Early-life nutrition and metabolic disorders in later life: a new perspective on energy metabolism

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Abstract
Type 2 diabetes mellitus and metabolic disorders have become an epidemic globally. However, the pathogenesis remains largely unclear and the prevention and treatment are still limited. In addition to environmental factors during adulthood, early life is the critical developmental window with high tissue plasticity, which might be modified by external environmental cues. Substantial evidence has demonstrated the vital role of early-life nutrition in programming the metabolic disorders in later life. In this review, we aim to overview the concepts of fetal programming and investigate the effects of early-life nutrition on energy metabolism in later life and the potential epigenetic mechanism. The related studies published on PubMed database up to March 2020 were included. The results showed that both maternal overnutrition and undernutrition increased the risks of metabolic disorders in offspring and epigenetic modifications, including DNA methylation, miRNAs, and histone modification, might be the vital mediators. The beneficial effects of early-life lifestyle modifications as well as dietary and nutritional interventions on these deleterious metabolic remodeling were initially observed. Overall, characterizing the early-life malnutrition that reshapes metabolic disease trajectories may yield novel targets for early prevention and intervention and provide a new point of view to the energy metabolism.

Keywords: Early-life nutrition; Energy metabolism; Epigenetics; In later life

Introduction
Diabetes mellitus and other metabolic disorders have been characterized as pandemics. The World Health Organization reported that high blood glucose would be the third leading global risk factor for the mortality in the world, secondary to high blood pressure and tobacco use. In 2019, the International Diabetes Federation estimated that there were approximately 463 million people with diabetes among 20 to 79 years, which accounted for 9.3% of the adult population. If these trends continue, there would be 700.2 million diabetic patients by 2050, which will bring a huge economic burden and become a "catastrophe of the 21st century."[1] China has become the country with the largest numbers of diabetic patients globally, and the prevalence of diabetes is still rising rapidly. Among them, type 2 diabetes mellitus (T2DM) accounts for the vast majority (approximately 90%) of global diabetes.[1] However, the etiology and pathogenesis of T2DM and other metabolic disorders are still largely unclear.

It is traditionally reported that genetic factors and adult lifestyles, such as obesity, high-calorie intake, physical inactivity, and smoke, have played an important role in the incidence and development of metabolic abnormalities. However, in recent years, a growing number of clinical studies[2-4] and experimental models[5-9] have shown that adverse early-life nutrition, including under-nutrition and over-nutrition, can reshape the disease trajectory and significantly increase the risk of metabolic abnormalities in adulthood. The Developmental Origins of Health and Disease hypothesis has been proposed and emphasized the link between the early life stages, including the perinatal fetus and infant, and the development of metabolic disorders in later life.[10,11] The fetus or newborn adjusts their homeostasis system by making predictive adaptations to the early life environment to help instant survival and to improve later survival in an expected postnatal environment of adversity. But inappropriate predictions of these changes to the early-life nutritional environment may lead to a mismatch between nutrition in early life and postnatal reality. As a result, these predictive responses lead to an increased risk of chronic disease in adulthood, which can be transmitted to future generations.[11]
Therefore, the incidence and prevention of metabolic disorders should be advanced to the early-life stage, and the pathogenesis of metabolic diseases should be explored from the perspective of different life-time windows, which would provide some new evidence, targets, and thoughts for the energy metabolism. This review summarized literature exploring the effects of early-life (perinatal fetuses or infants) malnutrition, including under-nutrition and over-nutrition, on energy metabolism later in life, and further investigated the role of epigenetics in mediating these effects, which could provide some evidence for the early and effective prevention and treatment of metabolic disorders from the perspective of early life [Figure 1].

Early-life Under-nutrition and Metabolic Disorders in Later Life

Large numbers of epidemiological studies and experimental animal models have shown that the metabolic programming of energy balance can be attributed to the very early stages of development.[12-14] Thus, pregnancy and lactation have been recognized as the critical periods when nutritional modulation may lead to lasting effects on energy balance in offspring and shape health and disease trajectory in adulthood. Barker first reported that the death rates from ischemic heart diseases were higher in men with lower birth weight compared with those with normal birth weight and thus put forward the “the thrifty phenotype hypothesis,” which proposed that maternal under-nutrition during pregnancy and early post-partum programmed offspring to adapt to this thrifty environment and develop various dysfunctions in later life.[15,16] Consequently, the effects of early-life nutrition on metabolic diseases in later life gained increasing attention.

Clinical evidence

Famine is a natural model for investigating the effects of early-life poor nutritional environment on energy metabolism in later life in humans. Dutch winter famine (1944–1945) was one of the classic famine in the world with a 5-month period of severe undernutrition in the urban western part of the Netherlands at the end of World War II. The Dutch Famine cohort was also one of the most cited human cohorts to detect the role of early-life undernutrition on later metabolic health. Lumey et al[17] established a birth cohort of 3307 singletons born between 1945 and 1946. Their mothers experienced a food restriction of 900 Cal per day during pregnancy. This Dutch Hunger Winter Families Study showed that maternal undernutrition (famine exposure) during pregnancy was associated with a higher prevalence of T2DM and disorders of lipid profiles in adult offspring aged 59. Furthermore, another Dutch Famine Birth Cohort Study done by Ravelli et al[18] also demonstrated that prenatal famine exposure led to significant glucose intolerance and insulin resistance in offspring at ages of both 50 and 58.

In addition to Dutch, several other countries also experienced famine in the 20th century, including Austria, Leningrad, British Channel Island, and China. Data from the Great Chinese famine cohort detected the relationship between famine exposure in early life and metabolic diseases in later life. Several studies showed that maternal undernutrition during pregnancy and lactation significantly increased the risks of metabolic syndrome, non-alcohol fatty liver disease, and visceral fat dysfunction in adult offspring.[19-25] We also worked on the effects of adverse intrauterine nutritional environment on metabolic health in later life. A cohort of 2019 subjects born at the Peking Union Medical College Hospital between 1921 and 1954 was established. And the results showed that those with low birth weight had increased risks of developing diabetes mellitus, impaired glucose tolerance, and metabolic syndrome in their elderly life compared with those with normal birth weight.[26-27] Therefore, the relationship between maternal undernutrition exposure and energy metabolism in later life has been well demonstrated in humans.
Animal models

Human evidence is limited because of long generation times for prospective studies, large individual differences, and the quality of data for retrospective studies. Therefore, a growing number of animal model studies were designed to explore and validate the effects of early-life poor nutrition on metabolism in later life. Isganaitis et al.28 established a mouse model of low birth weight through restricting food by 50% during gestational days 12.5 to 18.5, which reduced offspring birth weight by 25%. Consistent with human studies, they also found that maternal food restriction resulted in significantly increased glucose intolerance, lipogenic gene expression, and adipocyte size in adipose tissue of adult offspring, accompanied by catch-up growth. Interestingly, when they further restricted food intake in offspring to inhibit catch-up growth, the adult offspring had better glucose and lipid metabolism than those experiencing postnatal catch-up growth.29 This experiment verified the “metabolic memory” hypothesis that early-life malnutrition programmed their energy balance to adapt to the poor nutritional environment. If the postnatal nutrition mismatched the prenatal environment, the metabolic disorders would happen.

Furthermore, the maternal low-protein diet is another well-established early-life undernutrition model. Our team established the early-life poor nutrition mouse model through feeding pregnant females a low-protein diet (9.6% protein, 80.2% carbohydrate, and 10.2% fat as kcal%, D02041002, Research Diets) during pregnancy and lactation. Compared with offspring of dams fed the isocaloric normal control diet (23.5% protein, 66.3% carbohydrate, and 10.2% fat as kcal%, D02041001, Research Diets), maternal low-protein diet led to lower birth weight, impaired glucose tolerance, and decreased fasting serum insulin levels in offspring at weaning.30

Therefore, maternal malnutrition during pregnancy and lactation programmed increased risks of developing glucose intolerance and lipid metabolic disorders in offspring. Recently, with the development of economy and society, as well as changes in diet and lifestyle, early-life overnutrition has become another severe issue and should also gain increasing attention.

Over-nutrition in Early Life and Energy Metabolism in Later Life

Clinical evidence

Maternal obesity during pregnancy and lactation is one of the most typical representatives of early-life overnutrition in humans. A significant volume of evidence have shown that the prevalence of obesity in women of childbearing ages is still growing rapidly,30,31 which has been shown to increase the risks of metabolic disorders in offspring.32 In the Helsinki Birth Cohort Study, Eriksson et al.33 reported that maternal body mass index (BMI) during pregnancy was positively associated with offspring health outcomes in later life, especially including cardiovascular disease and T2DM. Similarly, in another population-based prospective cohort study, Gaillard et al.34 showed that compared with children from normal-weight mothers, those from obese mothers during pregnancy had higher risks of childhood obesity and adverse cardiometabolic outcomes, such as higher systolic blood pressure, insulin levels, and lower high-density lipoprotein cholesterol levels. Furthermore, a recent multi-center Hyperglycemia and Adverse Pregnancy Outcome study by Tam et al.35 included a total of 905 mother-child pairs and analyzed the gestational weight gain, which is another parameter to evaluate nutrition during pregnancy, and metabolic health in offspring at 7 years of ages. They showed that offspring of mothers with higher body weight gain during pregnancy than the Institute of Medicine guideline recommendations had increased body weight, adiposity, and risks of hypertension and insulin resistance compared with those of women with normal gestational weight gain, which was independent of maternal pre-pregnancy BMI, gestational hyperglycemia, and other factors. Consistent with this study, other cohorts also demonstrated that maternal over-nutrition characterized by increased gestational weight gain was an independent predictor for increased BMI, adiposity, and cardiovascular risks in offspring.36-38

Animal experiments

Furthermore, emerging animal studies were designed to verify the clinical finding and explore the specific mechanisms. Maternal high-fat diet (HFD) intake during pregnancy is a common mouse model for overnutrition, which mimics the continuous high-fat food intake in humans. This overnutrition leads to an adverse intruterine environment, which predisposes offspring to develop metabolic disorders. Some scholars have established this animal model and showed that the offspring of HFD fed dams through pregnancy and lactation gained more body weight and adiposity than the control diet-fed litters.39,40 Bringhenti et al.41 found that offspring of HFD fed dams developed metabolic disorders, including hypercholesterolemia, hypertriglyceridemia, and hyperinsulinemia, and had an elevated level of serum leptin but a decreased level of adiponectin. They also explored the mechanisms mediating the metabolic abnormalities in adult offspring by analyzing the structure and function of the islet. The results showed significant increases in the masses of the islet, numbers of beta cells, and alpha cells, along with the migration of the alpha cells from edge to the core of the islet, whereas down-regulation of insulin receptor substrate 1, phosphatidylinositide 3-kinase, pancreatic and duodenal homebox 1, and glucose transporter 2 protein levels in offspring of HFD fed dams compared with the chow diet-fed mice. This study indicated that maternal HFD was responsible for the impairments in the insulin signaling pathway and altered islet structure in adult offspring. At the same time, another animal experiment showed the increased predisposition to steatohepatitis and the decreased α-diversity of gut microbiota in the offspring of HFD fed dams in comparison to those in the normal control group.42 In addition to the effects of maternal overnutrition on offspring peripheral metabolic health, increasing studies focused on the central metabolic changes in offspring. A recent study showed that maternal HFD resulted in an
increase in the brain insulin receptors (IRβs) in offspring at birth followed by a long-term decrease in brain glucose uptake and expression of glucose transporter 4 and IRβ in minipigs, which may increase the offspring predisposition to metabolic-neurodegenerative diseases. Our team also established the mouse model of maternal HFD during pregnancy and lactation and investigated the intergenerational effects of maternal overnutrition on offspring. Similarly, our results also verified that perinatal overnutrition (HFD) changed health and disease trajectory in offspring and significantly increased the risks of glucose and lipid metabolic disorders.

**Role of Epigenetics in Mediating the Metabolic Programming**

What is the critical mechanism mediating the “metabolic memory”? Although emerging studies began to pay attention to the potential role of central hypothalamic regulation, gut microbiota, circadian rhythm, and brown adipose tissue in linking the early-life nutritional environment on offspring metabolic health rather than genetic material. Epigenetics was first proposed by Dr. Waddington and was defined as heritable changes in gene expression without alterations in the DNA sequence. The major epigenetic mechanisms include DNA methylation, histone modifications, and non-coding RNA (ncRNAs). As an important molecular mechanism that regulates transcription, genetic stability, nuclear structure, and genomic imprinting, the altered epigenetic state was reported by a large number of studies to be associated with various types of diseases, including cardiovascular diseases, cancers, neurodegenerative diseases, mental disorders, immune system diseases, diabetes, and obesity.

**DNA methylation**

DNA methylation is one of the most widely studied epigenetic mechanisms at present, which usually occurs in regions rich in CpG clusters (CpG islands). Most of the gene promoters are located in CpG islands, and CpG methylation in these promoter regions is usually associated with transcriptional silencing. However, DNA methylation is not limited to the CpG islands and is also found in the vicinity of the CpG islands. DNA methylation is a covalent modification that the methyl group from donor S-adenosylmethionine is transferred to C5 of cytosine under the catalysis of DNA methyltransferase (DNMT). In mammals, there are five kinds of DNA methyltransferases, including DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. But only DNMT1, DNMT3A, and DNMT3B have the activity of methyltransferase, of which DNMT1 is responsible for the maintenance of extrauterine DNA methylation, whereas DNMT3A and DNMT3B are responsible for the establishment of intrauterine DNA methylation. DNA methylation is a reversible modification. The 10-11 translocation enzyme family acts as a demethylase and has the opposite effect to DNMTs. DNA methylation inhibits gene expression through two mechanisms. The first is that methylated cytosine can directly prevent the binding of transcription factors to the target DNA sequences; The second is that methylated CpG-binding domain proteins recognize and bind to the methylated cytosine to further recruit chromatin-inactivating complexes, resulting in silencing of transcription. Persistent changes in the modifications of DNA methylation of metabolic associated genes might partly decipher the metabolic programming.

We have previously reviewed the published literature detecting the role of DNA methylation in mediating the interaction between early-life nutrition and glucose metabolism in later life before 2014. After that, substantial associated studies were emerging. Shen et al recently investigated the relationship between early-life exposure to the Chinese Great Famine (1959–1961) and DNA methylation in insulin-like growth factor 2 (IGF2) and its effects on blood lipid levels in late adulthood in the Genomic Research of the Chinese Famine cohort. They found that elevated methylation level in IGF2 was associated with exposure to famine in early life, and this modification was also positively correlated with total cholesterol levels in late adulthood. Consistently, Tobi et al. also showed that DNA methylation changes in metabolic associated genes, including serine/threonine-protein kinase pim-3, thioredoxin-interacting protein, ATP-binding cassette sub-family G member 1, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, and mRNA N(3)-methylhytidine methyltransferase 8, mediated the influence of prenatal famine exposure on long-term energy metabolic health. In addition to food restriction, early-life overnutrition also changed the DNA methylation in both placenta, umbilical cord, infants, and adult. The placenta is widely accepted to have multiple functions, including nutrient transport for the fetus and exchanges of a wide range of cytokines, endocrine signals, and growth factors between the mothers and the fetuses. A recent clinical study showed that maternal obesity was associated with down-regulation in DNA methylation of the adiponectin and leptin in the third-trimester placenta of humans. The changes in DNA methylation of critical metabolic genes were also reported to be associated with maternal obesity in the human umbilical cord, infant mesenchymal stem cells, offspring spermatozoa, and other tissues. Furthermore, experimental animal models also provide strong supporting evidence. Modulation of maternal diet, including a HFD, low-protein diet, and calorie restriction during pregnancy and lactation resulted in a persistent shift in DNA methylation levels of metabolism specific genes in offspring, which were associated with their metabolic disorders.

Overall, DNA methylation is an important mechanism mediating the effects of early-life nutrition on energy metabolism in later life. However, the specific regulating mechanisms are still largely unclear and require further exploration.
miRNAs

In addition to the programming effects of DNA methylation, there is also evidence for the changes of miRNAs after early-life malnutritional exposure. Over the past decade, the importance of ncRNAs in most epigenetic regulatory events, such as gene transcription regulation, transposon activity and silencing, and X chromosome inactivation, has been gradually revealed. ncRNAs include a variety of RNA transcripts, such as miRNAs, long non-coding RNAs, small nucleolar RNAs, and circular RNAs, which can regulate the gene expression at a post-transcriptional level. Currently, the most widely studied ncRNAs are miRNAs, which are small molecular RNAs of 21 to 25 nucleotides in length. They are usually transcribed from the introns and exons of non-coding genes and the introns of protein-coding genes, partly from transposons and processed pseudogenes. miRNAs recruit RNA-induced silencing complex predominantly through complementary pairing with the 3’-untranslated-region of the target genes to further induce degradation or inhibition of translation.

miRNAs have been shown to play an important role in insulin sensitivity and glucose homeostasis. T2DM, obesity, and metabolic syndrome were also associated with dysregulation of miRNAs (eg, miR-103, miR-107, and the let-7 family). Lie et al. showed that periconceptional undernutrition induced changes in the expression of 22 miRNAs, which might mediate the altered expression of the key insulin-signaling molecules in skeletal muscle and insulin resistance in adult life. This was also confirmed in the sheep model. Our team detected the hepatic miRNAs levels in the intergenerational HFD and low-protein diet mouse models and found that both of maternal high-calorie intake and undernutrition significantly changed several important miRNAs in offspring liver, which were involved in mitogen-activated protein kinase signaling pathway, transforming growth factor-beta signaling pathway, Toll-like receptor signaling pathway, Janus kinase [JAK]/signal transducer and activator of transcription (STAT) signaling pathway, nucleotide-binding and oligomerization domain (NOD)-like receptor signaling pathway, cytokine-cytokine receptor interaction, chemokine signaling pathway, and adipocytokine signaling pathway. However, how early-life nutrition changes levels of miRNAs and how altered miRNAs regulate metabolic health remain unknown.

Histone modifications

Histone modification is another important epigenetic mechanism. In eukaryotic cells, the nucleosome is the basic structural and functional unit of chromatin. It is composed of about 147 bp of DNA wrapped around a histone octamer. Histone modification occurs at the tail of histones, including methylation, acetylation, phosphorylation, ubiquitination, and histepatization. Histone modification usually regulates the structure and function of chromatin by changing the interaction between histones and DNA, further regulating gene expression. Among them, the methylation and acetylation of histones mediate the formation of transcriptionally active euchromatin and transcriptionally silent heterochromatin. In mammalian cells, heterochromatin has higher levels of DNA methylation, histone deacetylation, and trimethylation of H3K9, H3K27, and H4K20. Overall, different types of modification of histones and modification of different histone residues may produce different regulations of gene expression. Studies linking histone modification changes with metabolic programming remain limited. One animal study explored the transgenerational effects of prenatal restricted diet on histone modifications in rats and found that maternal food restriction affected the level of global histone H3 acetylation in fetoplacental tissue. Yang et al. reported that decreased Wnt1 gene expression induced by perinatal HFD in the neonatal liver was associated with changes in acetylation of H4 at its promoter as well as acetylation of H4 and methylation of H3K9 at the coding region.

Therefore, epigenetic modification might be an essential mediator for the influence of early-life nutrition on energy metabolism in later life. Nevertheless, there are still a lot of questions that need to be answered. Which epigenetic modification is the most important mediator? How do they mediate the effects? How long could they persist? Which is the most important tissue for the epigenetic regulation of metabolic homeostasis? Can these epigenetic alterations be reversed?

Overview of Early-life Interventions and Metabolism in Later Life

Early life is the critical window for tissue plasticity, thus it can be modified by external environmental cues. Malnutrition in early life can program increased susceptibility to energy metabolic disorders in later life. Can this deleterious metabolic memory be blocked fundamentally? During the last decade, early-life interventions have gained increasing attention. For safety and effectiveness of fetal or infant stages, published studies mainly detected the effects of lifestyle management, supplementation of specific types of bioactive ingredients and nutritional interventions during the critical developmental period, especially pregnancy and lactation. Numerous prospective clinical trials have done lifestyle intervention in obese women during pregnancy and detected offspring metabolic health. Parts of these studies had positive outcomes, such as avoiding excessive gestational weight gain and decreasing adverse perinatal outcomes. However, there was still a large proportion of these studies which showed limited success in improving both maternal and offspring parameters. Although poor compliance during pregnancy and lactation in human and statistical power might be important reasons for the lack of success, the initiation of lifestyle intervention, duration, and specific means of intervention are also significant influencing factors.

Besides, emerging evidence demonstrated the beneficial effects of dietary bioactive compounds on energy metabolism. Resveratrol (trans-3,5,4'-trihydroxystilben) is a natural polyphenol mainly from plants, fruits, peanuts, and red wine. It has been widely reported that resveratrol has multiple health benefits against cancer, aging, obesity, diabetes mellitus, and cardiovascular disease. Several experimental animal models also validated the benefits of maternal resveratrol intake on...
Offspring health. Maternal resveratrol supplementation during pregnancy and lactation could fight against the adverse effects of the HFD or low-protein diet on offspring, such as glucose intolerance, obesity, cholesterol metabolic disorders, non-alcoholic fatty liver disease, or even hypothalamic leptin signaling dysregulation. As for the metabolic reprogramming of maternal bioactive ingredients intake, our team also established a mouse model to detect the intergenerational effects of maternal genistein intake by feeding dams a chow diet, HFD, or a HFD supplemented with genistein 3 weeks pre-pregnancy and during gestation and lactation. Genistein is one of the most important ingredients of soy isoflavone and also plays a vital role in metabolic metabolism. Our results showed that perinatal genistein intake significantly countered the adverse effects of maternal HFD on glucose and lipid metabolism in offspring, which can persist to later adult from weaning and is body weight independent. Thus, both our research and previous studies confirmed that dietary bioactive compounds supplementation in early life can block the adverse metabolism trajectory in later life induced by early-life poor nutritional exposure. However, almost all of the present evidence is from animal models and is preliminary. In the future, more animal and clinical evidence should be provided to transfer this basic finding to human physiology. And the specific mechanism still needs to be explored.

Furthermore, nutritional interventions were another potential way to prevent the intergenerational transmission of metabolic disorders, especially those associated with epigenetic regulation. Cordero et al. supplemented methyl donors (choline, betaine, folic acid, vitamin B12) to high-fat-sucrose fed dams during lactation and showed that this can protect offspring against hepatic fat accumulation when challenged by an obesogenic diet, which also indicated that DNA methylation might be an important mediator. Andraos and colleagues summarized the randomized controlled trials assessing the impact of nutritional interventions in pregnant women on DNA methylation patterns of the offspring. The results showed that maternal micronutrient supplementation did not substantially change DNA methylation in neonatal tissues. However, the effects of nutritional interventions on DNA methylation depended on maternal baseline health and nutritional status, including BMI and smoking status. Folic acid has been recognized as an important nutritional supplementation during pregnancy and was also a regulator of DNA methylation. Clinical studies in human and animal experiments both detected the effects of folic acid supplementation during pregnancy on offspring energy metabolism. Most of the studies indicated the metabolic proects of folic acid supplementation during pregnancy on offspring. However, Lewis et al gave folic acid to the mothers at 18 and 32 weeks of pregnancy and evaluated body composition in offspring at age 9 years among 5783 children from a population-based birth cohort study in the UK. But they did not find the relationship between intrauterine exposure to folate and childhood body composition. These inconsistent results might be attributed to the differences in population and the dosage and duration of folic intake. Thus, larger cohort studies are urgently needed to verify the effect.

Conclusion and Future Prospect

This review summarized recently representative articles about the important role of early-life nutrition in metabolic health. Perinatal nutrition intake plays a vital role in shaping the health and disease trajectory in later life. Maternal malnutrition programs significantly increased risks of developing energy metabolic disorders in offspring. These studies indicated that metabolic disorders should not only be attributed to the genetic factors and the inappropriate lifestyle in adulthood, but also to the nutritional environment in early life. Epigenetics are reported to be the potential mechanisms mediating the “metabolic memory.” Early-life interventions, such as lifestyle modification (food management and physical activity), dietary bioactive ingredients supplementation, and nutritional interventions, are considered as promising strategies to block the deleterious effects of maternal malnutrition on offspring metabolic health and further correct the disease trajectory.

Overall, this review proposes a new perspective on energy metabolism that early-life nutrition is another important influencing factor determining the development of metabolic diseases other than environmental exposures. Therefore, it is suggested that prevention and management of metabolic disorders are extended to early life, even during the fetal and infant stages, which is the critical window for physiological programming. We emphasize and call for more widespread attention to early-life environments. The treatment, management, and especially prevention actions in early life might dramatically restrain the rapid increase of patients with T2DM and other metabolic disorders and alleviate the huge economic burden globally.

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Conflicts of interest

None.

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