REVIEW ARTICLE

Predictive Role of Oral Biomarkers and Periodontal Status in Gestational Diabetes Mellitus: A Review of Literature

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Gestational Diabetes Mellitus (GDM) is a type of diabetes that occurs during pregnancy in women who did not previously have diabetes. It is characterized by high blood sugar levels that develop during pregnancy and typically resolve after childbirth. GDM occurs when the body is unable to produce enough insulin to meet the increased demand during pregnancy or when the body becomes resistant to the action of insulin. It can have significant implications for both the mother and the baby if not managed properly.In Pakistan, GDM prevalence is reported to be from 4 to 10%. While Asian countries report a wide range from 1.2 to 49.5%, largely accounting for differences in diagnostic criteria, sample size, and population source.
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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is a type of diabetes that occurs during pregnancy in women who did not previously have diabetes.[1] It is characterized by high blood sugar levels that develop during pregnancy and typically resolve after childbirth. GDM occurs when the body is unable to produce enough insulin to meet the increased demand during pregnancy or when the body becomes resistant to the action of insulin. It can have significant implications for both the mother and the baby if not managed properly.[2]

The exact cause of GDM is not entirely understood, but it is believed to result from a combination of hormonal, genetic, and lifestyle factors. During pregnancy, certain hormones produced by the placenta, such as human placental lactogen, estrogen, and progesterone, can cause insulin resistance. This is a normal physiological response to ensure that an adequate supply of glucose is available for fetal growth and development.[3,4]

However, in some women, insulin resistance becomes excessive, and the pancreas may not be able to produce enough insulin to overcome it. As a result, glucose accumulates in the blood, leading to gestational diabetes.[5]

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PREVALENCE OF GESTATIONAL DIABETES MELLITUS (GDM)

On a global scale, it is estimated that about 1 in 7 births are affected by gestational diabetes.[6] However, prevalence rates have been seen to differ significantly between regions and ethnic groups. Certain ethnic groups, such as South Asian, Hispanic, African-American, and Native American women, have a higher predisposition to gestational diabetes.[7] In Pakistan, the prevalence of gestational diabetes mellitus (GDM) ranges from 4% to 10%, Asian countries reported a broader range from 1.2% to 49.5%, which largely results from differences in diagnostic criteria, sample sizes, and population sources.[9]

GENERIC RISK FACTORS FOR GESTATIONAL DIABETES MELLITUS

The prevalence of gestational diabetes is influenced by various other factors that can increase the likelihood of developing gestational diabetes. These include: Family History: Having a family history of diabetes, especially a first-degree relative (parent or sibling) with type 2 diabetes, increases the risk of gestational diabetes.[10]

Maternal Age: Older Women who are older, particularly over the age of 25 or 30, have a higher risk of developing gestational diabetes.[5]

Body Mass Index (BMI): Women with a higher pre-pregnancy BMI, especially those who are overweight or obese, have an increased risk of gestational diabetes.[11] Previous History of Gestational Diabetes: If a woman has had gestational diabetes in a previous pregnancy, she is at a higher risk of developing it again in subsequent pregnancies.[12]

Polycystic Ovary Syndrome (PCOS): Women with PCOS have a higher likelihood of developing gestational diabetes.[13-18]

Glycemic Markers: Abnormal blood glucose levels before pregnancy or early in pregnancy may indicate an increased risk of gestational diabetes.

Pregnancy with Twins or Triplets: Women carrying multiple fetuses are at a higher risk of developing gestational diabetes.[19]

Sedentary Lifestyle: Lack of physical activity and a sedentary lifestyle can contribute to an increased risk of gestational diabetes.[20,21]

Hypertension: Pre-existing high blood pressure or hypertension can be a risk factor for gestational diabetes.[22]

MOLECULAR BASIS OF GESTATIONAL DIABETES MELLITUS

The exact molecular basis of GDM is not fully understood, but it is believed to result from a combination of genetic and environmental factors. Some of the key molecular factors that contribute to the development of GDM include:

Insulin Resistance: Insulin resistance occurs when the body's cells become less responsive to the effects of insulin, a hormone responsible for regulating blood sugar levels. During pregnancy, certain hormones like estrogen, progesterone, and human placental lactogen increase, leading to insulin resistance. This helps ensure that enough glucose is available for fetal development. However, in some women, insulin resistance becomes excessive, leading to high blood sugar levels and GDM.[23]

Beta-cell Dysfunction: Beta cells in the pancreas are responsible for producing and secreting insulin. In some cases of GDM, the beta cells may not function properly, leading to insufficient insulin production to overcome insulin resistance. This results in elevated blood glucose levels.[4]

Genetics: Family history and genetic factors can play a role in predisposing some women to develop GDM. Certain genetic variations may affect how the body processes glucose and insulin, increasing the risk of developing diabetes during pregnancy.[24]

Adipokines and Inflammation: Adipokines are signaling molecules produced by adipose tissue (fat cells). During pregnancy, the increased production of certain adipokines can lead to inflammation and interfere with insulin signaling, contributing to insulin resistance.[25]

Placental Hormones: The placenta, an organ that develops during pregnancy, produces various hormones that can affect glucose metabolism. Some of these hormones can promote insulin resistance and impact glucose regulation.[5]

Epigenetic Changes: Epigenetic modifications, which involve changes in gene expression without altering the underlying DNA sequence, can influence how certain genes related to glucose metabolism are expressed. These changes can be influenced by environmental factors, such as diet and lifestyle, and may contribute to the development of GDM.[26]

Oxidative Stress: Pregnancy is associated with increased oxidative stress, which occurs when there is an imbalance between reactive oxygen species (ROS) production and the body's ability to neutralize them with antioxidants. Oxidative stress can impair insulin signaling and contribute to insulin resistance.[27]

GDM is a complex condition, and the interplay of these molecular factors may vary from one individual to another. Research into the molecular basis of GDM is ongoing, and a better understanding of these mechanisms may lead to improved prevention and management strategies for GDM in the future.

PREDICTIVE BIOMARKERS IN GESTATIONAL DIABETES MELLITUS

Predictive biomarkers in gestational diabetes mellitus (GDM) are biological indicators that can help identify women at risk of developing GDM during pregnancy. Early identification of these individuals allows for timely interventions and better management of the condition.[28] Several potential predictive biomarkers have been studied, although more research is needed to establish their clinical utility fully. Some of the promising predictive biomarkers for GDM include:

Maternal characteristics: Certain maternal characteristics,

such as age, pre-pregnancy body mass index (BMI), family history of diabetes, and previous history of GDM, can be indicative of an increased risk for developing GDM.29 Glycemic Indicators: Biomarkers related to glucose metabolism, such as fasting plasma glucose levels, oral glucose tolerance test (OGTT) results, and glycated hemoglobin (HbA1c) levels, are commonly used to diagnose GDM and can also indicate a higher risk for the condition.[30]

Adipokines: Adipokines are signaling molecules produced by adipose tissue (fat cells). Higher levels of certain adipokines, such as adiponectin and leptin, have been associated with insulin resistance and an increased risk of GDM.[31]

Insulin Sensitivity Markers: Biomarkers that reflect insulin sensitivity, such as homeostatic model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), can provide insights into the risk of developing GDM.[32]

Hormones from Placenta: The placenta produces various hormones during pregnancy, some of which can influence glucose metabolism. Biomarkers like placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1) have been studied for their association with GDM risk.[33]

Genetic Markers: Specific genetic variations may be associated with an increased risk of GDM. Identifying these genetic markers could help predict susceptibility to GDM in certain populations.[24]

Inflammatory Markers: Increased levels of inflammatory markers, such as C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-alpha), have been linked to insulin resistance and may serve as potential biomarkers for GDM risk.[34]

INFLAMMATORY MARKERS IN GESTATIONAL DIABETES MELLITUS

Inflammatory markers have been investigated as potential predictors of gestational diabetes mellitus (GDM).[35] During pregnancy, a low-grade state of inflammation is normal and necessary for various physiological processes. However, in some cases, this inflammation can become dysregulated, leading to adverse effects on glucose metabolism and insulin resistance, contributing to the development of GDM.[36]

The dysregulation of these inflammatory markers during pregnancy can contribute to insulin resistance, impaired glucose uptake, and affect pancreatic beta-cell function. Chronic inflammation may also promote oxidative stress, which further exacerbates insulin resistance. Several inflammatory markers have been studied in relation to GDM.[36]

C-Reactive Protein (CRP): CRP is a protein produced by the liver in response to inflammation. Elevated levels of CRP have been associated with insulin resistance and an increased risk of GDM. High CRP levels during pregnancy may indicate a state of chronic inflammation, which can impair glucose regulation.[37,38]

Tumor Necrosis Factor-alpha (TNF-alpha): TNF-alpha is a pro-inflammatory cytokine that plays a role in inflammation and immune responses. Increased levels of TNF-alpha have been linked to insulin resistance and impaired glucose metabolism, potentially contributing to the pathogenesis of GDM.[39,40]

Interleukin-6 (IL-6): IL-6 is another pro-inflammatory cytokine that can promote insulin resistance. Higher levels of IL-6 have been associated with an increased risk of GDM.[37]

Interleukin-1 beta (IL-1β): IL-1β is a pro-inflammatory cytokine involved in the inflammatory response. Elevated levels of IL-1β have been linked to impaired insulin secretion and glucose intolerance, which may contribute to GDM development.[38]

Adiponectin: Adiponectin is an adipokine with anti-inflammatory properties. It plays a role in insulin sensitivity and glucose metabolism. Low levels of adiponectin have been observed in women with GDM, potentially indicating reduced insulin sensitivity.[31]

Leptin: Leptin is another adipokine that regulates energy balance and metabolism. Higher leptin levels have been associated with insulin resistance and an increased risk of GDM.[31]

It is important to note that the relationships between these inflammatory markers and GDM are complex and multifactorial. The exact mechanisms by which inflammation contributes to GDM development are still not fully understood.

Further research is needed to better understand the role of inflammatory markers in GDM and their potential as targets for therapeutic interventions or predictive tools for identifying women at risk of developing GDM.

PREDICTIVE ROLE OF INFLAMMATORY MARKERS IN GDM

The predictive role of inflammatory markers in gestational

diabetes mellitus (GDM) has been a subject of research to identify potential risk factors and develop early detection methods for the condition.

While inflammatory biomarkers show promise, they are not yet routinely used for predicting GDM in clinical practice. Further research and validation studies are necessary to establish their accuracy and reliability. GDM prediction is a complex process, and a combination of biomarkers and clinical risk factors will provide reliable prediction models in the future.

ELEVATED INFLAMMATORY MARKERS FROM SOURCES OTHER THAN PREGNANCY

Inflammation is the body's natural response to infection, injury, or other stimuli. While inflammation is a normal and essential part of the immune response, chronic or excessive inflammation can be harmful and is associated with various health conditions. Elevated inflammatory markers can result from various sources other than pregnancy.

It is important to note that elevated inflammatory markers are not specific to any one condition or source. They are general indicators of inflammation in the body and may require further evaluation to determine the underlying cause. Additionally, while inflammation is a part of the body's defense mechanism, chronic inflammation can contribute to the development and progression of various diseases.[41]

Conditions like rheumatoid arthritis, lupus, inflammatory bowel disease (IBD), and multiple sclerosis involve the immune system attacking the body's tissues, leading to chronic inflammation and elevated inflammatory markers.[42]

Excess body fat, particularly in the abdominal region, is associated with increased production of inflammatory cytokines and adipokines, leading to chronic low-grade inflammation. Smoking and exposure to tobacco smoke can cause inflammation in the respiratory system and increase inflammatory markers in the bloodstream.

Prolonged stress can lead to the release of stress hormones, which can promote inflammation and elevate inflammatory markers. A diet high in processed foods, saturated fats, and refined sugars can promote inflammation, while a diet rich in fruits, vegetables, and healthy fats can have anti-inflammatory effects.

Trauma or injuries to the body can lead to local inflammation as part of the healing process. Conditions such as type 2 diabetes, cardiovascular disease, and chronic kidney disease are associated with chronic inflammation and elevated inflammatory markers. Exposure to pollutants, chemicals, or allergens can trigger an inflammatory response. Most importantly bacterial, viral, or fungal infections can trigger an immune response, leading to elevated inflammatory markers such as C-reactive protein (CRP), white blood cell count (WBC), and pro-inflammatory cytokines. These among others include common oral diseases which affect almost half of the world's population.[39]

ELEVATED INFLAMMATORY MARKERS IN ORAL AND PERIODONTAL DISEASES

Elevated inflammatory markers have been observed in various oral diseases, especially in chronic inflammatory conditions like periodontal disease. Periodontal disease is a common oral condition characterized by inflammation and infection of the tissues surrounding and supporting the teeth.

The inflammatory markers raised in periodontal disease include C-Reactive Protein (CRP). Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin-6 (IL-6), Interleukin-1 beta (IL-1β), and Matrix Metalloproteinases (MMPs).[43]

MMPs are enzymes that contribute to the breakdown of connective tissue in the periodontium. Their elevated levels are associated with tissue destruction in periodontal disease. Other acute-phase proteins, such as fibrinogen, haptoglobin, and serum amyloid A, may also be elevated in response to periodontal inflammation.[43]

It is important to note that while elevated inflammatory markers are commonly observed in periodontal disease, they are not specific to this condition. Other oral diseases, such as dental abscesses, oral infections, and oral cancers, may also result in increased inflammatory markers.[43]

Inflammatory markers released in response to periodontal disease can not only affect the local tissues in the oral cavity but also enter the bloodstream and potentially contribute to systemic inflammation. Chronic inflammation in the body is associated with an increased risk of various health conditions, including cardiovascular disease, rheumatoid arthritis, diabetes, and GDM among others.[44,45]

POTENTIAL CONTRIBUTION OF PERIODONTAL DISEASE IN ELEVATION OF INFLAMMATORY MARKERS IN GDM

There is evidence to suggest that oral diseases, particularly periodontal disease, may contribute to the elevation of inflammatory markers in gestational diabetes mellitus (GDM). This potential contribution of oral diseases, especially periodontal disease, in the elevation of inflammatory markers in GDM, can be explained through several mechanisms:

Chronic Inflammation: Periodontal disease is characterized by chronic inflammation of the gums and surrounding tissues due to the presence of dental plaque and bacteria. This chronic inflammation leads to the release of pro-inflammatory

cytokines, such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), in the periodontal tissues.[46]

Bacterial Products: The bacteria present in dental plaque can release toxic byproducts and endotoxins that further stimulate the inflammatory response. These bacterial products can enter the bloodstream and contribute to systemic inflammation, potentially impacting glucose metabolism and insulin resistance.[46]

Immune System Activation: The body's immune response to the bacterial invasion in periodontal disease involves the activation of immune cells, such as neutrophils and macrophages. These immune cells release inflammatory mediators, which can circulate in the blood and contribute to systemic inflammation.[46]

Endothelial Dysfunction: Chronic inflammation associated with periodontal disease can lead to endothelial dysfunction, impairing the function of blood vessel walls. This dysfunction may promote inflammation and insulin resistance, contributing to GDM.[46]

Oxidative Stress: Periodontal disease is associated with increased oxidative stress in the oral cavity. Oxidative stress can trigger the release of inflammatory cytokines and contribute to systemic inflammation.[27]

Immune-Mediated Mechanism: Inflammatory mediators from periodontal disease can activate immune-mediated pathways that impact glucose metabolism and insulin sensitivity.

It is noteworthy that while research has shown associations between periodontal disease and inflammatory markers in GDM, not all women with periodontal disease will develop GDM, and other factors also contribute to the development of GDM. GDM is a complex condition influenced by genetic, hormonal, and lifestyle factors. Therefore, further research is needed to fully understand the role of periodontal disease in the inflammatory response and its impact on GDM development.[47]

THE COMMONALITY OF INFLAMMATORY MARKERS RELATED TO GDM AND PERIODONTAL DISEASES

Inflammatory markers related to gestational diabetes mellitus (GDM) and periodontal diseases share some commonalities due to the inflammatory processes involved in both conditions. Both GDM and periodontal diseases are characterized by chronic inflammation, and as a result, there is an overlap in the inflammatory markers that may be elevated in both conditions.

Elevated levels of Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin-6 (IL-6), Interleukin-1 beta (IL-1β), and Matrix Metalloproteinases (MMPs) are seen in both GDM and periodontal diseases. Some adipokines, such as adiponectin and leptin, are associated with insulin resistance and inflammation, and their levels may be altered in both GDM and periodontal diseases. While these inflammatory markers are commonly observed in both GDM and periodontal diseases, it's important to note that the specific patterns and levels of these markers may vary between individuals and disease severity. Additionally, while there is evidence suggesting an association between periodontal disease and GDM, more research is needed to fully understand the underlying mechanisms and potential causality between these two conditions.[48]

CORRELATION BETWEEN PERIODONTAL DISEASE AND GESTATIONAL DIABETES

Some studies have found an association between periodontal disease and gestational diabetes. Pregnant women with periodontal disease may have an increased risk of developing gestational diabetes compared to those without periodontal disease. Both periodontal disease and gestational diabetes involve inflammation. It is hypothesized that the chronic inflammation caused by periodontal disease may contribute to insulin resistance and impaired glucose metabolism, increasing the risk of gestational diabetes.

Hormonal changes during pregnancy can affect oral health, making pregnant women more susceptible to periodontal disease. Conversely, periodontal disease may also impact hormonal regulation, potentially influencing the development of gestational diabetes.

Periodontal disease and gestational diabetes share common risk factors, such as obesity, poor oral hygiene, smoking, and a history of diabetes. These shared risk factors may contribute to the observed correlation between the two conditions.[49]

While studies have found associations between periodontal disease and gestational diabetes, the exact nature of the relationship is still being investigated. The evidence suggests that addressing periodontal disease during pregnancy may help reduce the risk of gestational diabetes and improve overall maternal and fetal health. However, further research is needed to establish a causal relationship and determine the precise mechanisms linking the two conditions.

Periodontal Status as a Predictor of Gestational Diabetes Research suggests that periodontal status may serve as a

potential predictor for gestational diabetes. Several studies have explored the association between periodontal disease and the risk of developing gestational diabetes, with some findings indicating that the presence and severity of periodontal disease may increase the likelihood of developing gestational diabetes. Periodontal status has been proposed as a potential screening tool to identify women at higher risk of developing gestational diabetes. Some studies suggest that the presence of periodontal disease can be an independent predictor for gestational diabetes, regardless of other risk factors such as age, BMI, and previous history of gestational diabetes.

Chronic inflammation associated with periodontal disease may contribute to insulin resistance, a key factor in the development of gestational diabetes. It is hypothesized that the inflammatory mediators released during periodontal disease can impact insulin sensitivity and glucose metabolism, increasing the risk of gestational diabetes.[50]

Interventions targeting periodontal health during pregnancy have shown promising results in reducing the risk of gestational diabetes. Treating periodontal disease through dental procedures such as scaling and root planning or providing oral hygiene education and support has been associated with a lower incidence of gestational diabetes. Whilst there is evidence supporting the relationship between periodontal status and gestational diabetes, further research is necessary to establish a definitive cause-and-effect relationship and determine the clinical implications of using periodontal status as a predictor for gestational diabetes.[51]

CONFLICT OF INTEREST

None declared

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