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Association of gestational diabetes and proinflammatory cytokines (IL-6, TNF-α and IL-1β)

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Absatract

Changes to proinflammatory cytokines as a result of gestational diabetes mellitus (GDM), and the pregnancy complications that these changes can cause, are of vital importance to the effective prevention and optimal management. Interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) are cytokines that are associated with gestational diabetes. Therefore, the aim of this review is to draw attention to the relationship between gestational diabetes and these diseases

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Gestational diabetes and proinflamatuar cytokines

GDM is the most prevalent metabolic disorder to occur during pregnancy and is defined as any type of glucose intolerance that starts or is first diagnosed during pregnancy. GDM typically develops in the second or third trimester of pregnancy and can cause hyperglycemia of varying severity. Due to recent increases in pregnancy age and the rate of obesity, the incidence of GDM has risen worldwide (1, 2). GDM can lead to severe pregnancy complications, such as macrosomia, cesarean delivery, shoulder dystocia, and neonatal hypoglycemia (3). Furthermore, the offspring of women with GDM frequently develop defects, injuries, or illnesses, such as birth trauma, prematurity, and respiratory distress syndrome (4). In addition, women with GDM are more likely to develop type 2 diabetes mellitus (DM) and cardiovascular disorders (CVD) after gestation (5, 6). The children of women with GDM are also more likely to develop type 2 DM, in addition to obesity, during their early days of life (7).

It has been determined that the incidence of GDM in pregnant women is related to the prevalence of type 2 DM in that population (2). Overeating and sedentary lifestyles are the most considerable factors to have caused the pandemic spread of type 2 DM worldwide (1). This spread of type 2 DM has contributed significantly to recent increases in the incidence of GDM (2). The prevalence of GDM varies drastically from country to county and from region to region within the same countries (2). Current studies have illustrated that the incidence of GDM is close to 10% in America, varies from 3% to 21.2% in Asian countries, and affects 5% to 8% of the pregnant population in Australia (8, 9). Furthermore, GDM has been more frequently observed in the winter than in the summer (10).

GDM can impact an organism in several different ways. For instance, it can increase the risk of CVD and type 2 DM (by as much as 7 times the normal rate) in expecting mothers (5). Women with GDM have markedly higher rates of obesity, hypertension, and metabolic syndrome than other populations. They also undergo various changes to the levels of their blood inflammatory cytokines (11, 12). Cytokines, such as IL-6, IL-8, and TNF-α, can prevent insulin signaling and have been associated with insulin resistance during cases of type 2 DM. IL-1β is a proinflammatory cytokine that is an effector molecule of inflammatory beta-cell destruction (13, 14). In addition, IL-1β has frequently been observed in the pancreatic sections of patients with type 2 DM (15).

IL-6 (interleukin-6)

IL-6, which is encoded by the IL6 gene in humans, is both a pro-inflammatory cytokine and an interleukin that acts as an anti-inflammatory myokine (16). IL-6 is secreted by T cells and macrophages to stimulate immunity, and it plays an important role in the fight against infection (17). Furthermore, osteoblasts secrete IL-6 during the stimulation of osteoclast formation. IL-6 is produced as a pro-inflammatory cytokine in muscle cells within the tunica media layers of several blood vessels. While the role of IL-6 as an anti-inflammatory cytokine is mediated through the activation of IL-10 by inhibitory effects on TNF-α, and IL-6 is the first stimulator of acute-phase protein production, other cytokines affect the subgroups of acute-phase proteins, as well (18).

Several cytokines, particularly IL-6, stimulate the production of acute-phase proteins in response to a variety of stimuli. In addition, IL-6 stimulates the production of the IL-1 receptor antagonist, which is an anti-inflammatory mediator (19). IL-6 may therefore have a protective effect. Increases in IL-6 during pregnancy have been linked to gestational insulin resistance, particularly due to placental production (20). IL-6 is also upregulated in women with GDM during labor (21). Previous investigations have determined a positive correlation between the concentration of IL-6, insulin sensitivity and plasma glucose levels, and gestational and postpartum body fat percentages (22-25). In case-control studies, plasma IL-6 levels are a significant predictor of GDM (26). The association of IL-6 with gestational diabetes is described as follows: the inflammation of macrophages in the pancreas and adipocytes that cause an increase in the production of IL-6. Other immunocytes also contribute to infiltration (27). Therefore, the destruction of pancreatic β-cells results in low insulin synthesis and apoptosis, which leads to high levels of blood glucose (28, 29).

TNF-α (Tumor necrosis factor alpha)

TNF-α, which is also known as cachectin, plays an important role in the many inflammatory and immune responses that are generated by T lymphocytes and macrophages. It is also a cytokine that is secreted by NK cells, monocytes, endotoxins, macrophages, T and B lymphocytes, and other cells that have been stimulated by microbial products (30). It has been reported that TNF-overexpression is responsible for the development of obesity, insulin resistance, and even TNF-α in rodents. Antagonism also increases insulin sensitivity and the activity of the insulin receptor tyrosine kinase (31-33). As one of the most common metabolic diseases, GDM is characterized by carbohydrate intolerance and insulin resistance during pregnancy (34-36). It has recently been suggested that TNF, one of the proinflammatory cytokines, plays an important role in the development of insulin resistance that has developed due to pregnancy (37, 38).

Although the role of TNF-α in the pathophysiology of insulin resistance is not fully understood, opinions have concentrated on at least two of its mechanisms. Researchers have suggested that TNF-α may either be inhibited during the phosphorylation of the insulin receptor or may result in a decrease in the glucose transporter-4 expression (39, 40). Winkler et. al. declared that TNF-α concentration in patients with GDM significantly increased with surges in C-peptide and BMI during the third trimester of physiological gestation (41). Moreover, Rao et. al. indicated that gestational diabetes, pre-eclampsia, and intra-uterine infection during pregnancy had profound effects, such as the development of endothelial dysfunction, on both the mother and the fetus (42). When endothelial cells are exposed to long-term hyperglycemia and proinflammatory cytokines, they can cause increases to the production of ROS in cells (43, 44). Under these conditions, increased vascular permeability, and ultimately, endothelial dysfunction have been reported (45).

IL-1β (Interleukin-1Beta)

IL-1β is a member of the IL-1 family that presents agonistic activity (46). IL-1β is produced by hematopoietic cells, such as monocytes, tissue macrophages, skin dendritic cells, and brain microglia that develop in response to Toll-like receptors (47). In healthy subjects, 6 ng of IL-1β are produced every day (48). This amount increases with the development of autoinflammatory diseases and can become 5- to 10-times higher than it is in healthy subjects (49). IL-1β stimulates the synthesis of IL-6, chemokines, nitric oxide, cyclooxygenase-2, and adhesion molecules (50). IL-1β exerts its biological function by binding to the IL-1 type I receptor and activating the inhibitor-κB kinase/ nuclear factor-κB pathway and three types of MAPKs: ERK, JNK, and p38 MAPK.

Due to the increased rates of IL-1β concentration in the nondiabetic children of diabetic individuals, recent studies have suggested that IL-1β could be added among the cytokines associated with insulin resistance (51). While chronic overproduction of IL-1β has been associated with many immune system disorders, it has primarily been linked to type I diabetes (52). It has been expressed that the incidence of IL-1β in genetically predisposed individuals furthers the impairment of insulin sensitivity through the secretion of insulin and thus contributes to the development of type II diabetes and macrovascular complications (53). In addition, it has been indicated that proinflammatory cytokine IL-1β levels are higher in patients with type 2 diabetes than in non-diabetic individuals (54). It has also been suggested that increased levels of IL-1β are associated with impaired pancreatic β-cells and decreased secretion of insulin (55). Oztop et al. reported that individuals with DM had significantly higher levels of IL-1β levels than normal pregnant women (56).

Conclusion

In summary, GDM is a significant problem throughout the world. Therefore, knowledge about the roles of certain cytokines in GDM, such as varying levels of IL-6, TNF-α, and IL-1β, may provide insight into future research about the condition.

References

1. American Diabetes Association (2016) Classification and diagnosis of diabetes. Diabetes Care. 10.2337/ dc16-S005.
2. Zhu, Y., and Zhang, C. (2016) Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep.

10.1007/s11892-015-0699.

3. HAPO Study Cooperative Research Group et al (2008) Hyperglycemia and adverse pregnancy outcomes. N Eng J Med. 10.1056/NEJMoa0707943.
4. Thomas, F., Balkau, B., Vauzelle-Kervroedan, F., and Papoz, L.(1994) Maternal effect and familial aggregation in NIDDM. The CODIAB Study.CODIAB-INSERM-ZENECA Study Group. Diabetes. Jan;43 (1):63-7.
5. Bellamy, L., Casas, JP., Hingorani, AD., and Williams, D. (2009) Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 10.1016/S0140-6736(09)60731-5.
6. Sullivan, SD., Umans, JG., and Ratner, R. (2012) Gestational diabetes: implications for cardiovascular health. Curr Diab Rep. 10.1007/s11892-011-0238-3
7. HAPO Study Cooperative Research Group (2002) The hyperglycemia and adverse pregnancy outcome (HAPO) study. Int J Gynecology Obstetrics 78:69–77.
8. Yuen, L., and Wong, VW. (2015) Gestational diabetes mellitus: challenges for different ethnic groups. World J Diabetes. 10.4239/ wjd.v6.i8.1024.
9. Beischer, NA., Wein, P., Sheedy, MT., and Steffen, B. (1996) Identification and treatment of women with hyperglycaemia diagnosed during pregnancy can significantly reduce perinatal mortality rates. Aust NZ J Obstet Gynaecol 36:239–247.
10. Moses, RG., Wong, VC., Lambert, K., Morris, GJ., and San Gil, F. (2016)Seasonal Changes in the Prevalence of Gestational Diabetes Mellitus. Diabetes Care.10.2337/dc16-0451.
11. Carpenter, MW (2007) Gestational diabetes, pregnancy hypertension, and late vascular disease. Diabetes Care. 10.2337/dc07-s224.
12. Kitzmiller, JL., Dang-Kilduff, L.,and Taslimi, MM. (2007) Gestational diabetes after delivery. Short-term management and long-term risks. Diabetes Care.10.2337/dc07-s221.
13. Dinarello, CA. (1996) Biologic basis for interleukin-1 in disease. Blood 87:2095-2147.
14. Mandrup-Poulsen, T. (1996) The role of interleukin-1 in the pathogenesis of IDDM. Diabetologia 1996;39:1005-29.
15. Maedler, K., Sergeev, P., Ris, F., Oberholzer, J., Joller-Jemelka, HI., Spinas, GA., Kaiser, N., Halban, PA.,and Donath, MY.(2002) Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. J Clin Invest. 110(6):851-60.
16. Ferguson-Smith, AC., Chen, YF., Newman, MS., May, LT., Sehgal, PB., and Ruddle, FH. (1988) "Regional localization of the interferon-beta 2/B-cell stimulatory factor 2/hepatocyte stimulating factor gene to human chromosome 7p15-p21". *Genomics*. **2** (3): 203–8.
17. Van der Poll, T., Keogh, CV., Guirao, X., Buurman, WA., Kopf, M., and Lowry, SF. (1997). "Interleukin-6 gene-deficient mice show impaired defense against pneumococcal pneumonia". *The Journal of Infectious Diseases*. **176** (2): 439–44.
18. Gauldie, J., Richards, C., Harnish, D., Lansdorp, P., and Baumann, H. (1987) Interferon β2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. Proc Natl Acad Sci USA. 1987;84:7251–7255.
19. Gabay, C., Smith, MF., Eidlen, D., and Arend, WP. (1997) Interleukin 1 receptor antagonist (IL-1Ra) is an acute-phase protein. J Clin Invest. 99:2930–294.
20. Briana, D.D., and Malamitsi-Puchner, A. (2009) Adipocytokines in normal and complicated pregnancies. Reprod. Sci. 16:921–937.
21. Atègbo, J.M., Grissa, O., Yessoufou, A., Hichami, A., Dramane, K.L., Moutairou, K., Miled, A., Grissa A., Jerbi, M., and Tabka, Z. (2006) Modulation of adipokines and cytokines in gestational diabetes and macrosomia. J. Clin. Endocrinol. Metab. 91:4137–4143.
22. Briana, D.D., and Malamitsi-Puchner, A. (2009) Adipocytokines in normal and complicated pregnancies. Reprod. Sci. 16, 921–937.
23. Vozarova, B., Weyer, C., Hanson, K., Tataranni, P.A., Bogardus, C., and Pratley, R.E. (2001) Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes. Res. 9:414–417.
24. Morisset, A.-S., DubÉ, M.-C., CÔTÉ, J.A., Robitaille, J., Weisnagel, S.J., and Tchernof, A. (2011)

Circulating interleukin-6 concentrations during and after gestational diabetes mellitus. Acta Obstet. Gynecol. Scand. 90:524–530.

25. Kuzmicki, M., Telejko, B., Szamatowicz, J., Zonenberg, A., Nikolajuk, A., Kretowski, A., and Gorska, M. (2009) High resistin and interleukin-6 levels are associated with gestational diabetes mellitus. Gynecol. Endocrinol. 25:258–263.
26. Hassiakos, D., Eleftheriades, M., Papastefanou, I., Lambrinoudaki, I., Kappou, D., Lavranos, D., Akalestos, A., Aravantinos, L., Pervanidou, P., and Chrousos, G. (2015) Increased maternal serum interleukin-6 concentrations at 11 to 14 weeks of gestation in low risk pregnancies complicated with gestational diabetes mellitus: Development of a prediction model. Horm. Metab. Res. 48(1):35-41. 10.1055/s-0034-1395659.
27. Calderon, B., Suri, A., Pan, XO., Mills, JC., and Unanue, ER. (2008) IFN-gammadependent regulatory circuits in immune inflmmation highlighted in diabetes. J Immunol 181: 6964-6974.
28. Meier, JJ., Ritzel, RA., Maedler, K., Gurlo, T., and Butler, PC. (2006) Increased vulnerability of newly forming beta cells to cytokine-induced cell death. Diabetologia 49: 83-89.
29. Welsh, N., Cnop, M., Kharroubi, I., Bugliani, M., and Lupi, R, , (2005) Is there a role for locally produced interleukin-1 in the deleterious efects of high glucose or the type 2 diabetes milieu to human pancreatic islets? Diabetes 54: 3238-3244.
30. Beutler, B., and Cerami, A. (1989) The biology of cachection / TNF-α primary mediator of the host response. Annu Rev Immunology.7: 625-655.
31. Hotamisligil, G. S., N. S. Shargill, and B. M. Spiegelman. (1993) Adipose expression of tumor necrosis factor-a: direct role in obesity-linked insulin resistance. Science (Wash. DC). 259:87-91.
32. Hotamisligil, G. S., A. Budavari, D. Murray, and B. M. Spiegelman. (1994) Reduced tyrosine kinase activity of the insulin receptor in obesity-diabetes. Central role of tumor necrosis factor-a. J. Clin. Invest. 94:1543-1549,
33. Kern, PA., Saghizadeh, M., Ong, JM., Bosch, RJ., Deem, R., and Simsolo, RB. (1995) The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest. 95(5):2111-9).
34. Friedman, JE., Ishizuka, T., Shao, J., Huston, L., Highman, T., and Catalano, P. (1999) Impaired glucose transport and insulin receptor tyrosine phosphorylation in skeletal muscle from obese women with gestational diabetes. Diabetes 48:1807–1814.
35. Ate`gbo, J.-M O., Grissa, A., Yessoufou, A., Hichami, K. L., Dramane, K., Moutairou, A., Miled, A., Grissa, M., Jerbi, Z., Tabka, and Khan, N. A. (2006) Modulation of Adipokines and Cytokines in Gestational Diabetes and Macrosomia. The Journal of Clinical Endocrinology & Metabolism. 91 (10):4137–4143,
36. Gabbe, S. **(**1986) Gestational diabetes mellitus. N Engl J Med 315:1025–1026.
37. Kirwan, JP., Hauguel-De Mouzon, S., Lepercq, J., Challier, JC., Huston-Presley, L., Friedman, JE., Kalhan, SC., and Catalano, PM. (2002) TNF-α is a predictor of insülin resistance in human pregnancy. Diabetes 51:2207–2213.
38. Winkler, G., Cseh, K., Baranyi, E., Melczer, Z., Speer, G., Hajos, P., Salamon, F., Turi, Z., Kovacs , M., Vargha, P., and Karadi, I. (2002) Tumour necrosis factor system in insülin resistance in gestational diabetes. Diabetes Res Clin Pract 56:93 –99.
39. Hotamisligil, G.S., Murray, D.L., Choy, L.N., and Spiegelman, B.M. (1994) Tumor necrosis factor-α inhibits signaling from the insulin receptor Proc. Natl. Acad. Sci. USA, 91 pp. 4854–4858.
40. Stephens, J.N., Lee, J., and Pilch, P.F. (1997) Tumor necrosis factor-α induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT-4 expression without a loss of insulin receptor-mediated signal transduction J. Biol. Chem. 272 pp. 971–976.
41. Winkler, G., Cseh, K., Baranyi, E., Melczer, Z., Speer, G., Hajós, P., Salamon, F., Turi, Z., Kovács, M., Vargha, P.,and Karádi, I. (2002) Tumor necrosis factor system in insulin resistance in gestational diabetes. Diabetes Res Clin Pract.56 (2):93-9.

42. Rashmi, R., Suvajit, S., Bing, H., Sivakumar, R., and Gautam, C. (2014) Gestational Diabetes, Preeclampsia and Cytokine Release: Similarities and Differences in Endothelial Cell Function.Adv Exp Med Biol. 814:69-75.

43. Goossens, V., Grooten, J., De Vos, K., and Fiers, W. (1995) Direct evidence for tumor necrosis factor-induced mitochondrial reactive oxygen intermediates and their involvement in cytotoxicity. Proc Natl Acad Sci U S A 92: 8115–8119.

44. Julia, V., Busik, Susanne, Mohr., and Maria, B. Grant. (2008) Hyperglycemia-Induced Reactive Oxygen Species Toxicity to Endothelial Cells Is Dependent on Paracrine Mediators. Diabetes 57:1952–1965.

45. Lefer, DJ., Nakanishi, K., and Vinten-Johansen, J. (1993) Endothelial and myocardial cell protection by a cysteine-containing nitric oxide donor after myocardial ischemia and reperfusion. J Cardiovasc Pharmacol 22 (7):34 –43.

46. Garlanda, C., Dinarello, CA., and Mantovani, A., (2013) The Interleukin-1 Family: Back to the Future. Immunity 39, 1003-1018.

47. Dinarello, CA. (2011) Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 117, 3720–3732.

48. Lachmann, HJ., Lowe, P., and Felix, SD. (2009) In vivo regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. J Exp Med. 206(5):1029–1036.

49. Gattorno, M., Tassi, S., and Carta S. (2011) Pattern of interleukin-1beta secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with CIAS1 mutations. Arthritis Rheum. 2007;56(9):3138–3148.

50. Dinarello, CA. (2005) Interleukin-1β. Crit Care Med, 33, 460-462.

51. Jager, J., Gre´meaux, T., Cormont, M., Marchand-Brustel, YL., and Tanti, JF. (2007) Interleukin-1β-Induced Insulin Resistance in Adipocytes through Down-Regulation of Insulin Receptor Substrate-1 Expression. Endocrinology 148(1):241–251.

52. Salmenniemi, U., Ruotsalainen, E., Pihlajamaki, J., Vauhkonen, I., Kainulainen, S., Punnonen, K., Vanninen, E., and Laakso, M. (2004) Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation 110:3842–3848.

53. Mandrup-Poulsen., T. (1996) The role of interleukin-1 in the pathogenesis of IDDM. Diabetologia 39, 1005–1029.

54. Donath., M.Y. (2014) Targeting inflammation in the treatment of type 2 diabetes: time to start. Nat. Rev. Drug Discov. 13, 465–476.

55. Mojtaba, E., Mahdi, K., Mehdi, KJR., and Amir, S. (2011) Serum interleukin-1 beta plays an important role in insulin secretion in type II diabetic. International Journal of Biosciences, 1: 3, 93-99.

56. 56. Oztop, N., Kusku-Kiraz, Z., Dervisoglu, E., Dinccag, N., and Genc, S. (2016) The Association of Glycemic Markers with Plasma Adipocytokine Levels in Women with Gestational Diabetes. J Diabetes Metab, 7:9, 1-5