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Review Article

Preemptive Medicine for Diabetes from the Viewpoint of the DOHaD Theory

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Summary

The Developmental Origins of Health and Disease (DOHaD) theory posits that prenatal and infancy environmental factors influence future health and disease susceptibility.

Epidemiological and animal studies reveal that factors like nutritional status, maternal illness, chemical exposure, and drug use during pregnancy influence offspring's diabetes risk. Low birthweight correlates with later cardiovascular diseases (Barker's theory), later expanded into DOHaD theory. Dutch Famine links fetal malnutrition to adult diabetes. Animal studies replicating prenatal undernutrition show insulin resistance and altered gene expression.

Maternal hypernutrition studies using high-lipid or high-fructose diets demonstrate offspring's increased diabetes risk. Gestational Diabetes Mellitus (GDM) research shows maternal hyperglycemia affects offspring's glucose tolerance. Other maternal factors like deficiency in zinc, vitamin D, sleep disturbances, endocrine disruptor exposure, and substance intake contribute to diabetes risk.

Paternal factors, including protein restriction, high-lipid diets, and hyperglycemia, also affect offspring's diabetes risk, possibly through DNA methylation. Pathogenesis involves oxidative stress, gut microbiota, and nutrient-sensing signal disruption. Reprogramming efforts involve interventions during pregnancy or infancy, including antioxidants, green tea, flavonoids, melatonin, resveratrol, and folic acid.

The concept of "preemptive medicine" is introduced for diabetes prevention. The "First 1000 days" from fetal life to age 2 and adolescence to young adulthood are critical periods. Understanding epigenomic memory's role and promoting life-course medicine is crucial for preemptive diabetes treatment. Epigenetics, especially DNA methylation, emerges as a key molecular mechanism. Reprogramming epigenomic memory becomes a potential therapy. Overall, this review underscores the importance of comprehensive approaches for diabetes prevention in the context of DOHaD theory.

Key Words: Developmental Origins of Health and Disease (DOHaD), Diabetes, epigenetics, preemptive medicine, life-course medicine

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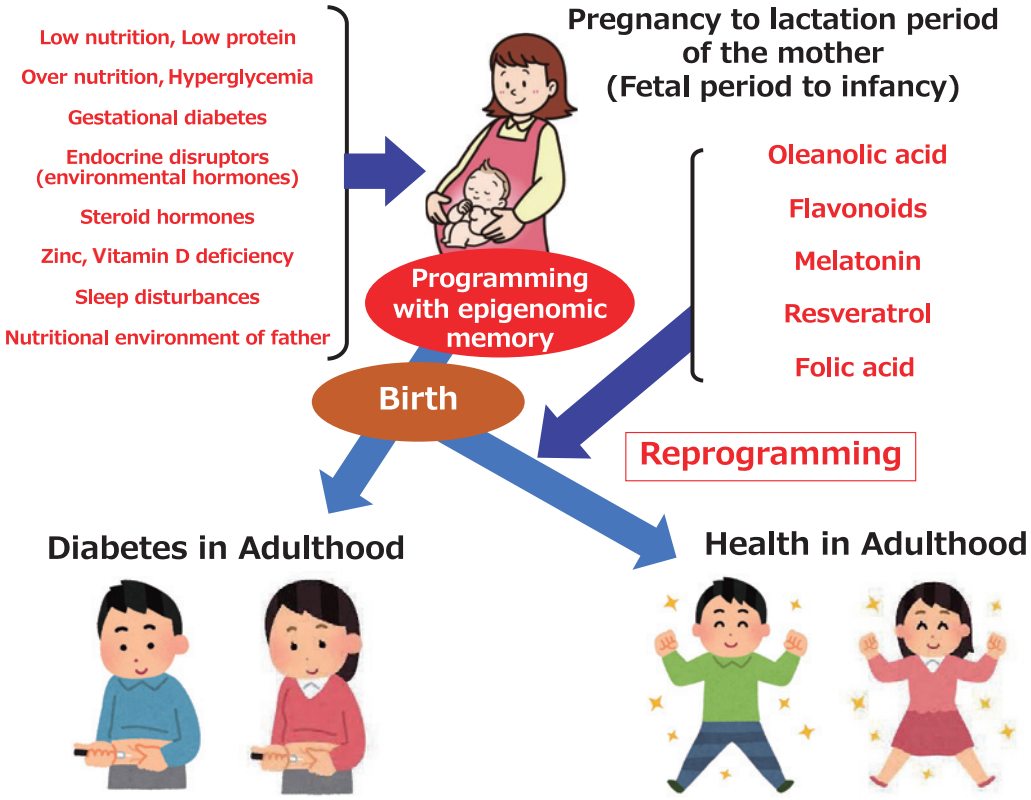

Figure 1 Pathogenesis of diabetes from the viewpoint of the DOHaD theory and attempts at reprogramming.

1. Introduction

The Developmental Origins of Health and Disease (DOHaD) theory holds that various environmental factors from prenatal to infancy determine future health and susceptibility to disease. Epidemiological studies and animal studies have recently demonstrated that the nutritional environment, maternal illness, maternal chemical exposure, and drug use during the prenatal and infancy period influence the future onset and progression of diabetes in the offspring. This review outlines the latest findings on the pathogenesis of diabetes from the perspective of the DOHaD theory and introduces an attempt at "preemptive medicine" for diabetes (Fig. 1).

2. Findings from Epidemiological Studies

Barker et al. found from epidemiological studies that low birthweight infants have an increased risk of dying from cardiovascular disorders in adulthood[1], and proposed the concept that birth weight determines the risk of developing diseases in adulthood (Barker's theory). Barker's theory was later expanded and became the DOHaD theory. The Dutch Famine is an epidemiological fact that proves that low nutrition during fetal life increases the risk of developing lifestyle-related diseases. In the Netherlands at the end of World War II, the population was exposed to severe malnutrition due to a cold wave and food deprivation, and many people died of starvation. Many children born to pregnant women who were undernourished at that time developed metabolic syndrome, diabetes, ischemic heart disease, and mental illness[1]. Furthermore, during the Ukrainian famine of 1932-33, it is known that diabetes developed more frequently in children born during the famine than in those who were not. Similar findings were observed in famines in Australia and China[2].

3. Maternal Hyponutrition and Protein Restriction

Many animal studies have been conducted to replicate the hyponutritional environment *in utero* during pregnancy by restricting maternal nutrition during pregnancy[3]. Caloric restriction is a technique that does not target specific nutrients but simply limits energy. Caloric restriction by 50% during gestation and lacta-

tion of rat dams results in insulin resistance in their offspring during adulthood. Adequate protein intake during pregnancy is important for the future health of the offspring[4]. Maternal protein restriction during pregnancy leads to low body weight in the offspring and subsequent glucose intolerance[5]. Several animal studies have reported that a low-protein diet of the dam during pregnancy is likely to induce diabetes in the offspring[6]. Sex differences in onset have also been reported, but the results depend on the species of animal used and the protocol of maternal low-protein diet intake during pregnancy. A report that mouse female pups were more likely to develop diabetes was thought to involve increased expression of neuropeptide Y in visceral fat[7]. On the other hand, in an experiment using Wistar rats, it was reported that male pups develop insulin resistance due to impaired mitochondrial function of pancreatic beta cells[8]. In experiments using pigs, male pups showed impaired glucose tolerance, possibly due to increased binding of glucocorticoid receptor (GR) due to DNA hypomethylation in mitochondrial DNA and Glucose-6-phosphatase (G6PC) gene promoter compared to females[9]. In rat experiments, protein restriction during gestation in the dam resulted in a decrease in hepatocyte nuclear factor 4α (HNF-4α) gene expression, a transcription factor important for pancreatic β cell differentiation and blood glucose regulation in the offspring. It is assumed that diabetes develops in adult animals by decreasing HNF-4α gene expression through an epigenetic mechanism (DNA methylation changes)[10]. It has also been reported that intrauterine hyponutrient deprivation (50%) of maternal rats due to food deprivation during pregnancy contributes to the development of adult-onset diabetes in the offspring by reducing skeletal muscle glucose transporter (GLUT) 4 gene expression through an epigenetic mechanism (histone code changes)[11]. In addition, it has been shown that in the rat offspring whose dams were protein-restricted during pregnancy, the PPARα gene promoter and GR gene in the liver become hypomethylated during the fetal period due to decreased expression of Dnmt1, a DNA methyltransferase and that this DNA methylation change is maintained until adulthood[12]. Protein restriction during pregnancy also alters the DNA methylation status of the phosphoenolpyruvate carboxykinase (PEPCK) gene promoter, an enzyme important for gluconeogenesis in the liver of the offspring, and is thought to induce impaired glucose tolerance by affecting its expression. Furthermore, in the offspring from pregnant rat dams that were subjected to 50% dietary restriction, gene expression in the pancreas was reduced due to changes in the histone code of the pancreatic insulin 2 (INS2) gene promoter. Interestingly, it was also found that its epigenetic changes, such as DNA methylation and histone code, are passed from one generation to another[13]. Thus, although there are differences in species, sex, and mechanism of pathogenesis, maternal protein and/or caloric restriction during pregnancy generally has a negative impact on the future glucose tolerance of the offspring. Moreover, based on the findings of recent animal studies and epidemiological surveys, the future development of diabetes in children due to maternal undernutrition and low protein during pregnancy is thought to be mediated by epigenetics[14].

4. Maternal Hypernutrition

On the other hand, the administration of a high-lipid diet (60% lipid) to pregnant dams is often used as a model for an intrauterine hypernutritional environment[15]. Pups from dams fed a high-lipid diet before and during pregnancy show impaired glucose tolerance, such as insulin resistance, in adulthood, although some sex differences have been reported[15]. It is also known that impaired glucose tolerance in adult animals is more pronounced when pups are fed a high-lipid diet[16]. Furthermore, when high-fructose diets (60% fructose) are administered to pregnant to lactating rat dams, their offspring develop insulin resistance[17]. Thus, it is clear that an intrauterine hypernutritional and hyperglycemic environment also influences the future development of diabetes in the offspring. Moreover, the mechanism by which maternal overnutrition and obesity during pregnancy induce insulin resistance in the offspring, as well as maternal undernutrition and protein restriction during pregnancy, is thought to alter DNA methylation of metabolism-related genes in the offspring, which in turn becomes metabolic programming that is stored over time and has a significant impact on the development of obesity and diabetes in adulthood[18].

5. Gestational Diabetes Mellitus (GDM)

It is known that children born to pregnant women with gestational diabetes or diabetic complications have an extremely high risk of developing diabetes in the future[19,20]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Follow-up Study (HAPO FUS) analyzed the glycemic control of 4832 children between the ages of 10 and 14 years whose mothers underwent a 75 g OGTT by 28 weeks' gestation. The results showed that children from mothers who were more hyperglycemic during pregnancy had significantly more impaired glucose tolerance, which is mainly attributed to increased insulin resistance, independent of maternal or child BMI or family history of diabetes. This suggests that *in utero* exposure to hyperglycemia affects the child's insulin resistance and impaired compensatory insulin secretion against insulin resistance[21]. Recently, one of the mechanisms by which children born to GDM mothers develop impaired glucose tolerance is assumed to be alterations in the intestinal microbiota during fetal life[22].

6. Other Maternal Factors

Experiments in rats have shown that zinc and vitamin D deficiency[23], hypoxia, and inflammation such as gingivitis during pregnancy can also induce insulin resistance in the offspring[24]. In addition, sleep disturbances and changes in the daily clock during pregnancy may induce insulin resistance in the rat offspring, and melatonin secretion is thought to be involved[25]. Exposure of rat dams to endocrine disruptors (diethylhexyl phthalate (DEHP) and bisphenol A) during gestation and lactation has been reported to induce insulin resistance in the adult offspring[26]. Alcohol and nicotine intake (smoking) during gestation and lactation are also thought to be involved in the development of insulin resistance and diabetes mellitus in the adult rat offspring[27]. In addition, it has been reported that pups from rat dams treated with dexamethasone during pregnancy show insulin resistance in adulthood and increased intestinal gluconeogenesis during fructose feeding[28]. In human, it was recently reported that cannabis use during pregnancy is associated with impaired glucose tolerance in the children during infancy[29]. Animal experiments and epidemiological studies have also reported that exposure to arsenic via the dam during the fetal period is associated with an increased susceptibility to diabetes mellitus in rodent offspring after birth[30].

7. Nutritional Environment of the Father

Epidemiological studies and animal experiments also suggest that paternal protein restriction, high-lipid diets, and hyperglycemia are involved in the future development of insulin resistance and diabetes in offspring[31]. It has also been shown that hyperglycemia induced before fertilization in rat sires increases DNA methylation of the PPARα gene promoter in the liver of their offspring, and that this methylation state is maintained from generation to generation[32]. Compared to maternal programming, paternal factors prior to conception may also have a greater impact in terms of transgenerational programming of offspring, and further research is required.

8. Pathogenesis of Diabetes Mellitus Based on the DOHaD Theory

8.1. Oxidative stress

It has been suggested that the environment from embryonic to infancy causes an imbalance between the production of reactive oxygen species (ROS) and antioxidant mechanisms in mitochondria, which is involved in the development of insulin resistance and diabetes in the child's adult life[33].

8.2. Intestinal microflora

It has been suggested that the gut microbiota may be altered by the early postnatal environment, depending on whether the baby is delivered vaginally or by cesarean section, and that this may define future insulin resistance[34].

8.3. Nutrient-sensing signals

AMP-activated protein kinase (AMPK), sirtuins (SIRT), peroxisome proliferator-activated receptors (PPARs), PPARα coactivator-1α (PGC-1α) and mammalian target of rapamycin (mTOR) pathway regulate systemic metabolic homeostasis[35]. However, it has been reported that impaired nutrient-sensing signaling from embryonic to infancy is involved in the future development of insulin resistance and diabetes[36].

9. DOHaD Reprogramming and Preemptive Medicine for Diabetes

As the pathogenesis of diabetes based on the DOHaD theory has been gradually elucidated, various attempts have been made to reprogram the metabolic programming established by the environment during the embryonic and infant stages of the child's life, taking into consideration the mechanism of its establishment. These attempts include avoidance of maternal risk factors, nutritional intervention, exercise, and lifestyle modification[37], and drug therapy has recently received attention as one such strategy.

It has been reported that oleanolic acid, which has antioxidant properties, can prevent insulin resistance in adult rats when ingested during the neonatal period[38]. In addition, administration of green tea along with a high-lipid diet (30%) during gestation and lactation in mothers improved insulin resistance in their male pups during adulthood[39]. In addition, flavonoids such as quercetin and genistein have been reported to improve insulin resistance in litters programmed by high-fat diet feeding in mothers when administered during gestation and lactation[40].

Melatonin is a hormone secreted at night by the pineal gland and is essential for pregnancy and fetal development[41]. Recently, melatonin administration has attracted attention for its potential to reprogram the child's metabolic syndrome, which is programmed by the mother's gestational to lactational environment[42].

Resveratrol is a type of polyphenol that has strong antioxidant properties and is known to extend the life span across species[43]. It has been reported that administration of resveratrol for protein restriction during gestation in mothers and animals improves glucose intolerance in the offspring[44], suggesting a reprogramming effect[45].

Folic acid is essential for fetal development, and inadequate maternal folic acid intake during pregnancy can cause congenital abnormalities such as low fetal weight and spina bifida[46], but a reprogramming effect has also been reported[47].

In recent years, "preemptive medicine" has been proposed to prevent or delay the onset of diabetes through highly accurate prediction of disease onset and pre-diagnosis, and implementation of therapeutic interventions before health problems occur. Preventive medicine is primarily aimed at the population, whereas preemptive medicine is aimed at the individual. The first is the "First 1000 days," the first 1000 days of the life course from fetal life to about age 2. This is the period during which susceptibility to non-communicable diseases (NCDs) such as diabetes and other lifestyle-related diseases that develop later in adulthood is formed and is a target period for disease prevention. Successful intervention during this period may be effective in significantly reducing the risk of NCDs developing in adulthood and beyond. The second is the period from adolescence to young adulthood, just before entering adulthood. If the individual's epigenomic and programming status can be accurately ascertained and susceptibility to diabetes can be assessed by this time, appropriate therapeutic interventions including body weight control by diet therapy and exercise, can be tailored to the individual. In addition, the medical treatment for the mother's gestational period, or for the child, should be changed from chronological medical treatment to life-course medicine (Fig. 2) as comprehensive medical treatment that covers the entire life of an individual. Life-course medicine is the most promising preemptive medical treatment for diabetes mellitus.

10. Conclusion～Toward DOHaD Awareness and Social Penetration～

Recent epidemiological studies and animal experiments have gradually clarified the pathogenic mechanism of diabetes based on the DOHaD theory. Epigenetics, especially programming by DNA methylation (epigenomic memory), is thought to be the main molecular mechanism of pathogenesis, and epigenomic memory genes have been identified as the molecular entities[48]. In the future, how to reprogram the epigenomic memory once established will be the focus of attention as a molecular therapy for DOHaD. Furthermore, the understanding and penetration of life-course medicine in society is a major issue for preemptive medicine for diabetes and obesity from the DOHaD perspective. However, unfortunately, the DOHaD theory has yet to catch on among the medical community, let alone the general public. The Liggins institute at the University of Auckland, New Zealand, invites all fourth-grade stu-

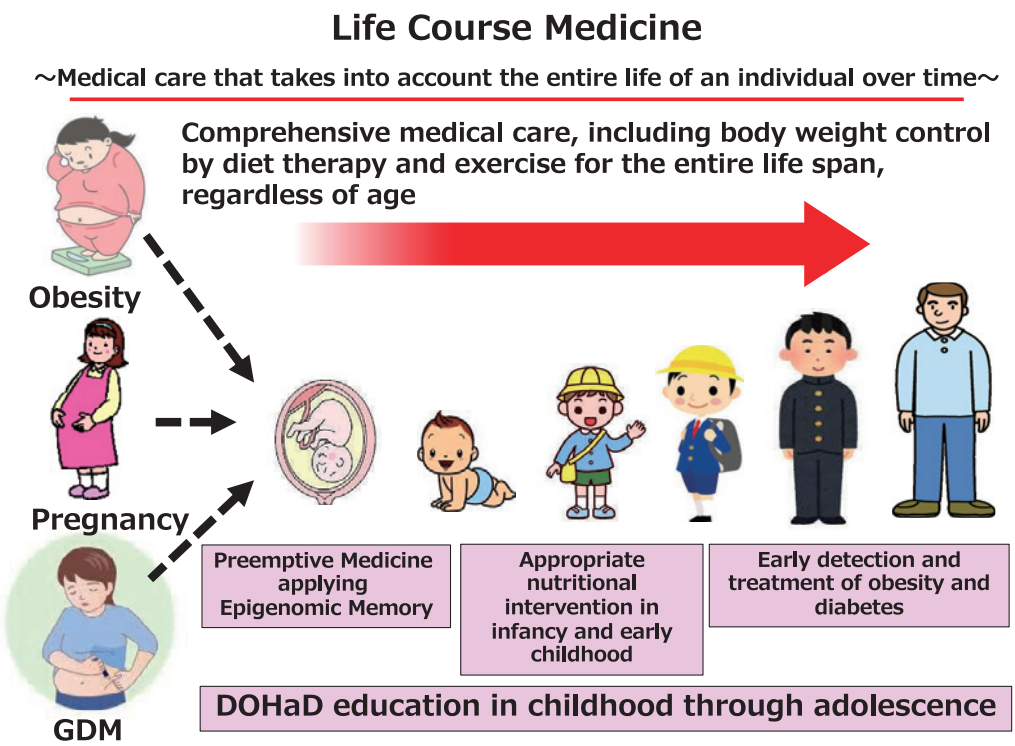

Figure 2 Life-course Medicine for diabetes prevention. GDM: Gestational Diabetes Mellitus.

dents nationwide to participate in DOHaD education. In other words, they are teaching children approaching puberty the importance of DOHaD by informing them that their proper nutritional status will affect the next generation. Similar DOHaD education is urgently needed in Japan, where the birthrate is declining and the population is aging at an unprecedented rate.

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Disclosure

The author has nothing to disclose.

Competing interests

The author declares no competing interests.

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