IJBCS
ISSN: 2147-1428

Review Article

International Journal of Basic and Clinical Studies (IJBCS)
2020; 9(1): 9-16 Ciraci E.

T Cell Immune Profile and Related Cytokines in Gestational Diabetes

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Abstract

Gestational diabetes mellitus (GDM) is a pregnancy complexity and characterized by a pro-inflammatory immune system response and systemic inflammation with insulin resistance . Because physiological alterations during normal pregnancy are characterized by a live immune response and insulin resistance, it may be owing to improper adaptation of the maternal immune system of GDM. For this reason, studies have focused on investigating the response of T helper cells, in either normal and complex pregnancy. Many of the current studies have investigated relevant alterations in the level of cytokines in the circulation that reflect T helper cell I (Th1) and Th cell 2 (Th2). It is also suggested that different T-cell subsets play a status in regulating the immune response in pregnancy complexities. In particular, these different T cell subsets play a status in various pregnancy complexities. This review provides links among gestational diabetes and T cell subsets in the light of guidelines and literature.

Key words: Gestational Diabetes, T cell subsets, GDM, cytokines, pregnancy complications.

Introduction

Diabetes Mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia. Chronic hyperglycemia leads to disorders in carbohydrate, fat and protein metabolism, which happens owing to insulin release, insulin effect, or either of these factors (1).

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According to the etiological sorting of diabetes advised by ADA (American Diabetes Association), diabetes types are seperated into 4 groups. These are Type 1 DM, Type 2 DM, GDM and different specific types. 90-95% of all diabetics constitute type 2 diabetics approximately. GDM is a pregnancy complexity and it is identified in the second or third trimester of pregnancy. In this period, it is characterized by low-grade systemic inflammation with insulin resistance and a pro-inflammatory immune system response that was not apparent before pregnancy (2). While the prevalence of gestational diabetes is seen among 1% and 14% of pregnancies worldwide (3), seen that the prevalence of GDM varies among 2.6 and 27.9% according to the results of the studies conducted in our country (4). The rise in the prevalence of GDM is in all likelihood to continue because obesity is rising in women all over the world (5,6).

GDM and T2DM Relationship

When comparing to women without GDM in the long term with women with GDM, the potential of being T2DM is 7.4 times higher in women with GDM (7). Insulin resistance, impaired glucose tolerance and cardiovascular disease are the potential risk factors for T2DM and this considirations enhance in children who are exposed to hyperglycemia in the womb. (8). It is suggested that about half of GDM will form T2DM in 10 years (9). In the later stages of life, the risk of cardiovascular morbidity enhances (10). In maternal glucose metabolism, remarkable alterations take place during pregnancy. Insulin sensitivity characteristically diminishes in late pregnancy (11).These alterations take place against the frame of the pregestational metabolic state (12). GDM and T2DM appear to have many widespread risk factors and they have similar pathophysiology. Either are associated with a high body mass index (BMI) and a history of anormally glucose tolerance. The most prominent feature of either conditions is that peripheral insulin resistance combines with the relative inability of pancreatic β-cell insulin production. Therefore, the presence of striking similarities among these two diseases suggests a marked overlap between genetic additives (13).

Pathophysiology of Gestational Diabetes

A normal pregnancy is a condition that progresses with insulin resistance, hyperinsulinemia and mild postprandial hyperglycemia under the action of diabetogenic hormones such as growth hormone secreted from the placenta, corticotropin-releasing hormone, placental lactogen, tumor Necrosis Factor-α (TNF-α) and progesterone. This situation prepares the mother to provide the enhanced need of some amino acids and glucose for the fetüs. Adipokines, leptin, adiponectin, TNF-α, interleukin-6 (IL-6) are secreted from white adipose tissue. The placenta also shows a similar cytokine gene expression profile, with the exception of adiponectin. It is thought that inflammation caused by secreted cytokines may be related with enhanced insulin resistance in gestational diabetes (14,15).

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Widespread Complications of Gestational Diabetes

GDM has many deleterious effects on the fetus and mother. Widespread complexity of gestational diabetes are; macrosomia, birth injuries, cesarean, hydramniosis, preeclampsia, , Type 2 DM in the postnatal mother, metabolic disorders in newborn (16). Hyperglycaemia stimulates fetal β cells, leading to enhanced insulin secretion and high insulin levels in the blood. High insulin level stimulates hematopoietic cells. As a result, polycythemia enhances, hyperplasia and hypertrophy take place (17).

High insulin levels can lead to damage to brain cells. In consequence of blood and urine glucose concentrations enhance abnormal glucose metabolism, , which rises the susceptibility to urinary tract infections. The Hyperglycemia and Harmful Pregnancy Results (HAPO) study on the effect of hyperglycemia on pregnancy results confirmed that glucose during pregnancy is relevant to an enhanced risk for macrosomia, cesarean delivery and neonatal hypoglycemia rates (18,19).

Risk Factors for Gestational Diabetes

The major risk factors that cause the emergence of GDM in women;

- Obesity
- Having given birth previously to an infant weighing > 9 pounds
- Diabetes history in family
- Women >25 years old
- Race
- Impaired glucose tolerance (20).

Immune Response in Gestational Diabetes

The innate immune system and the adaptive immune system are the parts of the immun system. Natural immune cells activate and stimulate the naive T helper (Th0) cells for managing the adaptive immune response. Th0 cells differentiate to Thl, Th2, Treg or Th17 effector cells. The this system shows to play a very important status in the formation of insulin resistance, especially with the capacity to differentiate into Th0 cells, pro-inflamatory or anti-inflammatory Th cells (22).

CD4 + Th cells are among the basic building blocks of the immune system. After activating Th cells, they begin to secrete cytokines that affect the function of almost all cells of the immune system (23). These cytokines activate and regulate B cells, Tcells, natural killer cells, macrophages and other immune system cells (24). The related cytokines are also generated by trophoblast cells, stromal cells, epithelial cells, maternal T lymphocytes, macrophages, NK cells and other maternal leukocytes (25). This suggests that the development and maintenance of the fetal-placental unit depends on these cytokines. The presence of these cytokines in the maternal-fetal range influences the provision of the appropriate environment by regulating processes such as implantation, placental development, cytotrophoblast proliferation, angiogenesis, extravillous trophoblast cell invasion, reconstruction of spiral arteries, cell growth and apoptosis (26). As seen in Figure 1, antigen presentation in the presence of IL-12 induces expression of T-bet and IFN-γ production. As a result of this, Th cell differentiation occurs in the

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Th1 direction. On the other hand, IL-4 induces GATA3 expression and IL-4 production, and this is necessary for its differentiation to Th2 cell direction. Expression of IL-6 and TGF (Transforming Growth Factor-βRORγt induces IL-17 production in Th17 cells. TGF-β is required for Foxp3 expression and Treg cell differentiation (27).

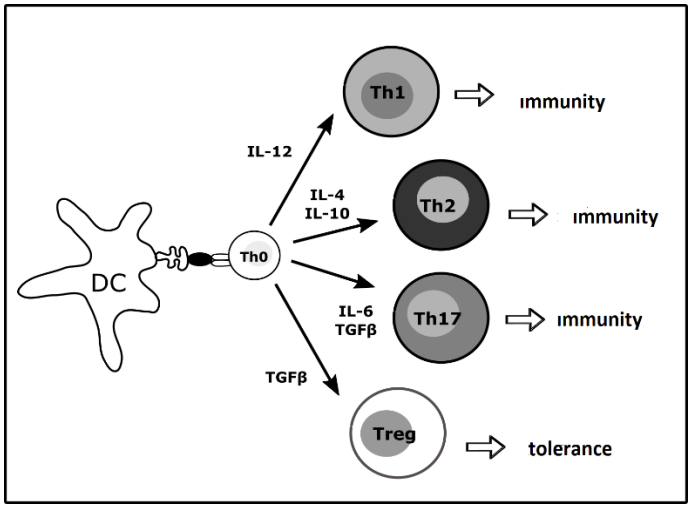

Figure 1: T cell differentation

Th2 cells have a critical status in immune response against extracellular parasites and work by producing IL4,5 and 13. Epithelial cells in intestines, skin, lungs and host cells of the natural immune system that are the entry point of parasitic infections, produce Th2 cytokines including IL-4, IL-25 and IL-33 (29,30). These cytokines affect the cells of the natural immune system, such as basophil and dendritic cells, or direct differentiation of naive T cells to the Th2 direction. IL-4 activates STAT6, which plays a role in Th2 differentiation by interacting with its receptor. STAT6 activation enhances the induction of GATA3 transcription factor. GATA3 is the main regulator of Th2 differentiation. When GATA3's function is impaired, Th2 differentiation does not occur. IL-4, produced from mature Th2 cells, promotes the differentiation of more naive T cells into Th2 cells after encountering the antigen. (30). In humans, it is thought that the pregnancy is recognized by the mother through the signals sent by the fertilized ovum during pregnancy, which leads to the predominance of intrauterine Th2 cells (31,32). Thl cells produce interferon-gamma (IFN-γ) and support the cell-mediated immune response. Th2 cells produce IL-4 and / or IL-10, a regulatory cytokine, and support antibody production and humoral immunity (33). Surgery reduces the rate of Th1 / Th2 responsible for suppressed cell-mediated immunity after surgery (34). The ratios of Th17 to regulatory Tcells (Treg) and Th1 to Th2 represent the state and direction of the immune response and play the status of an immunomodulator (35,36,37).

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Studies have also focused on Th17 cells, which are characterized by IL-17 secretion to understand the pathophysiology of pregnancy complexities (38). Through the secretion of IL-17, Th17 cells induce neutrophil uptake, activation and migration as well as pro-inflammatory mediators (39). Therefore, these cells play a vital proinflammatory status for defending against extracellular pathogens, but they also play a status in the pathogenesis of autoimmune diseases such as chronic inflammatory and rheumatoid arthritis (40).Th17 cells are thought to diminish in uncomplicated pregnancy compared to non-pregnant women. As a result of this, peripheral levels appear to remain low during the pregnancy period without any considerable alteration (41,42). In addition to the complexity of defining the environmental profile of the T cell immune response in GDM, Treg cells are thought to be necessary to maintain the immune homeostasis and tolerance as they regulate and suppress the immune response (43).
In the study of Ostlund et al. , the peripheral subset of Treg cells secreting IL-10 was measured. This measurument showed that in the third pregnancy trimester, this T-cell subset was substantially higher in GDM pregnant women than in controls. Considering the suggested link among the Th17 and Treg response (44), in the study of Arck et al., GDM women had higher levels of this regulatory / anti-inflammatory Treg subset, as well as higher pro-inflammatory Th17 cells. As a result of present data show that Treg cells rise during pregnancy. Treg cells peak in the second trimester and these cells play an important anti-inflammatory status in the necessary immuno-tolerance (45,46). On the other hand, different studies also suggest that Treg cells do not alternate or even diminish during pregnancy. Mor extensive research is needed to examine alterations in these T cell subsets in the first trimester of pregnancy to enlighten the definitive evolution of the Treg and Th17 response for GDM and noncomplicated pregnancy (47).

Conclusions

In the perinatal period and in the long term. GDM is an residual incidence in the world and is related with morbidity for either the mother and fetus. Future studies are required to specifically more comprehensive studies are needed in the future for exploring whether prenatal exposure to the dysregulated metabolic and immune environment of GDM may have an epigenetic impact on the neonatal immune function and increase the risk of subsequent disease.

Conflict of Interest

The author has any potential financial or commercial conflict of interest associated with this research manuscript (review article).

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IJBCS
ISSN: 2147-1428

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