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Review Article

Review on association between polymorphism of genes regulating insulin resistance and insulin secretion in gestational diabetes mellitus

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ABSTRACT

Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance that is discovered during pregnancy. It is associated with both maternal and various fetal and neonatal mobidity. Prevalence of gestational diabetes mellitus ranges from 3.8% to 17.8% in various studies done in different regions of Indian subcontinent. It has been observed in follow-up studies that both mother and child is more susceptible to develop type 2 diabetes mellitus later in life. Some studies have shown that pathogenesis of type 2 diabetes mellitus and GDM has many similar features and also observed that candidate genes involved in pathogenesis of type 2 DM might have role in pathogenesis of GDM. GDM is potentially induced by several etiologic factors such as genetic and environmental. Family, twins and trans-generational studies have provided evidence that GDM is heritable in some case. There is ample chance to develop GDM in subsequent pregnancies. In this review we will discuss the role of genes regulating insulin secretion ie KCNQ1 and two gene involved in insulin resistance and inflammatory processes ie Leptin and PPAR2.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance identified during pregnancy.[1] This condition affects about 3.8% to 17.8% of Indian pregnant women annually and is the cause of most common metabolic disorder complicating pregnancy.[2–4] Clarity of available data on the causes of this phenomenon is not obvious. Causes if increasing prevalence of GDM may be due to the higher prevalence of obesity in women of childbearing age, elderly primigravida, changing diagnostic criteria for GDM, and the widespread use of screening tests for GDM. Epidemiological studies have confirmed that GDM is associated with increased feto-maternal morbidity and long-term complications in mothers and offsprings. The American Diabetes Association (1999a) has concluded that fasting hyperglycemia defined as more than 105 mg/dL may be associated with an increased risk of fetal death during the last 4 to 8 weeks of gestation. Macrosomia is the principal neonatal adverse outcomes demonstrated in case of GD. It is the main factor related to the complications reported in case of GD.[5] Adverse maternal effects include an increased frequency of hypertension and cesarean delivery. In spite of lot of research in this domain, the pathogenesis of GDM is not fully understood. It is already known that women with history of GDM are at more risk of type 2 Diabetes Mellitus in subsequent life[6] and women with a family history of diabetes is more prone for GDM during pregnancy.[7] So it is prudent to think that GDM might share similar risk factors and genetic predisposition of T2DM. Due to placental factors there is increased insulin resistance during pregnancy which is followed by insufficient insulin secretion. T2DM also have insulin resistance as main component along with impaired insulin secretion. In postpartum period blood glucose level

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returns to normalcy in most of cases but there is more chance of T2DM in future. In some studies prevalence of 30–70% of T2D in women with history of GDM have been found. There is also risk of prediabetes in next 5 -10 years.[8,9]

Considering the same pathophysiological mechanism involved in pathogenesis of geatational diabetes mellitus as in type 2 DM, we focus on one of the studied gene regulating insulin secretion ie KCNQ1 and two gene involved in insulin resistance and inflammatory processes ie LEPTIN AND PPAR2.

2. KCNQ1 Gene Polymorphism and Gestational Diabetes Mellitus

Genome-wide association (GWA) studies leads to significant advances in identification of susceptibility genes for many diseases, like diabetes. Oflate, KCNQ1 (potassium voltage gated channel, KQT-likesubfamily, member 1) gene is added in armamentarium of candidate genes conferring susceptibility to T2DM. This gene transcript is important part of pore of voltage-gated potassium channel (KvLQT1) and is responsible in controlling the ventricular repolarization process. It is also expressed in pancreatic islets. Studies found three single-nucleotide polymorphisms (SNP) (rs2074196, rs2237892 and rs2237895) of this gene linked to T2DM.[10] Also, the risk allele of rs2237892 was associated with impaired insulin secretion, which is supposed to be mediated through an effect on β-cell function.[10] Similar SNP of KCNQ1 gene in T2DM has been studied in several populations[11–13] and also being recognized in gestational diabetes mellitus in some populations. Korean study on KCNQ1 polymorphisms of rs2237892 and rs2237895 were significantly associated with the risk of GDM(P 0.003 and 0.005, respectively while in another study from same place showed rs2074196 and rs2237892 were associated with the risk of GDM.[14,15] One of China study also showed SNP rs2237896 was the risk allele for GDM.[16]

3. Leptin Polymorphism in Gestational Diabetes Mellitus

Obesity and Gestational Diabetes Mellitus are conditions that have in common a state of chronic, low grade subclinical inflammation characterized by abnormal production of inflammatory cytokines. Genetic polymorphisms may influence the production of inflammatory mediators and predispose to different disorders, including diabetes.[17] Leptin is an adipocytokine is involved in regulation of food intake, puberty and various metabolic process is (ob) gene product.[18] Body adipose tissue store will determine serum leptin level[19] and regulate the amount of food intake by monitoring energy reserves through interaction with hypothalamic nucleus.[20] Leptin binds to its cytokine receptors on the cell membrane and leads to activation of signal transducer and activator of transcription-3 (STAT3), a member of the signal transducer and activator of transcription family of proteins.[21] Studies on humans found at least four types of splice variants of OBR messenger ribonucleic acid (mRNA) encoding proteins.[22] Apart from action on energy metabolism, leptin also influence various reproductive functions. DNA polymorphisms in leptin gene (LEP) are linked to extreme obesity.[23] G-2548A polymorphism in the 5´region of the LEP gene was reported not only to be associated with overweight[24] but also to have a strong influence on leptin gene expression and adipose tissue secretion.[25] It might also influence leptin levels during pregnancy, especially when taking into account that the polymorphic site is located approximately 1800 bp from the insulin response element within the leptin promoter. To support this a study from Czech Republic observed that significantly higher risk for gestational diabetes mellitus was in presence of A allele (AA and AG genotypes) against carriers of GG genotype in Leptin gene polymorphism (OR=2.84, 95%CI 1.14-7.07, p=0.02).[26]

4. PPAR γ 2, Gene Polymorphism

Nuclear hormone receptor superfamily has important member known as peroxisome proliferator-activated receptor-γ (PPARG) which is studied as a candidate gene for gestational diabetes mellitus (GDM) based on its function as a key factor involved in the regulation of adipocyte differentiation as well as lipid and glucose metabolism and insulin sensitivity. Scientific studies have examined the association between P12A polymorphism (rs1801282) in the PPARG gene and risk of GDM with inconsistent result. One of the studies from France investigated the association of Pro12Ala and C1431T polymorphisms of the PPAR γ gene, both separately and combined in haplotypes, with GDM. Mothers who were homozygous for the T allele of the C1431T SNP were found more obese and also had higher BMI before pregnancy, although the difference was not statistically significant. One study found the prevalence of GDM was significantly higher in the T/T homozygotes.[27] One of the Korean study also found significant differences in genotypes among GDM and non-diabetic controls in PPARγ2 gene (p=0.027).[28]

5. Conclusion

Gestational diabetes mellitus and type 2 diabetes mellitus share similar pathophysiology. This has been suggested in epidemiological studies and also genetic studies. Many single nucleotide polymorphism have been studied in various studies show some common genetic locus correlation in both condition. We have chosen three genotypes in this review but there are various other loci

studied in literature. With this review we give insight that multicentric large scale genetic studies can be planned in Indian subcontinent to find genetic marker for this morbid condition so that we can avoid both maternal and fetal complications.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Author biography

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