


Research Progress on Gestational Diabetes Mellitus and Endothelial Dysfunction Markers

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Abstract: Gestational diabetes mellitus (GDM) is the onset or first recognition of diabetes during pregnancy in women with normal glucose metabolism or potentially impaired glucose tolerance before pregnancy. Studies have shown that vascular endothelial cells (VECs) are an important target organ of insulin, which is injured by multiple factors in the case of GDM, thereby leading to worsened insulin resistance (IR) and the further development of GDM. When VECs are abnormal, there will be changes in the content of a variety of cell markers, which may be helpful for the clinical prediction and diagnosis of GDM. This study attempted to investigate the mechanism and markers of VECs injury in GDM patients.

Keywords: gestational diabetes mellitus, endothelial cells, biomarkers

Introduction

Nowadays, with the gradual improvement of people's living standard, the incidence rate of GDM in the world is increasing. GDM is the abnormal glucose metabolism that does not reach the dominant diabetes level during pregnancy, which accounts for over 90% of pregnancy diabetes mellitus, and 20% to 50% of the development of type 2 diabetes mellitus (T2DM) in postpartum. The occurrence of gestational diabetes mellitus will increase the probability of complications of pregnant women, such as: abortion, polyhydramnios, macrosomia, diabetic ketoacidosis (DKA), infection, pregnancy-induced hypertension, etc., as well as shoulder dystocia, prolonged labor, postpartum hemorrhage caused by fetal overgrowth during the production process. Because of the high blood sugar environment in the mother during pregnancy, the risk of fetal malformation, macrosomia and growth restriction will also increase.¹

A variety of factors trigger GDM, including inflammatory factors, adipokines, the release of anti-insulin hormones and genetic factors, etc. The classical view suggests that GDM is a consequence of the increased demand for glucose during pregnancy and relatively insufficient secretion of insulin and IR.¹ In the process of GDM, vascular endothelial dysfunction is a major contributing factor which considers as the main cause of IR. Therefore, a timely understanding of the functional status of VECs is of great significance in preventing the onset, delaying the development of GDM, and lowering the potential risk of vascular complications.²

Structure and Function of VECs

VECs are a thin layer of single connected flat cells lining the interior surface of blood vessels. A normal adult has about 1×10^{12} VECs, with visible round or oval apertures.

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VECs secrete cytokines in an endocrine, paracrine, or autocrine way, which regulate vascular tension and blood flow and maintain the steady-state of microcirculation.³ Apart from the functions of regulating the permeability of blood vessels and maintaining the integrity of the blood vessel wall, VECs have important endocrine functions.⁴ They can synthesize and release a variety of endothelial-derived vasoactive factors that play an important physiological roles, such as nitric oxide (NO), endothelin-1 (ET-1), interleukin, and asymmetric dimethylarginine (ADMA). Among them, NO is the strongest relaxation factor and ET-1 is the strongest contraction factor, both of which play an important role in maintaining the vasodilation and vasoconstriction of microvessels. VECs also have anticoagulant and antithrombosis effects, thereby maintaining sufficient blood flow and flow rate in microcirculation.³ Endothelial cell dysfunction includes functional changes of the endothelium, such as impaired regulation of vasodilation and vasoconstriction, impaired or excessive angiogenesis, decreased barrier function, and increased inflammation activation.

Mechanism of GDM-Induced Endothelial Cell Injury

Among the many views, IR is the universally recognized pathophysiological basis of GDM.⁵⁻⁸ Researches have shown that the body of GDM patients is chronically in a low-level inflammatory response, which is not only a typical manifestation of metabolic disease, but can further promote IR injury to endothelial cells.⁹ It is suggested that there may be a strong association between low-level inflammatory response status and GDM and its complications.¹⁰⁻¹³ It has been reported in the literature,^{14,15} inflammatory factors can make the body less sensitive to insulin, but also can promote the secretion of glucocorticoids, growth hormone, and so on, so that the body appears IR, eventually leading to a persistent increase in blood glucose levels in pregnant women during pregnancy.¹⁶ Advanced glycation end products (AGEs) are the main pathological consequence of persistent hyperglycemia, which is caused by nonenzymatic glycosylation of proteins, lipids and nucleic acids.^{17,18} Some studies have also shown that ages and their precursors can promote oxidative stress and inflammation through binding with receptors, leading to vascular injury.^{19,20} It is reported that AGEs can activate some signal cascades of injured endothelial

cells and play a role in the development of diabetic vascular complications.²¹ In addition, AGEs also cause eNOS enzyme inactivation, resulting in a decrease in NO, a higher risk of vascular endothelial cells and damage to vascular permeability.²²⁻²⁴

Ages mediate the activation of early growth response protein 1 (EGR-1) and its downstream factors through protein kinase C- β II (PKC- β II) and extracellular signal regulated kinase 1/2 (ERK 1/2) signaling pathways (AGEs/PKC- β II/ERK1/2/EGR-1 pathway), which trigger the secretion of proinflammatory cytokines such as interleukin-6 (IL-6), IL-1 α , intercellular adhesion molecule-1 (ICAM-1), and tumor necrosis factor- α (TNF- α),²⁵ which is a new mechanism of GDM induced vascular inflammation.^{26,27}

VECs are the most important target cells of insulin secreted in the body. In case of dysfunction, VECs will be unable to combine with insulin normally and thus fail to perform signal transduction, nor they will play the roles in regulating blood flow and directing insulin to move to their target organs and tissues, thereby worsening IR.²⁸ The binding of insulin with special receptors on VECs can activate endothelial nitric oxide synthase (eNOS), increase NO release, and decrease ET-1 secretion, thereby leading to vasodilation. GDM-induced high glucose, oxidative stress, and abnormal adhesion to vascular endothelium damage VECs leading to reduce NO synthesis and release. In this case, nutrient-stimulated insulin response gradually increases, and the body experiences relatively insufficient secretion of insulin.⁴ Pathologically high levels of insulin have multiple direct effects on VECs, affecting the synthesis and secretion of a variety of vasodilatory and vasoconstrictive factors and regulating the proliferation and apoptosis of VECs.²⁹ In a state of low-grade chronic inflammation, VECs undergo structural changes, which lead to the increased permeability of microvessels, the increased leakage of plasma and small molecule proteins, the decreased transport of insulin, and enhanced IR.³⁰ The impairment of VECs functions is also the initiating factor of hypertension, which, in turn, acts on the renin-angiotensin system (RAS) of VECs, reducing NO synthesis and increasing ET-1 secretion. These responses exacerbate endothelial cell injury and progressively worsen IR.³ The relationship between these factors above is shown in [Figure 1](#).

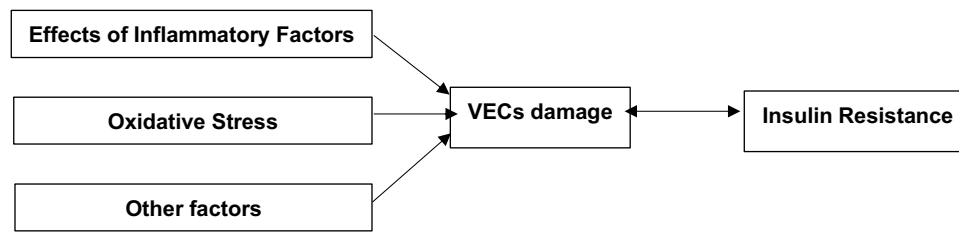


Figure 1 Relationship between influence factors, VECs and IR.

VECs Markers

As mentioned above, these markers are produced when VECs are damaged by high glucose and oxidative stress. Through these damaged cell markers, GDM can be indicated. At the same time, these markers can also be used to indicate the degree of endothelial cell damage, so as to predict and prevent the long-term complications of GDM.

Von Willebrand Factor (vWF) and Antithrombin (AT)

In the process of GDM, the increase of insulin release leads to the damage of VECs, so vWF and at are abnormal.²⁸ Under normal physiological conditions, vWF is a glycosylated protein,³ which is primarily synthesized in endothelial cells and partially in megakaryocytes, playing a role in promoting platelet adhesion and aggregation, stabilizing and enhancing the function of coagulation factor VIII.³² Besides, vWF can expedite the synthesis of plasma Fib. In the event of VECs injury, vWF is abundantly released into the blood. The normal concentration of plasma vWF is about 10 mg/L but is increased when endothelial cells are stimulated or damaged or when the body is under stress. Therefore, vWF can be considered as a marker of endothelial cell injury.³³ AT, mainly synthesized by the liver, is an important physiological anticoagulant factor in plasma, maintaining the balance between coagulation and anticoagulation. Moreover, AT also has the function of protecting blood vessels. The decrease of at activity and level will indicate the injury of vascular endothelial cells. In patients with GDM, elevated expression of vWF and reduced expression of AT in plasma suggest endothelial injury and endothelial dysfunction. Damaged endothelial cells could further promote more GDM development. Hence, the abnormal changes of vWF and at can be used as indicators of GDM and vascular endothelial cell injury.

Tumor Necrosis Factor α (TNF- α)

TNF- α is a cytokine secreted by neutrophils, monocytes, macrophages, NK cells, lymphocytes, eosinophils, and vascular endothelial cells, as well as the post-delivery placental tissue. TNF- α has a wide range of biological functions, such as promoting the aggregation and adhesion of inflammatory cells that cause VECs injury. TNF- α can directly inhibit the activity of glucose transport protein in adipocytes, reduce its expression, and enhance insulin resistance.¹⁶ According to Di Fulvio et al,³⁴ TNF- α stimulates VECs to increase vascular permeability and produces an inflammatory response, thereby damaging endothelial cell function. Thus, TNF- α acts as an inflammatory cytokine to promote the occurrence and development of GDM. Besides, their research also showed that the expression of TNF- α in the placental tissue of GDM patients was significantly higher than that in the normal group, and it was positively correlated with plasma TNF- α levels. The increased expression of TNF- α in placental tissue may cause damage to the placental vascular endothelium, resulting in placental dysfunction and the worsened hypoxic-ischemic state of the placenta.³⁵ Winkler et al³⁶ found that patients with GDM have higher serum TNF- α levels than normal pregnancies, and it is closely related to the degree of IR. According to Kirwan et al,³⁷ TNF- α may promote the occurrence and development of GDM by damaging VECs, which suggests that the abnormal changes in TNF- α can be used as an indicator indicating VECs injury status. Since TNF- α induces the occurrence and development of GDM by mediating IR, it can be used as an indicator to predict GDM and assess its prognosis.³⁸

Vascular Cell Adhesion Molecule-1 (VCAM-1)

VCAM-1 belongs to the immunoglobulin superfamily, which mainly plays a role in mediating the adhesion of lymphocytes, monocytes, eosinophils, and basophils to

the vascular endothelium. It is also involved in angiogenesis, endothelial injury, and other processes, playing an important part in leukocyte-endothelial cell signal transduction.³⁹ VCAM-1 is a biomarker of endothelial dysfunction. VCAM-1 can bind to the ligands on white blood cells (WBCs), promoting the adhesion of WBCs to VECs, which may result in VEC injury.⁴⁰ Healthy pregnant women have significantly lower plasma VCAM-1 levels than pregnant women with GDM. This suggests that VCAM-1 is closely associated with the onset of GDM. Researches also indicated that the placental tissue in the healthy group has significantly lower VCAM-1 expression than the GDM group and that the VCAM-1 expression in the GDM group is positively related to plasma VCAM-1 levels. Hence, it can be inferred that the high expression of VCAM-1 in patients with GDM may damage placental VECs and trophoblast cells, causing placental dysfunction, fetal ischemia and hypoxia, and increasing the risk of stillbirth.³⁵ Studies have also shown that patients with GDM experience significantly higher levels of VCAM-1 than healthy pregnant women and that VCAM-1 promotes the occurrence and development of GDM by damaging VECs. Therefore, VCAM-1 levels can be detected to assess the functional status of endothelial cells, and diagnose GDM in combination with the levels of glycated hemoglobin (HbA1C) and glycated albumin (GA).⁴¹

Asymmetric Dimethylarginine (ADMA)

ADMA is an endogenous L-amino acid that widely exists in cells and tissues inside the body.¹¹ Recent studies have shown that ADMA can be used as a clinically predictor of endothelial dysfunction.¹² According to some animal studies, the action of ADMA on endothelial function is worked by affecting the endogenous nitric oxide synthase (NOS)/NO pathway. In vitro studies show that ADMA is a NOS inhibitor that induces oxidative stress by inhibiting NO synthesis, thereby causing low-grade inflammation and the resultant vascular endothelial dysfunction.¹³ Studies are revealing that patients with GDM have significantly higher plasma ADMA levels but significantly lower NOS and NO levels than healthy pregnant women, suggesting that patients with GDM experience abnormally elevated plasma ADMA levels.⁴² According to

Mittermayer et al,⁴³ 14–16 weeks after delivery, patients with GDM experience higher plasma ADMA levels than healthy pregnant women. The injury of ADMA to VECs further promotes the occurrence and development of GDM.⁴⁴ These findings indicate that ADMA levels can be used as an indicator to identify whether VECs are injured,⁴⁵ and has the potential to serve as an indicator to diagnose GDM and assess the severity of the disease.⁴⁶

Vascular Endothelial (VE)-Cadherin

VE-cadherin is a VEC-specific cadherin, the main adhesion molecule on VECs.⁴⁷ It is located at junctions between endothelial cells and plays an important role in maintaining the integrity and physiological function of endothelial cells. Studies have shown that the expression of VE-cadherin can be used to indirectly infer whether there are increased vascular permeability and VECs injury, and thus to assess the degree of vascular endothelial dysfunction. Besides, VE-cadherin is found to play a role in pathological processes such as diabetes, and gestational hypertension. Recent studies⁴⁸ have also found that serum VE-cadherin levels in patients with GDM are significantly higher than that in the normal control group and that elevated levels of serum VE-cadherin increase the incidence of macrosomia and promote the occurrence of GDM. Therefore, VE-cadherin levels indirectly indicate the functional status of VECs, promising to be one of the predictors of GDM.⁴⁸

Soluble Intercellular Adhesion Molecule-1 (sICAM-1)

sICAM-1 is a member of the immunoglobulin superfamily. Plasma sICAM-1 contains most of the sequences within the extracellular domain of membrane-bound ICAM-1, and it binds to lymphocyte function-associated antigen 1 (LFA-1). ICAM-1 vascular expression is rare under normal physiological conditions, while pathogenic factors, such as hyperglycemia, activate its expression in endothelial cells, and an increase in sICAM-1 is also produced, reflecting VECs activation and dysfunctionality.⁴⁹ In the course of GDM, hyperglycemia stimulates adenosine diphosphate (ADP)-activated platelets to induce endothelial cells to express sICAM-1, and meanwhile, it increases

the response of platelets to ADP stimulation. In the case of hyperglycemia, AGEs increases, which may also induces increased expression of sICAM-1.⁵⁰ Su et al⁵⁰ showed that sICAM-1 was significantly increased in patients with GDM, which results indicate that there is a dysfunction of vascular endothelial function in pregnant women with GDM. Chen Ying et al⁵¹ indicated that the serum sICAM-1 level in GDM group was significantly increased. Monitoring the serum sICAM-1 level of GDM patients is helpful to understand the abnormal state of endothelial cells in pregnant women, the degree of IR, and to evaluate the incidence of GDM.⁵²

Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1, a single-chain globular protein which coupled with tissue-type plasminogen activator, is considered to be a pair of key substances that regulates the fibrinolytic activity. Both the substances are synthesized in VECs and released into the blood after synthesis. Under physiological conditions, PAI-1 can be produced in hepatocytes, but under inflammatory conditions, it will be abundantly secreted in VECs induced by inflammatory factors.⁵⁴ Considering the common characteristics of pathogenesis between GDM and T2DM, of whom PAI-1 is considered as a classic predictor, Salmi et al⁵³ explored the correlation between GDM and PAI-1 and concluded that PAI-1 levels were abnormally elevated in patients with GDM. According to Yan et al,⁵⁴ the significant elevation of plasma PAI-1 levels in patients with GDM was closely associated with IR, and therefore PAI-1 was involved in the onset of GDM. These findings suggest that PAI-1 has the potential to serve as a predictor of GDM.⁵⁵

Damage of Endothelial Cell Injury During GDM

There are studies have shown that women with gestational diabetes mellitus and mild gestational impaired glucose tolerance are at increased risk for type 2 diabetes and cardiovascular disease in the future.⁵⁶ A retrospective population-based cohort study in Canada examined the effect of gestational diabetes mellitus on vascular disease at 11.5 years postpartum, suggesting an association between GDM and vascular disease.⁵⁷ In the investigation of Freire et al.⁵⁸ compared with the control group, women with gestational

diabetes mellitus had increased carotid intima-media thickness (an early alternative marker of cardiovascular disease). Alexandra Oliveira et al⁵⁹ studied the changes of diastolic function in women with GDM, which is often one of the first symptoms of cardiovascular disease in the future. The results of echocardiography showed that the thickness of posterior wall and inter-ventricular septum was higher, the left ventricular mass and left ventricular mass index increased. There was a positive correlation between left ventricular mass index and fasting blood glucose and gestational body mass index, suggesting that the heart of patients with gestational diabetes mellitus has mild dysfunction.⁵⁹

Studies have shown that women with gestational diabetes mellitus and mild gestational impaired glucose tolerance have an increased risk of type 2 diabetes and cardiovascular disease in the future.⁶⁰ In women, high glucose during pregnancy predicts a gradient in the future risk of cardiovascular disease, which manifests itself over the next few decades.^{61–63} The current view is that over the time, exposure to enhanced cardiovascular risk factor can lead to vascular injury and dysfunction, which is an early event in the process of atherosclerosis.

Conclusion

In the pathogenesis of GDM, VECs are damaged by a variety of factors, such as inflammatory factors and oxidative stress. VECs injury leads to IR and promotes the development and progression of GDM disease. At the same time, the development of GDM further damaged vascular endothelial cells.

From the above discussion, it can be revealed that indicators including vWF/AT, TNF- α , VCAM-1, ADMA, VE-cadherin, sICAM-1, and PAI-1 reflect the functional changes of endothelial cells, so they promise to be the predictor of GDM and the revision guide of GDM risk factors. The summary of these indicators can be viewed in [Table 1](#). These indicators are probably of new significance in clinical practice for the prevention and treatment of GDM, for example, applying TNF- α and VCAM-1 to the monitoring of intrauterine and fetal conditions.³⁶ However, the changes in these indicators and their roles in the pathogenetic mechanism of GDM remain to be explored, needing more prospective researches. At the same time, in clinical work, special attention should be contributed to the abnormal changes in these indicators.

Table 1 Biomarkers and Characteristics of Endothelial Cells

Author and Year	Biomarkers	Synthetic Site	Changes in GDM	Effect	Mechanism of Action in GDM
Malyszko J, 2008 ³² Zhang X, 2009 ³³	vWF	Endothelial cells, megakaryocytes, etc	Rise	Promote platelet adhesion and aggregation and stabilize coagulation function	Increase the degree of IR
Wang F, 2014 ²⁸	AT	Liver	Reduce	Maintain the balance of coagulation function	Increase the degree of IR
Di Fulvio P, 2014 ³⁴ Winkler G2002 ³⁶	TNF- α	Neutrophils, macrophages, etc	Rise	Promote the aggregation and adhesion of inflammatory cells	Increased TNF - α level results in endothelial injury of placenta
Li H, 2012 ⁴⁰	VCAM-1	Endothelial cells	Rise	Mediating adhesion of leukocytes to vascular endothelium	Placental injury caused by elevated VCAM-1 level
Jin ZW, 2018 ⁴² Mittermayer F, 2002 ⁴³	ADMA	Widespread	Rise	Inhibition of NOS/no pathway	Induced oxidative stress, leading to low levels of inflammation
Ding GC, 2016 ⁴⁸	VE-cadherin	Endothelial cells	Rise	Maintain the integrity of endothelial cells	Increased incidence of macrosomia
Su N, 2013 ⁵⁰ Chen Y, 2016 ⁵¹	sICAM-1	Widespread	Rise	Play the role of the body in regulating cell adhesion	Indicate the degree of IR
Salmi AA, 2012 ⁵³ Yan YH, 2010 ⁵⁴	PAI-1	Endothelial cells and hepatocytes	Rise	Regulate fibrinolytic activity	Indicate the degree of IR

Abbreviations

GDM, gestational diabetes mellitus; VECs, vascular endothelial cells; IR, insulin resistance; T2DM, type 2 diabetes; DKA, diabetic ketoacidosis; NO, nitric oxide; ET-1, endothelin-1; ADMA, asymmetric dimethylarginine; eNOS, endothelial nitric oxide synthase; RAS, the renin-angiotensin system; vWF, von Willebrand Factor; AT, antithrombin; TNF- α , tumor necrosis factor α ; VCAM-1, vascular cell adhesion molecule-1; WBCs, white blood cells; HbA1C, glycated hemoglobin; GA, glycated albumin; NOS, nitric oxide synthase; VE, vascular endothelial; sICAM-1, soluble intercellular adhesion molecule-1; LFA-1, lymphocyte function-associated antigen 1; AGEs, advanced glycation end products; PAI-1, plasminogen activator inhibitor-1.

Statement of Ethics

This article does not contain any studies with human or animals performed by any of the authors.

Consent for Publication

This manuscript does not apply.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, analysis and interpretation; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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