and their effects in GDM placenta. The relevance of equilibrium between inductor and protector mechanisms in metabolic control, obstetric complications, and perinatal outcomes are reviewed.

KEYWORDS: gestational diabetes mellitus, oxidative/nitrosative stress, placenta, pregnancy

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is a glucose intolerance of varying severity with onset or first recognition, during pregnancy. The estimated incidence of GDM will depend, largely, on the screening strategies that are applied by each investigatory group since an international consensus has not yet been achieved. Overall, the prevalence is around 5% of all pregnancies [1]. Diabetes in pregnancy increases perinatal morbidity and mortality [2] and the subsequent development of diabetes mellitus type 2 (DMT2) in the mother [3]. The pathophysiology of GDM remains unclear. Increased pro-inflammatory environment in women with GDM has been described [4, 5], and we have recently demonstrated an unfavourable cytokine profile in women with GDM [6] that continues postpartum [7]. Hence, these women have more risk of developing impaired fasting glucose, glucose intolerance or DMT2 [8-10] and increased susceptibility to

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cardiovascular disease (CVD) and, as such, has been proposed as an additional risk marker of CVD.

Oxidative damage occurs as an outcome of an imbalance between formation versus inactivation of oxygen free radicals. This process leads to the destruction of membrane lipids and accumulation of lipid peroxides and their metabolic products. Indeed, oxidative stress is implicated in the pathogenesis of vascular diseases such as atherosclerosis, diabetes and hypertension as a result of an imbalance between the increase in the formation of reactive oxygen species (ROS) and the synthesis of anti-oxidative defence mechanisms. One hypothesis being favoured currently is that oxidative stress, following the mechanisms associated with the production of superoxide, is a pathogenic factor that is conducive to insulin resistance, β-cell dysfunction, glucose intolerance and, finally, to the development of DMT2. ROS is implicated in the regulation of important physiological functions including the activation of a variety of transcription factors such as, for example, nuclear factor-kB (NF-kB) which is recognised as the principal regulator of expression of genetic responses to stress. NF-kB regulates the expression of multiple immunological and inflammatory genes, including the pro-inflammatory cytokines, proteins and enzymes involved in the generation of ROS. The injurious effects of oxidative stress on the cardiovascular system are numerous and varied, but can be summarised as the reduction in the availability of nitric oxide (NO), increase in the inflammatory markers in accelerated atherosclerosis, and modifications of lipids and lipoproteins.

There is growing evidence that oxidative stress plays an important role in the pathogenesis of GDM and in the development of maternal and foetal complications. However, the relationships between GDM and oxidative stress, and the importance of oxidant/antioxidant balance, are not well understood.

A number of markers of oxidative stress and antioxidant status have been identified, including products of lipid peroxidation and intracellular antioxidants and enzymes. However, only a few have been studied in detail. Changes in biomarker status are inconsistent; often a biomarker will show no change or decrease or even increase in levels, even in the same disease state. Further, women with previous GDM have high catalase levels, which correlate positively with glucose intolerance, indicating the potential effect of oxidative stress on postpartum dysglycaemic status. These data suggest that increased oxidative stress and reduction in antioxidant defence mechanisms contribute to disease processes in GDM.

In GDM placenta, an increase in NO levels adds to the oxidative milieu and contributes to a synergistic effect. NO combines with molecular O₂ or free radicals to generate a set of secondary intermediates such as peroxynitrite anion, nitrogen oxides and nitrogen dioxides that are even more reactive than NO. These nitrating agents not only induce damage in biomolecules such as lipids or DNA, but are also capable of regulating protein activity and modifying signalling pathways related to glucose and lipid metabolism, placental function and oxidative/nitrosative balance.

2. Biomarkers of oxidative and nitrosative stress

ROS is a term used to describe free radical as well as non-radical derivatives of oxygen. ROS include superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), hydroxyl radical (OH), and organic hydroperoxide (ROOH). Direct measurement of ROS in vivo is difficult because ROS have an extremely short half-life, have a low concentration in the circulation, and cannot be detected directly with current techniques. As such, products of oxidative damage (to DNA, lipids, and proteins) are measured as biomarkers of oxidative stress.

Markers of lipid peroxidation

Lipid peroxidation results in the formation of a number of secondary metabolic products such as conjugated dienes and lipid hydroperoxides (LOOHs), and degradation products such as alkanes, aldehydes, and isoprostanes. Lipid oxidation intermediates are toxic to cells, mainly as a result of damage to the cell membranes and, as such, are etiologically involved in a variety of physiological, pathological, and clinical conditions. Lipid peroxidation leads to the
production of end products such as malondialdehyde (MDA) which is stable and toxic; the reactive aldehyde is commonly used as a biomarker of oxidative stress. It forms covalent protein adducts that are referred to as advanced lipoxidation end products, analogous to advanced glycation end-products (AGE) [32]. MDA forms a 1:2 adduct with thiobarbituric acid (TBA) and produces thiobarbituric acid reactive substance (TBARS), the measurement of which is a common method for screening and monitoring lipid peroxidation. However, this test is not specific for lipid peroxidation since MDA can also be formed by cyclooxygenase. The conventional measurement of lipid peroxidation has relied on the TBAR assay, which involves adding TBA to the sample and colorimetrically measuring the TBARS produced.

The TBARS measurement is notoriously unreliable. Conversely, one of a unique series of prostaglandin-like products derived from free-radical-catalysed, non-enzymatic oxidation of arachidonic acid independent of the cyclooxygenase enzyme is an F₂ isoprostane, 8-isoprostane (8-epi prostaglandin F₂a or 15-F₂t-IsoP or 8-iso-PGF₂) which is considered an accurate, stable, and sensitive indicator of oxidative stress and endogenous lipid peroxidation [33]. Plasma and urine are non-invasive sources in which 8-iso-PGF₂ can be measured, but other tissues such as placenta, are often used. Common methods for the assay of 8-iso-PGF₂ are by ELISA, radioimmunoassay, and gas chromatography-mass spectrometry (GC-MS).

Markers of protein damage
Proteins can undergo several types of oxidation, including carbonylation, nitration of tyrosine, and oxidation of methionine to methionine sulphoxide [34]. Carbonylation is an irreversible process that generates protein carbonyl derivatives which can serve as more general, and universal biomarkers of oxidative stress [35]. Protein carbonyl can be measured with commercially available ELISA kits, using blood erythrocytes.

Markers of antioxidant status
Antioxidants are soluble in water (hydrophilic) or in lipids (hydrophobic). Water-soluble antioxidants, which react with oxidants in the cell cytosol and plasma include vitamin C, glutathione, lipoic acid, and uric acid. Lipid-soluble antioxidants, which protect cell membranes from lipid peroxidation, include carotenoids, vitamin E, and ubiquinol (co-enzyme Q). Antioxidants are derived from exogenous sources such as the diet, or endogenous sources, i.e. produced within the cell [36]. The distribution and levels of antioxidants in tissues and other body fluids vary greatly. High pressure liquid chromatography (HPLC) is the most reliable method for quantifying vitamin E and C in plasma or in erythrocytes.

Enzymatic antioxidants are capable of detoxifying superoxides. A superoxide is, initially, converted to H₂O₂ and then reduced to water. SOD enzymes catalyse the first step and, subsequently, the catalases and various peroxidases remove the H₂O₂. The glutathione system, which includes glutathione, GSH, GPX, and glutathione S-transferases (GST), also controls superoxide formation. GPX, an inducible enzyme, contains four selenium cofactors that catalyse the breakdown of H₂O₂ and organic hydroperoxides [37]. Enzymatic methods, using erythrocyte or serum samples, to determine the activities of SOD, GPX, and catalase have been studied extensively. Rather than measuring the concentration of specific antioxidants, the measurement of total antioxidant capacity (TAC) has been used. It reflects the oxygen radical absorbance capacity, or capacity of a plasma sample to inhibit an oxidant reaction. However, the TAC assay does not always measure all of the major antioxidants.

Markers of NO-mediated DNA damage
The major reactive nitrogen species (RNS) targets are the DNA bases. Nitrogen free radicals interact with the C8 site of the guanyl radical to produce the mutagenic product 8-nitroguanine (8-NitroG) which is a potent biomarker of nitrosative stress-mediated DNA damage [38]; 8-NitroG are associated with sites of carcinogenesis and inflammation [39]. HPLC and immunohistochemistry methods have been developed to measure the circulating levels of these biomarkers of nitrosative stress [40].

Markers of NO-mediated protein modifications
RNSs are responsible for direct post-translational protein modifications that can result in the regulation of the protein’s activity. The most
Laboratory determination of nitro fatty acids is by mass spectrometry [53].

3. Oxidative stress and antioxidant status in GDM
The link between DMT2 (a condition which has clinical characteristics similar to GDM) and complications of DMT2 with oxidative stress, has been well described [54]. Increased oxygen radical-damage biomarkers and impairment of antioxidant defence have been identified in individuals with DMT2. In contrast, the relation of GDM to oxidative stress is an area of research that has been neglected. The importance of the oxidant/antioxidant balance is far from clear.

Results of several studies have shown associations between GDM and markers of oxidative stress [20-22, 24, 25, 54-56]. Maternal MDA and TBARS levels in serum and plasma have been shown to be higher in GDM women, compared to normal glucose tolerant (NGT) pregnant women [20-22, 55]. MDA levels were observed [56] to be higher in GDM group, but advanced oxidative protein products (AOPPs) and LPO levels were not changed in GDM when compared to normal pregnancies. Toescu et al. [24], in a prospective study that assessed changes in the lipid profile and oxidative stress markers per trimester, observed that the lipid and LPO levels were more elevated in each trimester in women with DMT2, DMT1 and GDM compared to control subjects. Recently, López-Tinoco et al. [25] in a case-control study, observed elevated levels of LPO in patients with GDM.

The altered concentrations of antioxidants suggest that the defence system is working, with lower levels suggesting depletion resulting from utilization. In much of the literature, consistently elevated levels of ROS are observed in the maternal circulation of women with GDM. However, there are discrepancies regarding the expression and activity of antioxidants in GDM. Lower TAC has been described in GDM [21, 56, 57] as well as in preeclampsia [56]. Decreased levels of SOD [21, 25, 57] have been observed in patients with GDM while, in other studies, levels of SOD were found to be increased in women with GDM [58].

In relation to GPX in GDM patients, decreased levels [20] have been described by some authors.

Markers of NO-mediated lipid modifications
Recently, a new interaction of reactive nitrogen species (RNS) with a biomolecule has been described. ·NO and its secondary intermediates can react with lipids to produce cis- or trans-nitroalkanes that have modified bioactivity, compared to their precursors [51]. This reaction occurs mainly in hydrophobic environments such as lipid bilayers, and has been related to regulatory mechanisms of inflammatory processes [52].
and increased levels by others [58]. López-Tinoco et al. [25] and others [58] have shown that the levels of catalase were decreased in patients with GDM. These results differ from studies in which no significant differences had been described. For example, in a study assessing the role of oxidative stress in pregnancy complicated with preeclampsia and DM, no significant differences in levels of GPX, GSH, GST, TBARS, CAT, and MDA were observed in GDM women compared to NGT pregnant women. A summary of these studies is shown in Table 1.

These data are relevant because oxidative stress could be implicated in the pathogenesis and clinical outcomes of the disease. The increased oxidative stress in GDM is attributed to increased levels of free radicals and deficiencies in antioxidant defence systems [59].

Evidence suggests that the foetus at term is exposed to oxidative stress, as higher ROS and lower antioxidants are evident in the umbilical cord blood of GDM women. Markers are increased in diabetic pregnancies, and MDA activity and GSH levels are increased in cord plasma [60]. The low-birth-weight offspring of women with GDM have enhanced TBARS levels [57]. Conversely, antioxidants are unchanged (higher or lower) in cord blood from diabetic women. Cord plasma catalase activity [58], GPX activity [24], SOD activity, and TAC activity are significantly decreased in GDM [60]. These data suggest that maternal diabetes during pregnancy may induce oxidative stress in the neonate.

Management of oxidative stress is considered, along with good glycaemic control, to be beneficial in pre-conception, and during pregnancy. However, there is no consensus on the pathophysiological events underlying oxidative stress in GDM. There is a significant positive correlation between maternal HbA1c and MDA [20], suggesting that higher levels of lipid peroxidation are evident in patients with poor glycaemic control. Two studies [25, 55] found no significant differences between the markers of oxidative stress and antioxidant status in women with GDM treated with insulin. Longitudinal studies over the course of gestation are needed to determine whether oxidative stress triggers the onset and the progression of GDM, and whether improved glycaemic control would reduce the severity of oxidative stress.

Data are preliminary and sometimes controversial but, in our opinion, increased oxidative stress and reduction in antioxidant defence mechanisms do contribute to disease processes in GDM. However, longitudinal studies are needed to determine whether oxidative stress triggers onset, progression, and complications of GDM.

4. Oxidative and nitrosative stress in GDM placenta

Insulin resistance is associated with a systemic inflammatory environment. Secretion of cytokines such as TNF-alpha and IL-1 can be found in a variety of locations, including subcutaneous adipose and placental tissues during pregnancy [61, 62]. The consequences are physiological changes in various territories, such as extracellular matrix and endothelium which direct events inherent in gestational insulin resistance. Contradictory data exist indicating that GDM can modify the role of pro-inflammatory cytokine in placenta physiology. Placenta tissues obtained from control pregnant women were capable of secreting TNF-alpha in a culture within a high glucose environment. This inductor effect, mediated by high glucose concentrations, was higher when placental tissues were obtained from GDM pregnant women. However, Lappas et al. [63] found no differences in TNF-alpha released by placenta tissue between control and GDM pregnant women. Recently, an increase in macrophages has been reported in placentae of pregnancies complicated by GDM, and this issue has been related to higher levels of TNF-alpha and IL-6 expression [40].

Independently of the described changes in pro-inflammatory cytokine expression induced by GDM in placenta, there have been clear demonstrations that oxidative stress markers are increased in this tissue. Polyunsaturated fatty acids (PUFA) are peroxidated, as shown by an increase in 8-isoprostane [64]. As reported by Lappas et al. [62], its production cannot be modified in vitro by stimuli such as LPS, which regulate pro-inflammatory cytokine secretion. This feature suggests that a chronic, mild, oxidative
Table 1. Summary of published markers of oxidative stress and antioxidants in women with GDM, compared to control individuals (reference numbers are those in the main text).

<table>
<thead>
<tr>
<th>Markers of oxidative stress and antioxidants</th>
<th>Reference</th>
<th>GDM/controls</th>
<th>Weeks of gestation</th>
<th>Results: GDM vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA</td>
<td>20</td>
<td>16/27</td>
<td>3rd trimester</td>
<td>↑ GDM</td>
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<tr>
<td></td>
<td>21</td>
<td>20/20</td>
<td>3rd trimester</td>
<td>↑ GDM</td>
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<td></td>
<td>23</td>
<td>3/16</td>
<td>3rd trimester</td>
<td>=</td>
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<td></td>
<td>55</td>
<td>22/20</td>
<td>Pre-partum</td>
<td>↑ GDM</td>
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<td></td>
<td>56</td>
<td>27/29</td>
<td>3rd trimester</td>
<td>↑ GDM</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>20/20</td>
<td>Not stated</td>
<td>↑ GDM</td>
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<tr>
<td>TBARS</td>
<td>22</td>
<td>6/18</td>
<td>Pre-partum</td>
<td>↑ GDM</td>
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<tr>
<td></td>
<td>23</td>
<td>3/16</td>
<td>3rd trimester</td>
<td>=</td>
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<td></td>
<td>57</td>
<td>59/60</td>
<td>2nd and 3rd trimester</td>
<td>↑ GDM</td>
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<tr>
<td>LPO</td>
<td>24</td>
<td>12/17</td>
<td>1st, 2nd and 3rd trimester</td>
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<td></td>
<td>25</td>
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<td>2nd and 3rd trimester</td>
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<td>27/29</td>
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<td>TAC</td>
<td>21</td>
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<td></td>
<td>58</td>
<td>20/20</td>
<td>Not stated</td>
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<tr>
<td>SOD</td>
<td>21</td>
<td>20/20</td>
<td>3rd trimester</td>
<td>↓ GDM</td>
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<td></td>
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<td>GPX</td>
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stress status in GDM placenta could induce a resistance to subsequent oxidative stimuli [63]. Also, high levels of protein carbonylation have been found in placenta obtained from GDM pregnant women, relative to healthy control individuals [64].

Tissue oxidative status depends on the balance between oxidant stimuli and antioxidant enzymes such as SOD, CAT and GPX that reduce ROS and inhibit oxidative stress. In placenta, antioxidant enzyme levels have been measured in GDM women and healthy control individuals, and an increment in SOD activity was observed. Further, no changes were observed in GPX [64]. Subsequent studies have shown an increase in mRNA expression of CAT and GSR [63], suggesting that this elevated antioxidant expression occurs in response to a sustained oxidative state, and is the cause of lack of placental tissue responsiveness to oxidative stimulus in vitro.

A pro-inflammatory milieu in GDM can induce an increase in NO in placenta which, in an oxidative environment, is combined with ROS to produce nitrating agents such as peroxynitrates. Elevated peroxynitrates induce nitrosative stress in addition to oxidative stress, as described above. Increase in the inducible isoform of NOS (iNOS) has been described in GDM placenta, probably in response to higher levels of pro-inflammatory cytokines [65]. These results have been confirmed by our group (unpublished data). RNSs could induce changes in protein activity by modifications such as nitration and nitrosylation, although this issue has not been thoroughly studied. Experimental models have shown that iNOS can trigger nitration by causing a decrease in its activity [66, 67]. This issue could fit within a negative feedback mechanism to avoid a sustained nitrosative stress status. No studies have been conducted with respect to nitration status of placental tissue in GDM. However, an increase in protein nitration has been observed in the placenta of obese individuals (who have a higher incidence of GDM), compared to lean controls [68]. Very little is known about protein nitrosylation in GDM placenta, albeit nitrosylation has been described in several proteins related to placenta function, control of oxidative/nitrosative status, insulin signalling, and lipid metabolism in other experimental systems. Nitrosylation of ERK induces a loss of its activity mediated by an inhibition of its phosphorylation. This could be related to MCF-7 cell apoptosis [69] and failure in trophoblast differentiation [70]. Conversely, a nitrosylation-mediated loss of function has been described in AKT/PKB protein resulting in impairment of insulin-stimulated activation of PI 3-kinase-Akt/PKB pathways. This reaction is accelerated in the presence of oxidative stress, and could be contributing to insulin resistance status in db/db mice [49]. Nitrosylation has been studied in relation to preeclampsia. Changes in nitrosylation profile have been found in proteins related to energy production, cell viability and free radical scavenging [71]; enzymes such as CAT, SOD, eNOS and PRDXs can be found in this last group indicating that NO itself participates in regulation of oxidative balance. Indeed, changes in nitrosylation levels of antioxidant enzymes have been noted by our group in GDM placenta tissue (unpublished data).

5. Implications of perturbed oxidative/nitrosative balance associated with GDM

The placenta acts as an interface between maternal and foetal circulation; alterations in its functionality are closely related to perinatal alterations. Oxidative/nitrosative stress associated with inflammatory status can act on placental vasculature [72], trophoblast differentiation [70], and lipid metabolism [73] resulting in the progress of pregnancy and delivery being compromised. Data on oxidative stress affecting the mode of delivery (Caesarean section vs. vaginal labour) do not seem to be conclusive. Higher SOD activities have been observed post-delivery in diabetic mothers undergoing Caesarean section, compared to diabetic mothers who had vaginal delivery [22]. This observation indicates that women with diabetes undergoing Caesarean section may have a relative advantage with respect to better decomposition of superoxide radicals and, hence, a better chance to cope with oxidative stress during the peri-partum period. In another study, however, the levels of LPO were found to be elevated, and the GPX decreased, in females who had had a Caesarean delivery [21]. This could be due to a greater oxidative capacity, and lower anti-oxidative, status in GDM.
In relation to the impact of GDM-induced oxidative/nitrosative environment on the foetus, results indicate that resistance to oxidative insult in the placenta by a chronic mild oxidative/nitrosative environment as evidenced by a higher expression of antioxidant enzymes could alleviate the effect of systemic elevation of ROS and RNS (see Figure 1).

6. CONCLUSION

GDM women have a higher risk of perinatal morbidity, susceptibility to DMT2, and cardiovascular disease. Oxidative/nitrosative stress could be implicated in the pathogenesis and clinical outcomes of the disease.

GDM placenta may play an important role in the pathogenesis of GDM and complications, by increasing oxidative stress and by an inhibition of antioxidant response. Maternal diabetes during pregnancy could induce oxidative stress in the neonate. Resistance to oxidative insults generated in the placenta by a chronic mild oxidative/nitrosative environment could alleviate the effect of systemic elevation of ROS and RNS.

The effects of oxidative and nitrosative stress in GDM placenta, and the impact these could have on perinatal morbidity, warrant more extensive investigation.

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CONFLICT OF INTEREST STATEMENT

The authors declare there is no conflict of interest.

ABBREVIATIONS

AOPP, Advanced oxidative protein products; DMT1, Diabetes mellitus type 1; DMT2, Diabetes mellitus type 2; ELISA, Enzyme-Linked Immuno Sorbent Assay; GCMS, Gas chromatography-mass spectrometry; GDM, Gestational diabetes mellitus; GPX, Glutathione peroxidase; GSH, Glutathione reductase; GST, Glutathione transferase; HPLC, High-performance liquid chromatography; iNOS, Inducible nitric oxide synthase; LPO, Lipoperoxides; LOOHs, Lipid hydroperoxides; MDA, Malondialdehyde; MetS, Metabolic syndrome; NGT, Normal glucose tolerant; NF-kB, Nuclear factor-kB; ROS, Reactive oxidative substances;
RNS, Reactive nitrogen substances; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances; TAC, Total antioxidant capacity

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