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Review

Role of immunological markers in gestational diabetes mellitus-a brief review

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ABSTRACT

Gestational Diabetes Mellitus (GDM) is a condition which develops due to insulin resistance. There are a number of immunological markers (IL-6, TNF-α, IL-10, etc), which play significant role during normal pregnancy and their irregular levels could likely cause some level of insulin resistance. There are studies which have compared the levels of different immunological mediators in GDM affected females and their healthy controls, but their findings are little controversial. Some of the studies have reported increased levels of IL-6, TNF-α, adiponectin, leptin, in females affected with GDM, while others do not confirm this. We have tried to summarize, in this short review, the findings of research studies being conducted globally, which have reported the association of insulin resistance, GDM and immunological markers. Our review suggests that there is a need for high quality data on the immunological parameters associated with GDM, especially from India.

1. Introduction

Gestational diabetes mellitus (GDM) is defined by the American Diabetes Association (ADA) as "any degree of glucose intolerance with onset or first recognition during pregnancy" [1]. It affects 1–22% of all pregnancies globally, depending on the population and diagnostic criteria used. The incidence of GDM has increased with the adoption of new one-step diagnostic criteria proposed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) guidelines [2]. Speaking of India, which has become the Diabetes Capital of the world; it is estimated by the Indian Diabetes Federation (IDF) that around 4 million women have been affected by GDM [3]. It is found to be more prevalent in urban areas (4.6–14%) than in rural (1.7–13.2%) parts of India [4]. GDM is a state which has long-term implications, both for the mother and offspring. Women with GDM are likely to give birth to large-for-gestational-age or macrosomic babies. It is largely associated with prenatal morbidity, preterm labour, dystocia, etc., and mother gets a high risk of developing type 2 diabetes within 5–10 years after delivery [5].

In normal pregnancy insulin resistance usually develops in mid-pregnancy and it progresses through 3rd trimester. It has been associated to be caused by increased maternal adiposity and different hormones released from the placenta [6]. Most of the women remain normoglycemic due to adequate beta-cell compensation with higher insulin secretion. However, GDM develops if beta-cell compensation is not adequate for the level of insulin resistance [7,8]. In recent years, the role of many cytokines and other immunological factors in GDM have been investigated [9]. Although, the relationship of cytokines and GDM is not very clear and in this review we have tried to focus on various immunological factors associated with GDM.

2. Inflammation and its link with type 2 diabetes

In the past few years, insulin resistance has been identified to be associated with low grade inflammation [10]. The most common cause of insulin resistance has been reported to be obesity or increased adipose tissue [11]. Many longitudinal and prospective studies have shown several pro-inflammatory cytokines and other inflammatory markers as predictors of diabetes [12–14]. TNF-α is the first pro-inflammatory cytokine whose levels were found to be increased in the adipose tissue of obese individuals and it was observed that reduction in weight leads to lowered TNF-α levels [15]. Other mediators of inflammation whose levels gets increased in type 2 diabetes include sialic acid, C-reactive protein, fibrinogen,

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IL-6, etc [16].

3. Obesity and gestational diabetes mellitus

Prevalence of obesity has been increasing tremendously worldwide. There is an inter-relationship established between obesity and diabetes and it is considered to be a major risk factor for the development of GDM as well [17,18]. Obesity might result in 3 fold increased risk for developing GDM [19]. Maternal obesity alone is responsible for major pregnancy outcomes, and in combination with GDM the impact is higher [20,21]. Obesity and GDM both involve inflammatory mechanisms in their pathogenesis [22,23]. Increase in inflammatory markers in case of GDM and to add on to the effect, obesity leads to higher risk of complications [22]. A Japanese study has shown that their study subjects who had higher abdominal fat had more insulin resistance [24].

4. Inflammatory markers of gestational diabetes

Unlike non-pregnant state, which has a balance between pro- and anti-inflammatory cytokines for normal development, pregnancy shows an altered inflammatory profile [25]. In pregnancy, non-lymphoid tissues including the placenta and trophoblast cells, in addition to local T cells are the major sites of cytokine production. During a normal pregnancy, the activity of T-helper cells is strongly shifted towards an anti-inflammatory profile characterized by Th-2 cytokines, which protects the foetal-maternal relationship and favour normal pregnancy outcomes. However, in case of GDM or other insulin resistance states, this balance is hampered and it compromises normal development [26,27].

An association between abnormal secretion of pro-inflammatory (TNF-α & IL-6) and anti-inflammatory markers (IL-4 & IL-10) and insulin resistance is established in various studies [28–30]. Levels of theses inflammatory markers have been investigated in GDM and healthy pregnant women worldwide, the quality data is still not available. Some of the researchers have confirmed increased levels of TNF-α & IL-6 and decreased levels of IL-10 [31–33] in GDM affected females, while others have not confirmed these findings [34,35]. According to a review of studies who have compared the cytokine levels in GDM and healthy controls, over 70% of the 15 studies on TNF-α reported an association between this cytokine and GDM [9,31,32,36]. TNF-α has also been reported to impair beta function and insulin signalling, which may be attributed as a cause for developing GDM [7]. Since, insulin resistance is reported to be one of the main causes for GDM; it can be hypothesized that abnormal levels of cytokines may be related to GDM. A recent study by Murthy et al. (2018) on Indian females has reported higher levels of TNF-α and IL-8 in those having GDM, as compared to the controls [37].

Another group of substances produced mainly by adipose tissue called adipokines are a focus of research nowadays. This group includes adiponectin, leptin, Retinol-Binding Protein-4 (RBP-4), and resistin. These substances and other inflammatory mediators (C-reactive protein, IL-6, PAI-1, TNF-α) have been reported to play an important role in glucose intolerance and dysregulation in women with GDM [38]. High sensitivity C-reactive protein (hsCRP) has been studied as a marker of GDM and HAPO study has reported an association of HsCRP with increasing maternal glucose levels, BMI & C-peptide [39].

5. Placenta and the cytokines network

Placenta serves as the main interface between the mother and fetus and it releases a variety of cytokines including TNF-α, leptin and resistin, which increases the complexity of the immune-metabolic network already existing in pregnant females. One of the existing hypotheses states that increased TNF-α, leptin and resistin leads to insulin resistance in females affected with GDM [36]. A case-control study by Lappas et al. has shown that the differential release of adiponectin, leptin and resistin in GDM may be a cause for its pathogenesis [40]. Placental leptin expression in GDM affected females is increased as compared to healthy pregnant females. Leptin itself increases the production of TNF-α which leads to a low-grade inflammatory condition [41].

Cytokines are mainly produced by cells of the immune system, Natural killer (NK) cells, and macrophages in response to an external stimulus like infection, stress or injury. Adipose tissue is also an additional source of cytokines [42, 43]. Placenta is also a source of cytokines in pregnancy [44]. Moreover, in pregnancies complicated by GDM, there is dysregulation in metabolic and inflammatory pathways which is mainly the result of increased circulating inflammatory molecules [45,46].

6. Role of adiponectin

Adiponectin, an anti-inflammatory agent secreted by adipose tissue have been shown to be down-regulated in GDM affected females [20]. In a study by Tsai et al., they have demonstrated that decreased maternal adiponectin levels and insulin sensitivity may increase risk of macrosomic baby in females with GDM [21]. Another study by Retnakaran and Associates have demonstrated a strong correlation between adiponectin levels and pancreatic beta cell function during late pregnancy [22]. Subclinical inflammation has been associated with lower levels of adiponectin [23]. A case-control study by Ategbo et al., has shown that the levels of adiponectin are decreased in women with GDM as compared to their healthy controls and similar results were observed by Meller et al. [24]. Lower levels of adiponectin has also been associated with beta cell dysfunction and also linked to future development of type 2 diabetes mellitus [22,25]. Based on these findings, adiponectin could be an associated factor for causing GDM. However, more clarity is required in this aspect, with the help of large-scale comparative studies.

7. Conclusion

Gestational diabetes is now considered to be an inflammatory condition due to its similarity with Type 2 diabetes, which has already been designated as a chronic inflammatory disease. Studies have shown variable levels of inflammatory markers (TNF-α, IL-6, IL-4, IL-10, etc) in females affected with GDM and those with healthy pregnancies. From this review we would like to highlight the necessity of large-scale studies which would provide confirmatory data on association of immunological factors and GDM, which could help clinicians to predict if a women would develop GDM or not by testing these markers at an early stage. Specifically, talking about India, there is a need for research studies to be conducted on immunological mediators and their association with GDM. There is a lack of literature from India, on this topic.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.07.018.

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