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REVIEW ARTICLE

Early-life Programming of Type 2 Diabetes Mellitus: Understanding the Association between Epigenetics/Genetics and Environmental Factors

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Abstract: Type 2 Diabetes Mellitus is an increasing public health problem that poses a severe social and economic burden affecting both developed and developing countries. Defects in insulin signaling itself are among the earliest indications that an individual is predisposed to the development of insulin resistance and subsequently Type 2 Diabetes Mellitus. To date, however, the underlying molecular mechanisms which result in resistance to the actions of insulin are poorly understood. Furthermore, it has been shown that maternal obesity is associated with an increased risk of obesity and insulin resistance in the offspring. However, the genetic and/or epigenetic modifications within insulin-sensitive tissues such as the liver and skeletal muscle, which contribute to the insulin-resistant phenotype, still remain unknown. More importantly, a lack of in-depth understanding of how the early life environment can have long-lasting effects on health and increased risk of Type 2 Diabetes Mellitus in adulthood poses a major limitation to such efforts. The focus of the current review is thus to discuss recent experimental and human evidence of an epigenetic component associated with components of nutritional programming of Type 2 Diabetes Mellitus, including altered feeding behavior, adipose tissue, and pancreatic beta-cell dysfunction, and transgenerational risk transmission.

Keywords: IUGR, protein deficiency, high fat diet, pancreas, diabetes mellitus, insulin resistance.

1. INTRODUCTION

The concept of a developmental origin of health and disease (DOHaD) is indisputably part of scientific, clinical and health policy activities that aimed to understand and reduce the risk of non-communicable diseases [1]. Attention was drawn to the critical periods in development, especially for obesity, which might have a serious effect on offspring physiology, sometimes even before a mother is aware that she is pregnant. Additionally, these effects appear to inherit across several generations [1].

In past years, studies used to focus more on small babies and maternal undernutrition. However, during the last decade, the interest in maternal obesity and the future life of the big babies increased dramatically.

Evidence shows that the worldwide prevalence of obesity doubled since 1980 and it seems that obesity generates obesity, and so the cycle continues which, unfortunately, sets the ground for other diseases such as Type 2 Diabetes Mellitus (T2DM) [2].

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T2DM is a worldwide chronic disease, which is caused by insulin resistance. Obesity and a sedentary lifestyle increase the risk of developing this disease over time [3]. Although usually, T2DM occurs after middle age, it is now rapidly diagnosed in younger patients and even in teenagers [4]. Both genetic and environmental factors play an important role in the process and an increasing number of studies show that the risk of developing T2DM can be influenced not only by the current adult lifestyle but also by conditions in fetal and neonatal programming (Figs. **1** and **2**) [5].

Additionally, the application of 'omics technology' for the systematic characterization of expression and structure holds great potential for learning physiological roles of different factors, epigenetic regulations and determining their impact on disease pathology and developmental biology [6]. Thus, the aim of this review is to survey current strategies employed in the early life such as fetal and neonatal programming of insulin resistance and T2DM and discuss future technological and scientific challenges, and potential opportunities presented in this area of studies.

2. DEVELOPMENT OF BETA-CELL AND GENETIC MODIFICATIONS LINKS THE PROGRAMMING OF INSULIN RESISTANCE AND T2DM

Pancreatic and specifically beta-cell development and their functions are crucial when considering the potential risk

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Fig. (1). Early life exposure to malnutrition, protein restriction, IUGR: intrauterine growth restriction, bisphenol A, high fat diet, alcohol, taurine deficiency, Gestational diabetes, and excessive weight during pregnancy may contribute to the beta cell dysfunction, decrease in beta cell mass, pancreatic islet abnormalities and impaired insulin sensitivity that increase the risk of T2DM in adulthood. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

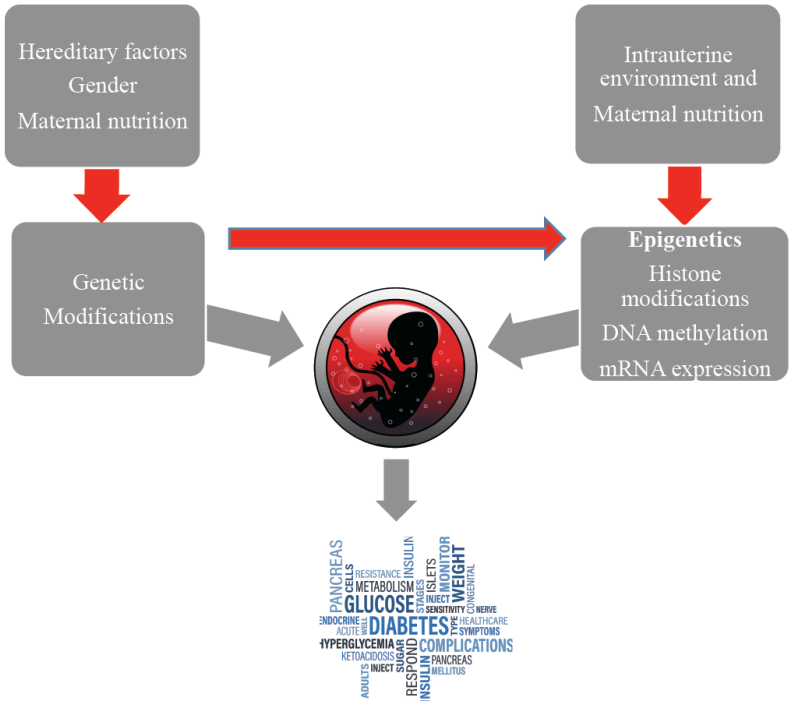

Fig. (2). Genetic and epigenetic modifications play a crucial role in the development of T2DM of the fetus later in life. The epigenetic modifications interact with the intrauterine environment as well as maternal diet and genetic alterations. Hereditary factors such as the family history of disease and heritability of epigenetic changes, sex and maternal nutrition regulate the genetic process which may link to the development of the T2DM. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

of developing T2DM. Beta-cell secretory dysfunction and decreased beta-cell mass are the two main causes that induce T2DM. Animal models have been established to study the relations between fetal and early postnatal malnutrition and susceptibility to diabetes later in life [7]. Several authors summarized the molecular mechanisms of early programming of the pancreas induced by maternal malnutrition [7]. Additionally, the role of mitochondria of beta-cell in mediating the impacts was emphasized in this review.

Green, *et al.* [8] summarized animal models of intrauterine growth restriction and stated that all of the models have shown a clear association between fetal growth restriction and beta-cell dysfunction. In addition, the effects of timing and duration of restricted nutrition on pancreatic morphogenesis and differentiation in different species expected to be different. Overall, the review has presented that the beta-cell dysfunction is likely depending on the species, timing, and duration of fetal malnutrition and how the factors coincide with fetal growth stages. Moreover, it is proposed that a reduction in the availability of nutrients during fetal development can program the endocrine pancreas and beta-cells.

Intrauterine growth restriction (IUGR) has been identified as a risk factor for T2DM and it seems to be linked to decreased beta-cell growth/function [9]. However, results from a study in mice embryos provided an IUGR-independent rationale for reduced beta-cell growth and T2DM development in adulthood; researchers' explanation has been related to the reduce p70 ribosomal protein S6 kinase 1 (S6K1) signaling in pancreatic beta-cells [10]. S6K1, a ribosomal protein, is a downstream effector in the mTOR complex 1 signaling pathway. Researchers found that $S6K1^{-/-}$ mouse embryos had fewer and smaller beta-cells (and contained less insulin) than wild-type embryos that S6K1 deficiency yielded an IUGR phenotype [10]. Given these results, it has been suggested that without S6K1, there is an improper growth of beta-cells; it has also been suggested that in regards to IUGR, loss of S6K1 may be a cause rather than a consequence [10]. Noticeably, S6K1 inhibitors are being considered as a potential treatment option for T2DM, due to their ability to increase insulin sensitivity [10]. Although S6K1 deficiency is likely not a widespread issue in humans, it is indeed interesting to contemplate its role in IUGR, beta-cell development, and potential development of T2DM.

One long-term consequence of IUGR may be an increased risk of developing adult-onset T2DM [11]. Furthermore, the development of T2DM requires insulin resistance and beta-cell dysfunction [12]. Therefore, it may follow that IUGR is associated with the detrimental changes in pancreatic beta-cells that eventually result in T2DM [13]. Multiple mechanisms have been proposed to explain this link and one of the key mechanisms considered as abnormal pancreatic islet signaling which involves hepatocyte growth factor (HGF) produced by endothelial cells and vascular endothelial growth factor A (VEGFA) produced by beta-cells [13]. HGF and VEGFA are important for the function and vascularity of pancreatic islets, and decreases in HGF and VEGFA were observed in islets of IUGR models [13]. A recent review article has elaborated on the evidence of supporting the HGF-VEGFA pathway's connection to IUGR and pancreatic islet abnormalities implicated in T2DM [13].

The growth of a fetus or offspring during gestation and lactation is strongly dependent on the nutritional condition of the moms [7]. Studies have shown that fetal growth restriction resulted from maternal malnutrition would increase their risks of T2DM. Nevertheless, this effect would be different when the restriction happened at different stages of growth [7]. To identify whether the period of gestation or lactation would have a greater impact, Matveyenko, *et al.* [14] compared the effects of prenatal and/or postnatal caloric/growth restriction on beta-cell mass development. Whether or not there was a growth restriction after birth, the prenatal malnutrition negatively reduced beta-cell fractional area and mass, and reduced rates of beta-cell replication in the fetal pancreas. The results indicated that prenatal nutrition is crucial for the early development of beta-cell mass and susceptibility to T2DM later in life. Evidence about the association between fetal beta-cell dysfunction and low birth weight as a result of malnutrition were reviewed [8]. Critical analysis of different IUGR animal models was presented on how beta-cell function mediates in different early life stages. Additionally, animal studies described the associations between IUGR and the development of T2DM [8]. For example, Nissen, *et al.* [15] used a naturally occurring IUGR piglet model to identify possible mechanisms during fetal development. The results have shown that piglets with low birth weight had a higher concentration of myoinositol and D-chiro-inositol in plasma, which indicated impaired glucose tolerance and insulin resistance in adulthood.

Glucocorticoids (GCs) are critical hormones mediating the effect of malnutrition on beta cells. Possible mechanisms, which, are in an attempt to discover new therapies for diabetes patients, are already reviewed [3]. The review also pointed out the importance of a specific period on the GC programming of beta-cell mass. Although late gestation has been recognized as the period that most profoundly influences birth weight, the first or early second trimester is most remarkable for GC-induced beta-cell dysfunction. Maternal food restriction during pregnancy results in increased maternal and fetal GCs, which impair β-cell development in rodent models [16, 17]. Valtat *et al.* further elucidated the molecular mechanism of peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α), a coregulator of the GCs receptor, and its role in pancreatic β-cell during fetal life [18]. GCs promote the expression of PGC-1α, which represses the expression of pancreatic duodenal homeobox1 (Pdx1) by binding of a GR/PGC-1α complex to the Pdx1 promoter region [18]. This study also showed that PGC-1α overexpression during the fetal period, not from adult age, impaired glucose tolerance, decreased glucose-stimulated insulin secretion (GSIS), and altered β-cell function [18]. Another study demonstrated abnormal shape and size of the mitochondria in β-cells and decreased expression of the mtDNA-encoded COX I gene in islet cells induced by protein malnutrition [19]. Moreover, a decreased number of insulin-secretory granules in β-cells, a decreased fraction of β-cells in the islets, reduced number and size of pancreatic islets, and a decreased insulin-secretory response *in vivo* were observed. Further, in the study, all these changes in the pancreas were restored by taurine supplementation [19]. Additionally, abnormal development of beta-cell mass during intrauterine and/or postnatal nutrient-restriction was ob-

served [14]. After feeding dams with a low-calorie diet, they found a reduction of beta-cell in fractional area and mass in progeny that characterized by a reduced rate of beta-cell replication and decreased evidence of neogenesis. Therefore, it is believed that the maldevelopment of beta-cell mass influenced by maternal diet may indicate an increased risk of T2DM later in adult life (Fig. **1**) [14].

3. DIETARY EFFECTS ON DISEASE PROGRAMMING AND GENETIC VARIATIONS

Environmental factors, such as the diet of the mother during pregnancy and/or lactation may influence the health status of the offspring early on in their lives and also in adulthood [20]. Altered maternal nutrition, can comprise both undernutrition and overnutrition impacting disease susceptibility later in life during sensitive windows of the development [21]. During the last decades, in many developed societies, maternal and postnatal caloric intake was either sufficient or excessive, and there is an increasing study examining fetal overnutrition that believed to produce a similar offspring phenotype to that of undernutrition [21]. High-fat diet (HFD) exposure is particularly pertinent because the Western-style diet is widespread and may promote the development of conditions like obesity and T2DM [20].

Proper nutritional status seems to be essential during developmental windows in life [22]. A review of how a maternal HFD impacts offspring islets and beta-cell function has been published [23]. Epigenetics may explain how the effects of HFD programming are passed on from mothers to future generations, and the review article also delves into potential mechanisms of high-fat programming in beta-cells [23]. Cerf, M.E. elaborates on how an HFD leads to hyperglycemia and eventually insulin resistance and issues with beta cells, such as beta-cell compensation, dysfunction, and death [23]. The hypothesis suggests that these issues ultimately may result in T2DM.

A high-fat diet during pregnancy and lactation can develop the features of metabolic syndrome, especially increased adiposity and impaired insulin and glucose tolerance in both wild-type and GLUT+/- genotypes [24]. Genotype-dependent effect of HFD was also observed; Heterozygous deletion of GLUT4 increased systolic blood pressure, leading to hypertension and increased serum cytokines levels compared to wild-type mice [24]. This implies the genetic contribution to the metabolic phenotype in response to dietary factors.

A theory of early programming assumes that excessive dietary intake during pregnancy may deteriorate the functionality of the hypothalamus infundibular nucleus which is responsible for food intake, primarily *via* leptin resistance development [25]. A report focused on the fetal overnutrition hypothesis suggested that offspring exposed to overnutrition and diabetes in utero have greater birth weight and greater weight for length during childhood [25].

Furthermore, genetics may also predispose people to develop these diseases. For example, when obesity-prone Wistar rats were fed an HFD during the perinatal period, they became glucose intolerant when tested after 3 months old [20]. These rats also tended to release more insulin, which suggests that insulin resistance is involved. In contrast, obesity-resistant Lou/C rats (an inbred strain of Wistar rats) fed the same HFD during the same perinatal period, were not glucose intolerant [20].

Adequate intake of particular micronutrients, such as folic acid and vitamin B_{12} both are especially important for women who are pregnant or lactating [26]. The importance of these micronutrients may extend to long-term outcomes of the offspring later in life, including the development of chronic diseases like T2DM. However, in mice dams, which fed a control diet, a folic acid supplemented the diet, or a folic acid and vitamin B_{12} supplemented the diet, maternal diet showed no effect on the glucose tolerance or blood glucose levels in offspring on a control diet [27]. Notably, the offspring of dams, which were fed a folic acid and vitamin B_{12} supplemented diet had significantly lower baseline plasma insulin concentrations than the offspring of dams, which fed a control diet [27]. More studies are required to address the potential relationship between micronutrient intake and biomarkers relevant to T2DM.

The possible link between prenatal/postnatal nutrient restriction and the eventual development of T2DM is not easy to elucidate in humans. However, retrospective cohort studies in which the participants experienced famine near birth can provide us with some clues [28]. Individuals born in the years during and around the time of the Ukrainian famine (1932-33) were more likely to develop T2DM (at >40 years of age) if they were born in regions that suffered extreme famine, compared to regions that did not endure famine conditions [29]. It is important to keep in mind, though, that retrospective cohort studies have severe limitations, even though they may suggest the hypothesized association; some are unable to fully take confounding factors such as lifestyle. For instance, prenatal nutrient deprivation has been linked to the development of T2DM in adulthood. To reverse the metabolic perturbations, a recent study examined the metabolic impact of postnatal nutrient restriction overlaid to IUGR in a rat model [30]. IUGR group showed an increase in subcutaneous and visceral adiposity with insulin insensitivity and metabolic inflexibility, prior to the development of insulin resistance and diabetes; however, pre- and postnatal nutrient restriction group remained lean and insulin sensitive, and active with metabolic flexibility, suggesting that postnatal nutrient restriction superimposed on IUGR could prevent metabolic perturbations by IUGR [30].

Among various dietary factors during pregnancy, maternal alcohol consumption has many adverse effects on the offspring [31-33]. In addition to the central nervous system injury, a common manifestation of fetal alcohol spectrum disorder may occur and, Dobson *et al.* investigated that the maternal ethanol exposure led to metabolic disturbances in a guinea pig model [34]. Chronic prenatal ethanol exposure showed IUGR-like manifestations including catch-up growth before weaning, increased visceral, subcutaneous, and pancreatic adiposity in adulthood [34]. In addition, offspring with fetal ethanol exposure showed a decrease in β-cell mass and β-cell insulin-like immune positive area, implying impaired insulin production and/or secretion in pancreatic islets [34].

Many studies suggest that not only nutrient restriction but norm caloric low protein diet and HFD during pregnancy develop IUGR and catch-up growth [35, 36]. Berends *et al.* showed that rats exposed to prenatal low protein diet (8% protein, w/v) without caloric restriction and postnatal control diet (20% protein, w/v) during lactation experienced IUGR and catch-up growth [36]. Moreover, prenatal protein restriction resulted in reduced mRNA expression of insulin-signaling genes (IRS-1, p110β, and Akt-2) in epididymal adipose tissue without any differences in blood glucose and insulin levels [36]. This implies that IRS-1 in adipose tissue may be an early target of nutritional programming. Another study showed that both protein-restricted and hypercholesterolemic dams had significantly reduced levels of specific essential amino acids and litters with significant IUGR [35].

The effect of low protein diet during pregnancy was investigated by Goyal *et al.* [37] and they showed IUGR in the prenatal protein restriction group. However, the study observed that blood glucose levels increased only in female offspring subjected to prenatal protein malnutrition [37]. The same study also showed that the pancreatic renin-angiotensin system was upregulated in offspring exposed to prenatal protein restriction, which may be responsible for the programming of hyperglycemia [37].

Epidemiological studies have linked small birth weight and lack of breastfeeding to T2DM [38, 39]. To investigate the underlying mechanism, McKnight *et al.* compared IUGR formula-fed, normal weight formula-fed, and normal weight suckled Yucatan miniature pigs [40]. IUGR pigs have shown compensatory growth before maturity and had greater subcutaneous fat depth. Moreover, intravenous glucose tolerance and insulin sensitivity test were not significant due to birth weight or suckling. Remarkably, visceral adiposity was associated with several glucose tolerance outcomes [40].

Taurine is a non-protein amino acid but acts as a neurotransmitter in cholesterol excretion [41]. Studies have shown that the lack of taurine in the fetus is a key factor in mediating pancreatic dysfunction induced by maternal malnutrition [19]. However, the mechanisms underlying is elusive. In addition to taurine's pancreatic function, the role of the mitochondria of beta-cells was further strengthened [19]. Retarded growth, abnormal shape and function of the pancreas with damaged insulin secretion ability and mitochondrial dysfunction were found in offspring from dams on a low-protein diet [42]. Additionally, a study has shown that by supplementing taurine on the maternal diet, these impacts could be diminished [43]. Moreover, the authors explained how the low protein diet changed fetal pancreatic function and how the supplementation of taurine restored the changes by focusing on mitochondria [43].

Recently, Vaiserman reviewed the consequences of early life undernutrition exposure which was caused by both natural and man-made disasters on long-term metabolic health and T2DM. In the review, it was mainly discussed that long-term exposure to famine demonstrated a link between nutritional intake in utero and impaired glucose intolerance, obesity and atherogenic lipid profiles, which known to be a risk factor for the development of T2DM [28]. Additionally, the impact of HFD and high birth weight in early life programming of T2DM has been examined [28].

High birth weight (> 4000 g) showed an increased risk of T2DM, similar to those with low birth weight (<2500 g) indicated that there is a relationship between birth weight and later-life risk of T2DM which found to be not linearly inverse but U-shaped [44]. Lately, a study reviewed fetal programming of the metabolic syndrome and explained that excessive body weight during pregnancy may be characterized by increased adipose tissue content in newborns and infants predisposing the escalation of childhood obesity, T2DM and cardiovascular diseases in adult life [45]. Heerwagen *et al.* also indicated that excessively developed adipose tissue produces and secrets a vast amount of proinflammatory cytokines, which activate immunological reactions leading to the development of insulin resistance in fetal epigenetic programming [46]. Moreover, offspring of rats on an HFD had increased pancreatic beta-cell mass, replication and neogenesis, leading to hyperglycemia and T2DM in the adult life [47]. However, in humans studies are limited and epigenetic studies are required to further support.

Several other factors also play an important role in the development of early life programming of T2DM. For instance, exposure to an endocrine disruptor called bisphenol A (BPA), which has shown to cause reproductive and metabolic abnormalities in offspring, is particularly concerning for pregnant mothers [48]. Since, pancreatic development is similar between sheep and humans, sheep have been used for several types of research in this field. Following an intravenous glucose tolerance test, the acute insulin response, cumulative insulin response, and insulin/glucose ratio response were higher in the adult female sheep that were exposed to BPA during the prenatal period [49]. There were also medium to large decreases in the insulin sensitivity index for three BPA treatments of various doses, but there was no observed dose-response relationship for BPA [48]. Although the insulin differences due to prenatal BPA exposure do support the idea that the maternal gestational environment impacts the offspring in adulthood, these results do not provide clear insight into the mechanisms or the overall risk of developing T2DM.

Ultimately, nutrient shortage during pregnancy, as well as excessive dietary and chemical intake, can lead to an elevated risk of T2DM and metabolic diseases. More genetic and epigenetic studies are required to identify underlying mechanisms in the early programming of T2DM.

4. GENETIC INTERFACE BETWEEN GESTATIONAL DIABETES AND T2DM

Women who had Gestational Diabetes (GDM) are at higher risk for developing T2DM post-pregnancy [50]. The role of exposure to diabetes in utero on infant and childhood growth has been examined [25]. Offspring of mothers with GDM and T2DM had a significantly higher prevalence of impaired glucose tolerance [51, 52]. Studies in newborns of diabetic mothers have shown an increased insulin secretion to a glycemic stimulus and beta-cell hyperplasia as they mentioned that insulin resistance becomes an important factor, which still needs better clarification [24]. Kajantie, *et al.* [53] showed that preterm birth before 35 weeks of gestation is associated with an increased risk of T2DM later in adult life.

Interestingly, the sex of the baby in mothers with GDM believed to impact the likelihood of developing T2DM [54]. Limited research has shown that mothers carrying a girl have a higher long-term risk of developing the condition than those who are carrying a boy [54]. This difference may be due to the effect of fetal sex on maternal beta-cell function during pregnancy, but the precise mechanism for this difference is not clear. However, in support of the beta-cell function theory, it has been shown that women carrying a boy are more likely to develop GDM [54]. This suggests that boys may alter the metabolic environment in a way that girls do not [54]. Hyperglycemia (due to the mother's diabetic state) has been commonly considered one cause of the offspring developing diabetes [55]. However, hyperglycemia as a driving force for the development of chronic diseases is still questionable [55]. Notably, to indicate the possibility that early life environmental exposures in utero may increase the risk of developing T2DM, more advanced studies are required.

Many studies have shown that GDM/maternal overnutrition are risk factors for the development of T2DM and obesity in offspring [56]. GDM leads to an adverse intrauterine environment, contributing to the poor long-term health of the offspring [57]. But the mechanisms underlying the observation is unknown. Telomeres are known to be vital for DNA replication and chromosomal integrity, and it shortens with increased oxidative stress and DNA damage. By studying cod blood from pregnant women, Cross, *et al.* [58] tried to find out the possible relations between GDM and telomeres in the progeny. Telomerase activity increased in GDM, while no changes in cord blood telomere length were found. They assumed that the telomerase activity increased as a response to telomere damage, however, no direct evidence was shown that GDM predisposes offspring to chronic diseases by mediating telomere activity [58].

Retinol-binding protein 4 (RBP4) is an adipokine mediating systemic insulin sensitivity. To test whether there is an association between maternal plasma RBP4 concentration and GDM, Mazaki-Tovi, *et al.* [59] conducted a cross-sectional study. The results have shown that GDM resulted in higher levels of RBP4 in either appropriate for gestational age (AGA) or large for gestational age (LGA) neonates than normal pregnant women who delivered an AGA neonate. However, the highest concentrations were observed in LGA newborns from women without GDM. It was indicated that RBP4 may play a role in accelerating fetal growth in the absence of GDM [59].

Maternal metabolic statue affects the fetal environment and the early programming of T2DM during critical developmental stages [60]. To test whether impaired glucose tolerance in pregnancy will affect fetal insulin sensitivity or beta-cell function, Luo, *et al.* [61] conducted a prospective pregnancy cohort study. The results have shown that maternal glucose intolerance may impair fetal insulin sensitivity but not beta-cell function, and predispose progeny to increase risks of T2DM.

5. GENETICS IMPACTS ON THE PROGRAMMING OF INSULIN RESISTANCE

Genetics plays a role in the development of numerous human diseases, such as T2DM [62]. *ABCC8* is a gene that encodes for a subunit of ATP-sensitive potassium (K_{ATP}) channels, which are located in the membranes of multiple cell types, including beta-cells; notably, the action of these channels can be affected by glucose metabolism [63]. A recent study on the Indian-American community showed that those who were carriers of a loss-of-function variant (R1420H) in the *ABCC8* gene had higher birth weights and had a twofold increased risk of diabetes with a 7-year younger age of onset [62]. The single study participant who was homozygous for R1420H had been diagnosed with diabetes at age 3.5 years after having hyperinsulinemic hypoglycemia of infancy (HHI) after birth [62]. In this community, it was found that a 3.3% carrier rate, given the community population of ~14,000, suggests that 1/3,600 births will be R1420H homozygous [62].

Interactions between genes and diet play a critical role in the early development of T2DM. Clinical studies have shown that dysfunction of the insulin-like growth factor 1 receptor (IGF-1R) gene is associated with low birth weight and postnatal growth [64]. On the other hand, HFD proposed to combine with genetic factors to increase risks of T2DM development later in life. But the question is will the loss of the IGF-1R gene exacerbates the negative impacts of HFD [65]. To address that, research established IGF-1R gene-mutated mice ($Igf1r^{+/-}$), and exposed both male and female mice of gene-mutated type/wide type to HFD. Noticeably, gender differences were found in the results of insulin resistance and glucose tolerance. It was shown that the loss of one *Igf1r* allele results in the loss of resistance to an HFD in the female gender, which further indicates that female offspring with the gene loss would have higher risks of T2DM in adulthood [65].

Maternal insulin resistance as the consequence of increased adiposity can influence susceptibility to T2DM in the progeny. Carmody, *et al.* [66] were interested in interactions between maternal IR and maternal consumption of HFD on fetal development. Offspring from *Insr(+/-)* or wide type dams fed with either chow or HFD were obtained. The results have shown that HFD is the major contributor to increased body weight, adiposity, insulin resistance and triglyceride phenotypes in the progeny. While the genetic factor maternal insulin resistance played a minor role in predisposing progeny to adiposity, though acted synergistically with maternal HFD.

Dutch Famine Birth Cohort is a historical birth cohort study composing of individuals born in Amsterdam around the famine during World War II. This cohort supports the fetal programming effects on many metabolic perturbations due to IUGR [67]. Using this cohort, Botden *et al.* investigate the role of SIRT1, a genetic factor related to fetal programming during malnutrition [68]. SIRT1 is a nutrient-sensing histone deacetylase and associated with the risk of metabolic syndrome including T2DM [69, 70]. They showed the significant interaction between two SNPs in SIRT1 (rs7895833 and rs1467568) and the risk of T2DM when exposed to prenatal malnutrition [68]. Minor allele carriers of these two SIRT1 variants had a lower risk of T2DM than non-carriers under prenatal famine [68].

Low birth weight restricted growth is associated with T2DM. A human study that was conducted on differential

Table 1. Researches, which studied the modifications of specific target genes in fetal and early life programming has been summarized.

Studies	Gene of Interest	Genetic and Epigenetic Regulations	Physiological Outcome
Um, S.H *et al.* (2015)	S6K1	Downstream effector in the mTOR complex 1 signaling pathway	Deficiency yielded an intrauterine growth restriction phenotype
Valtat, B *et al.* (2013)	PGC-1α	Coregulator of glucocorticoids receptor and Pdx1 promoter region	Overexpression during the fetal period impaired glucose tolerance and altered β-cell function
Vuguin P.M *et al.* (2013)	GLUT 4	Not cleared in the study	Deletion of GLUT4 led to hypertension and increased serum cytokines
Berends L. M *et al.* (2013)	IRS-1, p110β, and Akt-2	Prenatal protein restriction resulted in reduced mRNA expression of these insulin-signaling genes	No differences are shown in blood glucose and insulin levels
Mazaki Tovi S et.al (2010)	RBP4	Retinol binding protein is responsible for adipokine mediating systemic insulin sensitivity	Gestational Diabetes resulted in higher levels of RBP4 in which related to fetal growth
Baier L. J. *et al.* (2015)	ABCC8	Encodes for a subunit of ATP-sensitive potassium channels	Variation in the ABCC8 gene showed higher birth weights and an increased risk of diabetes
Garg N. *et al*. (2011)	IGF-1	Not cleared in the study	The loss of one *Igf1r* allele resulted in the loss of resistance to a high-fat diet in the female mice group
Guarente L (2006) and Liang F.S *et al.* (2009)	SIRT1	Nutrient-sensing histone deacetylase	Associated with the risk of metabolic syndrome including Type 2 diabetes
Cooper W.N *et al.* (2012)	IGR2R, GTPL2-2	2 methylated regions examined in cord blood showed DNA methylation alteration	IGR2R in girls and GTPL2-2 in boys were reduced after micronutrient supplementation

impacts of birth weight *versus* third-trimester growth velocity on adult metabolic phenotype showed a nongenetic association between low birth weight and high adult visceral and subcutaneous fat accumulation but no insulin action was observed. On the other hand, the third-trimester growth viscosity found to be nongenetically inversely associated with adult insulin action, not fat accumulation. In conclusion, the authors assumed that reduced fetal growth during verses before the third trimester may define distinct adult trajectories of metabolic characteristics influencing the risk of developing T2DM [71].

6. EPIGENETICS PROGRESS IN DEVELOPMENTAL PROGRAMMING OF T2DM

Growing curiosity has emerged to study the early life environment's impact on epigenetic modifications in the pancreatic beta cells which suggested to influence the function of insulin production [72]. Epigenetics is the alteration in the regulation of genes that occur without any change in the DNA sequence. Main epigenetic modifications are Histone modifications, DNA Methylation and microRNAs regulations [73]. The epigenetic modifications are crucial in the development of diseases because they alter the DNA accessibility and chromatin structure and therefore regulate the patterns of gene expression [74]. It has been proposed that epigenetic alterations during embryological development tend to have a greater phenotypic impact and are more stable in relation to the length of their impact [75]. Heijmans *et al.* showed that individuals who were prenatally exposed to Dutch famine had, 6 decades later, less DNA methylation of the imprinted insulin-like growth factor (*IGF2)* gene compared with their unexposed, same-sex siblings [76].

Furthermore, poor nutrition at both the pre-natal and post-natal life stages can cause epigenetic modifications in pancreatic beta-cells [77]. Some modifications have been shown to reduce the functionality of these cells, which may lead to the development of T2DM [72]. A report that explored epigenetic changes in gene expression of pancreatic processes indicated that nutrient-restriction may predispose the progeny to T2DM programming later in life by the epigenetic regulations of genes controlling beta-cell mass and function, and the cellular memory of these events in the pancreas [72].

Fetal IUGR increases its susceptibility to T2DM and is associated with changes in gene expression. To test whether epigenetic dysregulation mediates the cellular memory of intrauterine events Thompson, *et al.* [78] generated the first DNA methylation map in normal pancreatic islet cells to identify the changes that occurred as a consequence of IUGR. The results have shown that the epigenetic dysregulation occurred preferentially near genes regulating processes known to be abnormal in IUGR islets, which indicates that epigenetic dysregulation is a strong candidate for propagat-

ing the cellular memory of intrauterine events, causing changes in expression of nearby genes and long-term susceptibility to T2DM [78].

A series of studies investigated the effects of maternal micronutrient supplementation on mother and child, by using a completed randomized controlled trial of United Nations international multiple micronutrient preparations (UNIMMAP) in rural Gambia [79-81]. Using this cohort, scientists investigated the epigenetic alteration in infants when exposed to periconceptional micronutrient supplementation [82]. Notably, among 12 differentially methylated regions examined in cord blood, methylation levels at two of the differentially methylated regions, IGR2R in girls and GTPL2-2 in boys, were reduced in micronutrient supplementation group [82]. Hence, it is assumed that these DNA methylation alterations possibly may be linked to the disease risk such as T2DM in the longer-term.

Moreover, *IGF2* and *H19* fetal liver mRNA are pivotal proteins involved in normal pancreatic cell function [83]. The relationship between T2DM and these genes has been studied and it has been shown that *IGF2* and *H19* genes are epigenetically downregulated under the condition of intrauterine hyperglycemia mainly due to GDM. Additionally, the hypermethylation of these imprinted genes related to the reduction of the mRNA expression and later protein production translation along with an increased insulin response during feeding and decreased fasting insulin levels within pancreatic â-cells isolated from mice offspring of GDM mothers when compared to control offspring [83]. Another research studied the *PDX1* gene, which has a fundamental role in the regulation of beta-cell growth, function, and production of insulin similar to *IGF2* and *H19*. The researchers showed that reduced expression of *PDX1* contributed to the development of T2DM in offspring that experienced IUGR during embryological development. More importantly, it has been discovered that under the condition of limited oxygen and nutritional deficiency of the fetus, PDX1 promoter associated with the decreased acetylation of IUGR fetal islet cell H3 and H4 [84]. It has been discussed that without the histone hyperacetylation beta-cell metabolic function may impair [85].

Although recent epigenetic researches have shown that exposure of the fetus to numerous abnormal intrauterine environment can increase the risk of developing T2DM, more studies are required to clarify this relationship.

CONCLUSION

Type 2 diabetes is a rapidly increasing chronic disease, which commonly diagnosed after 40 years. However, in the last century, T2DM is effecting children and young adults worldwide. It is believed that developing T2DM is basically dependent on genetic and environmental factors. Recent genetic and epigenetic studies revealed that early-life environments could have long-lasting effects on health and increased risk of T2DM later in life (Table **1**) [27, 86]. Many epidemiological studies and animal studies showed that environmental exposure during the early life stage is associated with metabolic disorders including T2DM [87-89].

Association between intrauterine growth factor, maternal depression, an increased risk of developing GDM during pregnancy, environmental factors and genetic/epigenetic regulations has shown to be related to the dysregulation of beta cells and insulin metabolism during the fetal and neonatal programming (Fig. **1**). The association between low birth weight and high risks of T2DM later in life has been well established. Moreover, the results of the fetal programming studies clearly pointed out the importance of the quality and quantity of nutrition early in life as possible intervention points, during pregnancy, and in early postnatal life. However, the underlying mechanisms of these regulations are poorly understood.

Ultimately, most of the studies reviewed in this article supported the hypothesis that early life programming can influence the later development of T2DM. However, there are other relevant researches, which questions aspects of this causative link [53]. Of course, it is important to point out that the term ‘early life programming’ encompasses a wide variety of factors, so it is possible that some factors do play a role in future health outcomes such as T2DM, while others do not and the challenge is to find those that truly do hold significance, if they exist. Consequently, more epigenetic and genetic studies are warranted for an in-depth understanding of how the early life environment can have long-lasting effects on T2DM in adulthood.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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