Gestational Diabetes Mellitus: Risk Factors & Genetic Predispositions

Aditi Sarker [1], Rajib Majumder[2], Sanmitra Ghosh[3*]

ABSTRACT

About one-fifth of entire pregnant female population develop Gestational Diabetes Mellitus (GDM) in course of their pregnancies and its incidence has been considerably augmented during the last decade. Development of the multifactorial disease GDM can be attributed to elevated insulin resistance during pregnancy triggered by a genetic predisposition to retardation of pancreatic islet β-cell functionality. Polymorphisms in multiple genes like TCF7L2, GCK, HNF4 KCNJ11, CDKAL1, IRS1 and MTNR1B are associated with increased susceptibility to GDM. Epigenetic alterations like gene silencing of pdx1 by DNA methylation and histone modification coupled with dysregulation of microRNAs like miR-155-5p, miR-21-3p, miR210-3p etc. also increases menace of GDM. GDM is a trans-generational effect that might contribute to the vast increase in the prevalence of type 2 diabetes mellitus (T2DM). An elaborate understanding of connection between specific genetic and epigenetic components associated with it may be helpful in prognosis of this disorder.

I. Introduction

Gestational Diabetes Mellitus (GDM) is a health impairment characterized by hasty glucose intolerance and insulin resistance identified for the first time during pregnancy (Veeraswamy S et al., 2012). It is identified by a retardation in insulin secretion or greater insulin resistance (Barbour LA et al, 2007). GDM is found to be closely linked with the risk of perinatal complications and also with the pertinent risk of developing T2DM in the future life of both mother and child (Ramirez-Torres MA, 2013). During the period of a typical pregnancy, numerous physiological modifications occur within the maternal body that provides a metabolic environment to favour fat deposition and optimized foetal growth. In due course of gestation, insulin secretion enhances to its optima till the third trimester, and then insulin sensitivity decreases progressively by 70% (Mithal A et al,2015). In normal pregnancy, pancreatic β-cell recompense for the heightened insulin resistance to regulate blood glucose. However, in GDM-complicated gestation, the insulin secretion capability reduces with the reduction in β-cell function and leads to deterioration of glucose tolerance (Seshiah V et al, 22004). So, it is postulated that GDM is the consequence of elevated insulin resistance during gestation triggered by a genetic predisposition to non-functionality of pancreatic islet β-cells (Ferrara A et al, 2007). Recent studies showed that about 4 million women are affected by GDM in India, at any given point of time (Permutt MA et al, 2005). The child-bearing age of present generation of women being in 30s complemented by their tendency to suffer from overweight and obesity as well as fully established metabolic syndrome, plays an important role in the increasing incidence of GDM (Carpenter MW, 2007)

Being a complex multifactor metabolic d.isorder, GDM is likely an outcome of a combination of variations in different genetic attributes. According to affirmation by several

[1]Department of Biotechnology, Dr. B.R. Ambedkar National Institute of Technology, Jalandhar, India
[2]Department of Biotechnology, School of Life science & Biotechnology, Adamas University, Kolkata, India
[3]Department of Biological Sciences, School of Life science & Biotechnology, Adamas University, Kolkata, India
*Corresponding Author:
Sanmitra Ghosh:
sanmitra.ghosh@adamasuniversity.ac.in

Received 19 November 2022
Received in revised 14 January.2023
Accepted 27 January 2023

studies, females with a family history of diabetes have a greater predisposition to GDM regardless of whether the origin is maternal or paternal. Insulin deficiency as well as insulin resistance, being the hallmarks of GDM, are transmissible as genetic traits (Lobner K et al, 2006). Additionally, the recurrence of GDM in successive pregnancies despite the dietary amendments further confirms the contribution of a genetic component of the disease (Wahabi HA et al, 2013). A better understanding of the patho-mechanisms of this medical condition may be achieved through the identification and characterization of the underlying genetic causes of this indisposition.

1.1. Genetics of GDM

During a normal pregnancy, several adaptations occur in multiple systems. For ensuring appropriate development of the foetus, the equilibrium of glucose metabolism in mother shifts. In the advanced stages of conception, catabolic alterations within the mother's body begin to dominate encouraging an surge in insulinemia, glycemia, and overall levels of fatty acid (MacNeill S et al, 2001). At that time several adaptations like pancreatic β-cell adaptations or hepatic gluconeogenesis are crucial to preserve optimal glucose level once the decline in maternal insulin sensitivity begins (Ferber KM et al, 1999). Although identification of attributes instrumental to the development of GDM is challenging, a rising amount of evidence confirms that an interplay of genetics, epigenetic and environmental factors is associated with development of GDM.

Research showed that almost every woman who have been detected with GDM in their first gestation will have an increased chance of developing it in their subsequent pregnancies. A clinical history of GDM predisposes females to > 7-times greater susceptibility to developing postpartum diabetes in comparison to females without GDM (Kautzky-Willer A et al, 1997). These results are not surprising since insulin resistance playing the most important role in developing both GDM and T2DM (Fischer PM et al, 1998).

The gene products participating in various stages of glucose regulation and with functional relevance to GDM forms the panel of candidate genes for genetic studies. Diabetes being a multifactorial complex disorder is apparently a product of an amalgamation of various genetic variants of diverse rarities (Fischer PM et al, 1998; Lander ES et al, 2001). Most of those variations are single nucleotide polymorphisms (SNPs) that arise due to deletions or insertions of one or more base pairs and are located at ~300bp intervals in the genome (Lander ES et al, 2001).

1.2. Candidate genes under study

Out of all the candidate genes identified to be associated with GDM, TCF7L2, MTNR1B, CDKAL1, IRS1, and KCNQ1 are the most significant. Certain polymorphisms of these genes can modulate β-cell dysfunction, adiposity, obesity, and insulin resistance through several mechanisms (Lambrnoudaki I et al, 2010).

The Transcription factor 7-like 2 gene or TCF7L2 is a member of the Wnt signalling pathway and studies have shown its close association in the pathogenesis of GDM (Ye D et al, 2016). The Wnt signalling pathway is one of the major developmental pathways that regulates cell fate choices and patterning of tissue during the early embryonic and later developmental stages. The 10q2 locus of the TCF7L2 gene is most frequently found associated with GDM under a dominant genetic model (Papadopoulou A et al, 2011). Studies indicate strong association of rs12255372 allele of TCF7L2 with GDM as well as rs12255372 with adiposity to modify the insulin secretion (Kim C et al, 2002).

MTNR1B (Melatonin receptor 1B) gene encodes a G-protein coupled receptor for melatonin whose genetic variants influences glucose sensor activity of pancreatic, insulin output, and plausibly glucose tolerance which in turn can lead to GDM (Lyssenko V et al, 2008). Expression of MTNR1B in the pancreatic islets orchestrates the regulation of serum glucose levels during pregnancy. Elevated expression of this protein can impair insulin secretion and can thus also disturb glucose homeostasis. Reports suggest MTNR1B polymorphisms rs10830963 and rs1387153 are potent risk factors for the development of GDM (Jovanovic L et al, 2001).

SNPs of CDKAL1 gene, namely, rs9295478, rs6935599, and rs7747752 are reported to be linked with increased risk of developing GDM. This gene contributes to insulin resistance by interfering with the conversion of proinsulin to insulin through protein translation (Ober C et al, 1989).

In insulin-sensitive tissues the Insulin Receptor Substrate-(IRS-1) gene plays a vital role in insulin signalling pathway by expressing an endogenous substrate of the insulin receptor. A single nucleotide polymorphism rs1801278 encoding for Gly972Arg substitution in this gene increases the risk of GDM due to insulin resistance and diminished insulin secretion (Wahabi HA et al, 2013).

KCNQ1, located on 11p15.5 loci, is another candidate gene encoding for potassium voltage-gated channel that forms a close association with the occurrence of GDM (Shaat N et al, 2005). It shows expression in the pancreatic islets and insulin-secreting INS-1 cell culture. The rs2237892

polymorphism in this gene regulates insulin output of the celland is found to be associated with the disease risk (Hyoung DS et al, 2010).

Moreover, mutations in the rs1799884 variant within Glucokinase (GCK) gene and rs4812829 variants in Hepatocyte Nuclear Factor 4 Alpha (HNF4a) gene increases susceptibility to GDM (Lambrnoudaki I et al, 2010). Glucokinase plays a crucial role in glucose catabolism and catalyzes the initial step in the pathway of glycolysis. Studies identified that the T allele of rs1799884 is linked with an elevated risk of GDM (Aberg A et al, 2001). The HNF4a gene on the other hand induces β-cell dysfunction and leads to the pathogenesis of the disorder. Along with the rs4812829 variant, Thr130lle polymorphism in the HNF4a gene is also associated with GDM (Shaat N et al, 2006).

2. Epigenetic Regulation of GDM

Epigenetic modification in both somatic and gametic cells that are transmissible to subsequent generations, might upset insulin output and sensitivity, leading to metabolic disorders like GDM (Clouaire T et al, 2008).

One of the alleged mechanisms affecting development of GDM is the epigenetic silencing of the Pdx1 gene. Gene product of Pdx1, also referred to as insulin promoter factor 1 or Pancreatic and duodenal homeobox 1, is essential for β-cell maturation as well as duodenal differentiation. Expression of Pdx1 can be reduced by both DNA methylation and histone acetylation induced by oxidative stress that is characteristic of obesity and T2DM and is apprehended to have a connection with the development of GDM. Subsequently, the activity of insulin-stimulated GLUT4 in the skeletal muscles reduces (Kaaja et al, 2008).

In tissues of diabetic patients, predominantly in pancreatic islets, hypermethylation of the PPARGC1A gene was reported (Iqbal R et al, 2007) that plays a vital role in the mitochondrial gene expression regulating mitochondrial metabolism and ATP production. This hypermethylation can affect output of insulin from pancreatic β cells.

One of the major impediments that can afflict women with GDM is its conversion to T2DM (Simmons RA, 2007). The extent of demethylation of histone proteins at H3K27 and H3K4 was reported to be associated with T2DM progression. Females who develop T2DM later in life have lower methylation of H3K27 and H3K4 than the women who are unaffected by T2DM post GDM (Chang-Chen et al, 2008). Therefore, extent of histone modification in terms of level of methylation can be a predictive marker for GDM.

Studies found a close association between plasma level of specific microRNAs with the risk of GDM development (Kaiser NG et al, 2003). Women with GDM have significantly

lower expression levels of miR-29a, miR-222, miR-132. Here the main role is played by miR-29a which influences glucose metabolism (Kaneto H et al, 2005). Most of the microRNAs either reduce IRS gene expression or disrupt the MAPK signalling pathway and hence disturb glucose and insulin metabolism (Ishiki M et al, 2005).

Studies have also shown that plasma level of miR-155-5p and miR-21-3p in the early days of pregnancy to be associated with a higher risk of GDM. Moreover, miR-21-3p and miR-210-3p also showed close association with GDM but only in women with obesity (Petersen KF et al, 2006). Furthermore, women with conception of male foetus have a greater risk of GDM due to disturbances in plasma levels of miR-146b-5p, miR-223-3p, miR-517-5p, and miR-29a-3p (Colomiere et al, 2010).

3. Conclusion

GDM is a growing health concern that has emerged as a significant menace for pregnant ladies. Although conventionally supposed not as hazardous as pre-gestational diabetes for the developing foetus, recent research indicates that GDM might have grave longstanding consequences for both child and mother. The exact underlying factors in the development of the disease are still difficult to elucidate as it involves a combination of diverse environmental, genetic, and epigenetic factors. For fully understanding the disruption of the glucose mechanism within the body, it is necessary to identify the exact molecular mechanism behind it.

Ethical statement

There is no conflict of interest. All authors mutually agreed to submit the manuscript for publication.

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