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Environmental Epigenomics and New Trends in the Developmental Causes of Diabetes Mellitus

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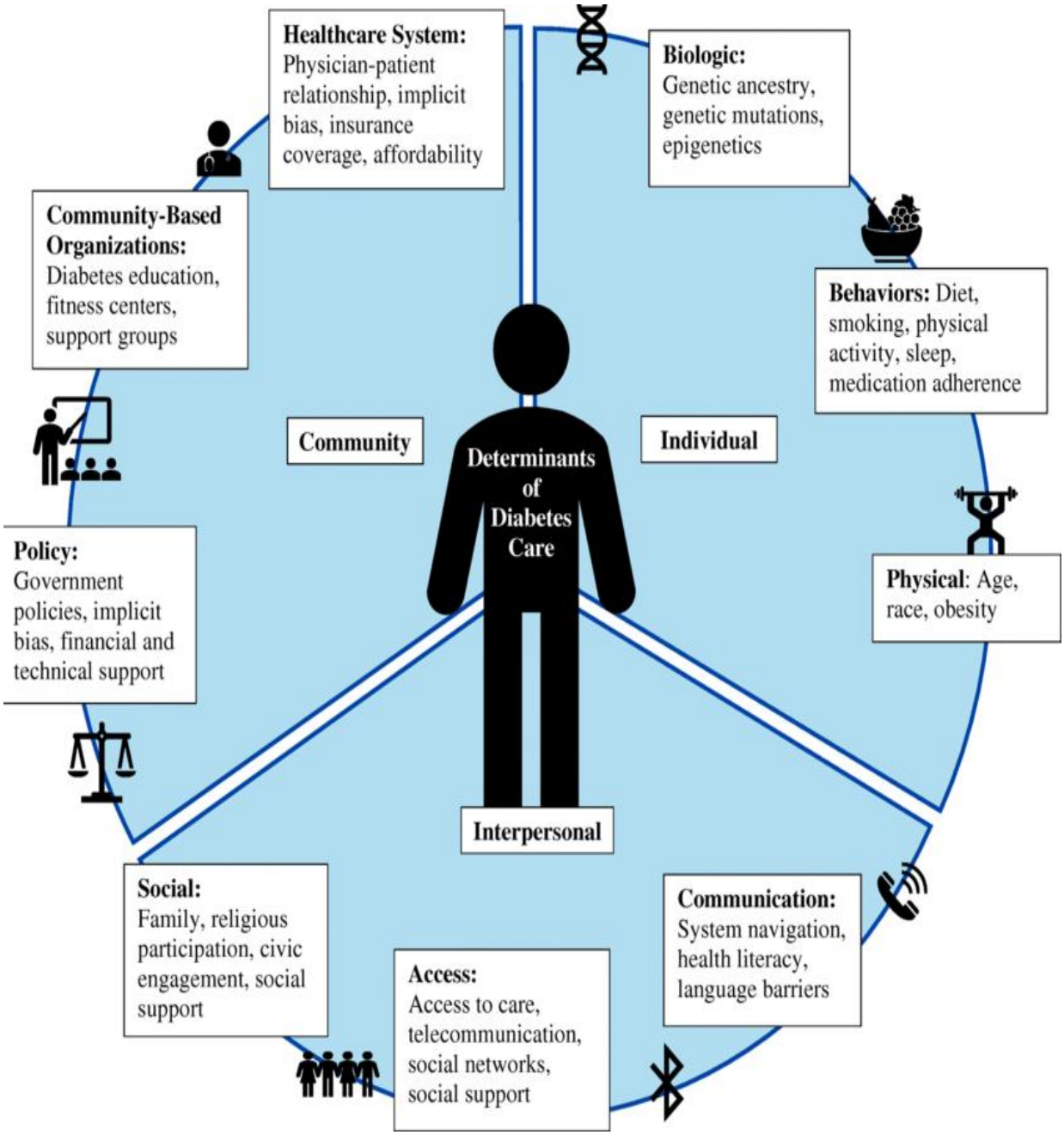
ABSTRACT

A growing amount of epidemiological data indicates that early environmental exposures affect an individual's later vulnerability to diabetes. Future generations may potentially inherit a heightened sensitivity to diabetes as a result of environmental factors. Epigenetic modifications may be linked to modifications in gene expression and environmental factors that might result in phenotypes of illness. Here, we demonstrate the growing body of data connecting early exposure to the environment to diabetes through modifications to the epigenetic code. This article initially provides a summary of the epigenetic targets that environmental factors can use to modify the epigenome. Metastable epialleles and imprinting genes are some of these targets. We then go on to discuss how epigenetic modifications result from environmental stress throughout key developmental windows, such as gametogenesis, embryogenesis, and the foetal and postnatal period, with a focus on diabetes susceptibility as an example. The mechanisms are still well understood, even though new research instruments are becoming more widely accessible and using animal models might lead to a deeper comprehension of the processes. This is especially true for human study. These present a novel perspective on the risk of diabetes brought on by environmental variables and have implications for future investigations into the relationship between the phenomena and diabetes in humans.

GRAPHICAL ABSTRACT



KEY WORDS: Epigenetic, transgenerational inheritance, housekeeping genes, gametogenesis, retrotransposon, hyperacetylation.

I. INTRODUCTION

Diabetes is becoming more and more common, which poses a serious risk to people's health and places a significant financial strain on the world economy [1]. Over the last few decades, diabetes has become a worldwide epidemic, affecting 537 million individuals worldwide, or 1 in 10 people aged 20 to 79 [2]. It is estimated that by, this figure would increase to 643 million till 2030, and by 2045, 783 million [3-4]. Prior studies often investigated the sensitivity to diabetes using a combination of lifestyle and genetics' combined effects, a significant risk factor is metabolic imbalance, which is caused by consuming too many calories and little energy use [5]. Genetic heterogeneity among individuals is another risk factor that emphasizes the significance of genotype in the development of diabetes [6]. The startling rise in diabetes mellitus, however, doesn't seem to be adequately explained by a person's unique lifestyle or genetic variance [7].

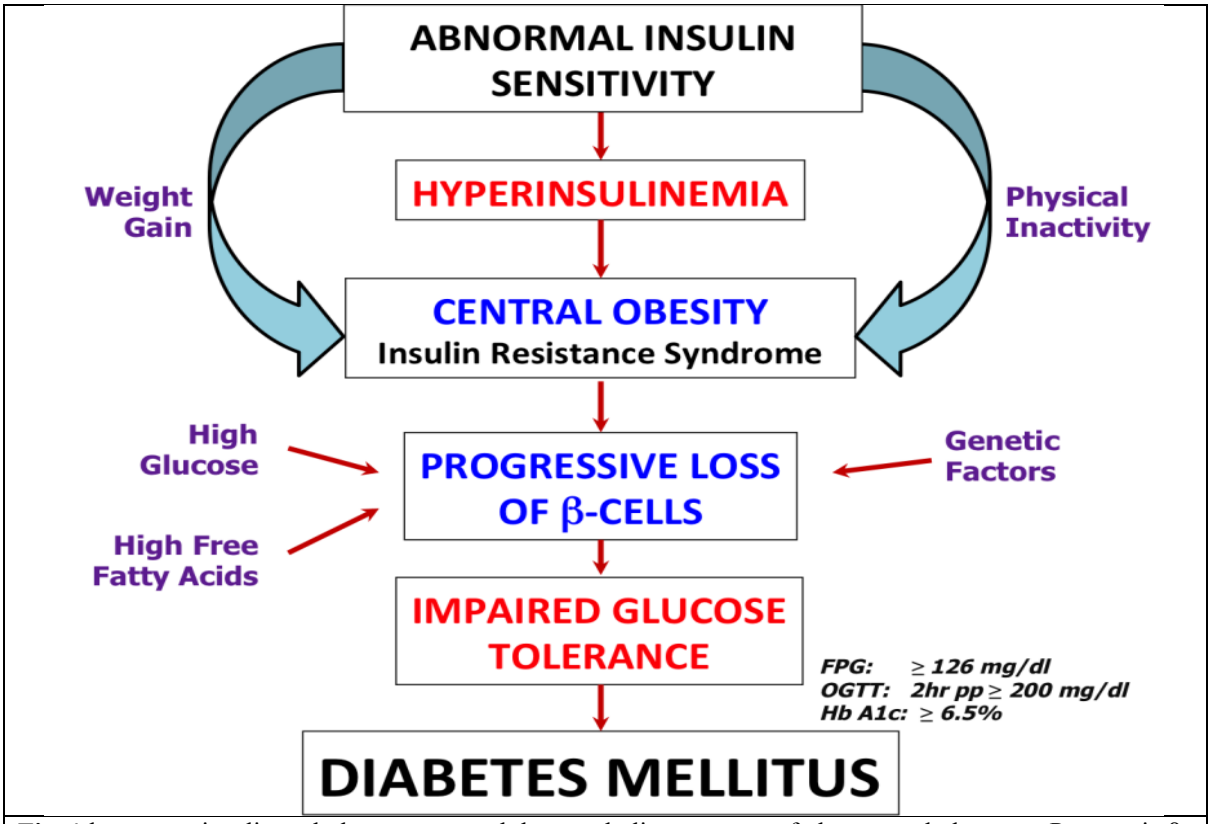
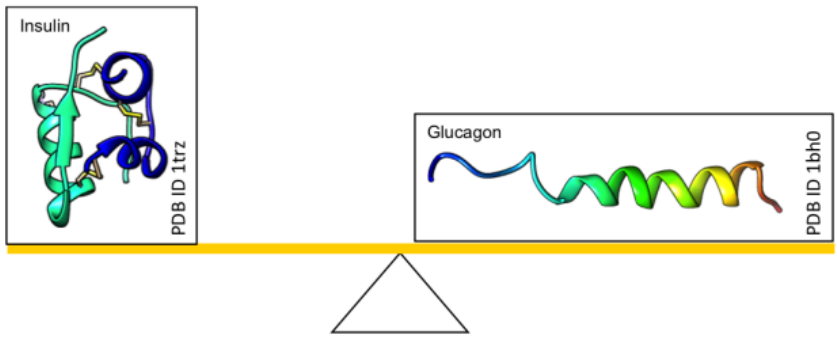


Fig. 1 hormones insulin and glucagon control the metabolic processes of glucose and glycogen. Pancreatic β-cells produce insulin when blood glucose levels rise after a meal. Insulin stimulates the process of glycogenesis in liver cells, which turns extra glucose into glycogen that may be stored. Glycogenolysis is the mechanism by which stored glycogen is transformed back into glucose when fasting and glucagon are present. Insulin promotes the absorption of glucose by fat and muscle cells. These cells use glucose to fuel glycolysis, which produces energy. Insulin is also in charge of encouraging cell division and growth, as well as fat and protein synthesis. Glucose may be kept as lipids in fat cells for a very long time. Extreme hunger can cause glucagon to release these fat reserves as energy [8-13].

A fresh perspective on the incidence of diabetes is offered by the developmental causes of adult diseases [14]. This point of view is amply supported by the Dutch Hunger Winter [15-17]. People who experienced the Dutch famine in their middle and late adult-onset diabetes were higher in those who were pregnant. Therefore, the hypothesis based on epidemiological data on humans implies that adjustments made by the fetus to its metabolic needs might alter the risk of adult illnesses including diabetes, heart disease, and cancer [18-25]. From this conceptual framework, "developmental origins of health and disease (DOHaD)" as a comprehensive concept was born. As of late, the DOHaD hypothesis has been extended to encompass the "gamete/embryo-foetal origins of adult disease," which argues that acquired alterations persist even in the absence of sustained exposure since gametes and embryos are equally vulnerable to environmental factors [26-32]. In addition, an increasing body of research in the field of diabetes, including studies on humans and animals, has supported the developmental origins theory. This hypothesis suggests that exposure to harmful environmental factors during the gamete, embryonic, or foetal stages may raise the chance of developing diabetes after birth [33-40]. Surprisingly, research conducted after the Dutch Hunger Winter revealed that childhood obesity risk was elevated in children exposed to both mother and paternal intrauterine starvation. Data from the Överkalix cohort, another historical cohort, also suggested that children who were overfed may have a higher chance of heart disease in their grandchildren due to diabetes. According to these findings, diabetes brought on by early-life environmental exposure can also pass on to the next generations the vulnerability to the illness. Intergenerational or transgenerational effects are the term used to describe the inheritance of acquired traits by subsequent generations; these effects were further corroborated by experiments conducted on animals. The most crucial query is how brief environmental changes made in infancy might have a lasting impact. Epigenetic modifications are one broad pathway [41-42].



		Insulin	Glucagon
Source	Pancreas	β-cells	α-cells
Target	Various	Muscle, liver, fat,	Liver, muscle, kidney,
Stimulus	For secretion	High blood glucose	Low blood glucose
Effect	Sugars/starch	Glycolysis and Glycogenesis	Glycogenolysis and Gluconeogenesis
	Lipids	Lipogenesis	Lipolysis and Ketogenesis
	Proteins	Protein Synthesis	Proteolysis

Fig. 2 The examination of the roles of both insulin and glucagon demonstrates how the two hormones balance one another [49-50]

The term epigenetics, which describes stable, mitotically inheritable translated literally as variations in gene expression without alterations to the DNA sequence, literally translates "above the genetics [43-45]. “It goes without saying that epigenetic alteration offers one potential route via which environmental influences on the epigenome may affect gene expression over the long run. Animal models are increasingly providing evidence that exposure to the environment changes gene expression epigenetically, resulting in a wide variety of phenotypes [46].

Here, we address the epigenetic changes that are probably the targets for an elevated risk of diabetes brought on by exposure to the environment while concentrating on the data that is now available. Subsequently, we explore the many temporal windows associated with the embryonic genesis of diabetes and its epigenetic processes. We conclude by talking about the influence of environmental factors that increase a person's risk of diabetes throughout generations. To ascertain the significance of environmental epigenetics in relation to human vulnerability to diabetes, we wrap up the review. Novel diabetes diagnosis, treatment, and prognosis might result from such research [47-48].

Environmental factors' Epigenetic targets

Histone modifications or changed DNA methylation have been linked to environmental-induced epigenetic changes in several studies. Since it occurs in cytosine-guanine (CpG), DNA methylation occurs at the carbon-5 position of cytosine. Has been the most extensively researched epigenetic process to date. dimeric molecule Genomic imprinting and transposable element silencing depend on DNA methylation mechanisms [51-55]. DNA chromatin packing is altered by histone modifications, which modulate gene expression.

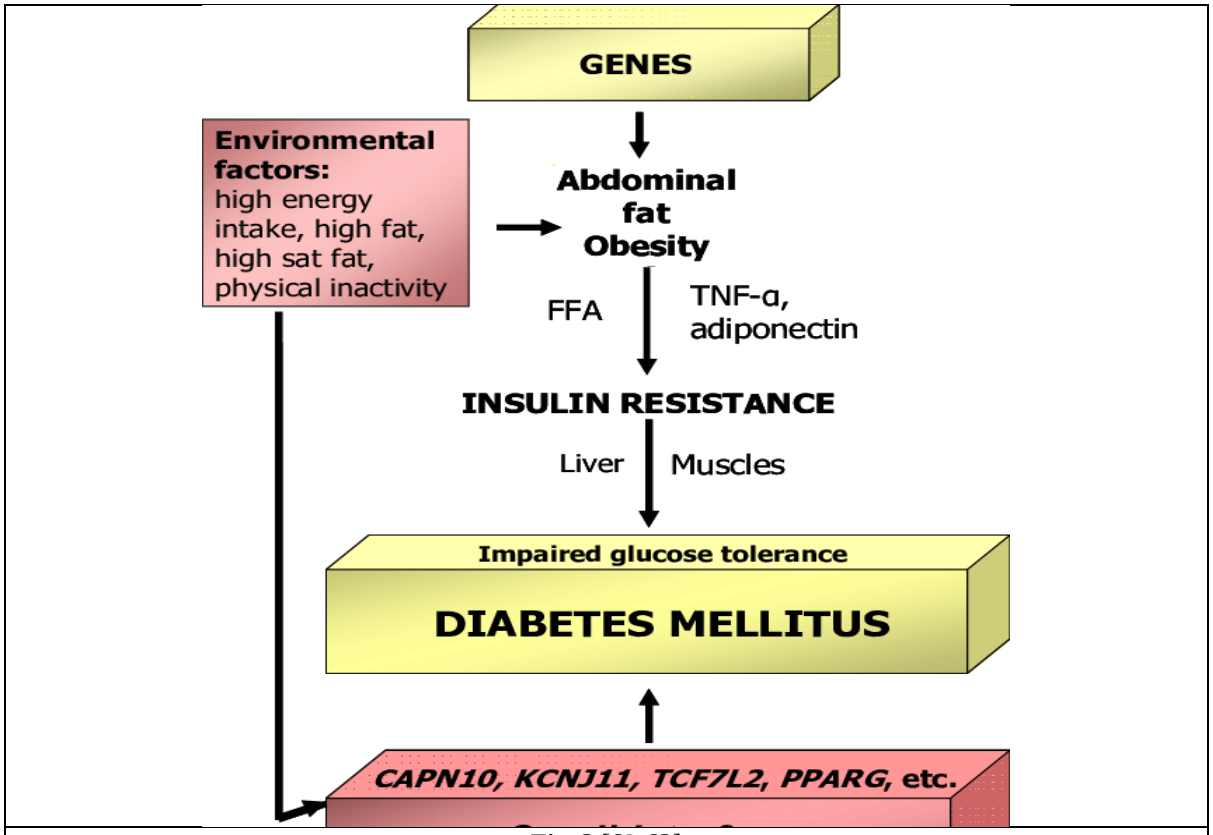


Fig. 3 [62-63]

Epigenetic regulation may also be facilitated by noncoding RNAs, an additional epigenetic mechanism, especially at repetitive DNA sequences. Research indicates that environmental influences have the ability to disrupt the regulation of Histones, methylation, and noncoding RNAs all assist in the regulation of gene expression [56-57]. On the other hand, it is less evident for the majority of histone modifications and noncoding RNAs whether they influence environmental attributes and inter- or transgenerational inheritance [58-61].

According to research on animals, early environmental exposures can cause variations in the epigenome that are particular to a locus. in particular, three genetic targets—transposable elements, imprinted gene regulatory regions, and promoter regions of certain housekeeping genes—are susceptible to environmental perturbations. The CpG dinucleotide sequences in these target areas are abundant, and the same region exhibits varying levels of histone modifications or methylation, which control the expression of certain genes [64-65].

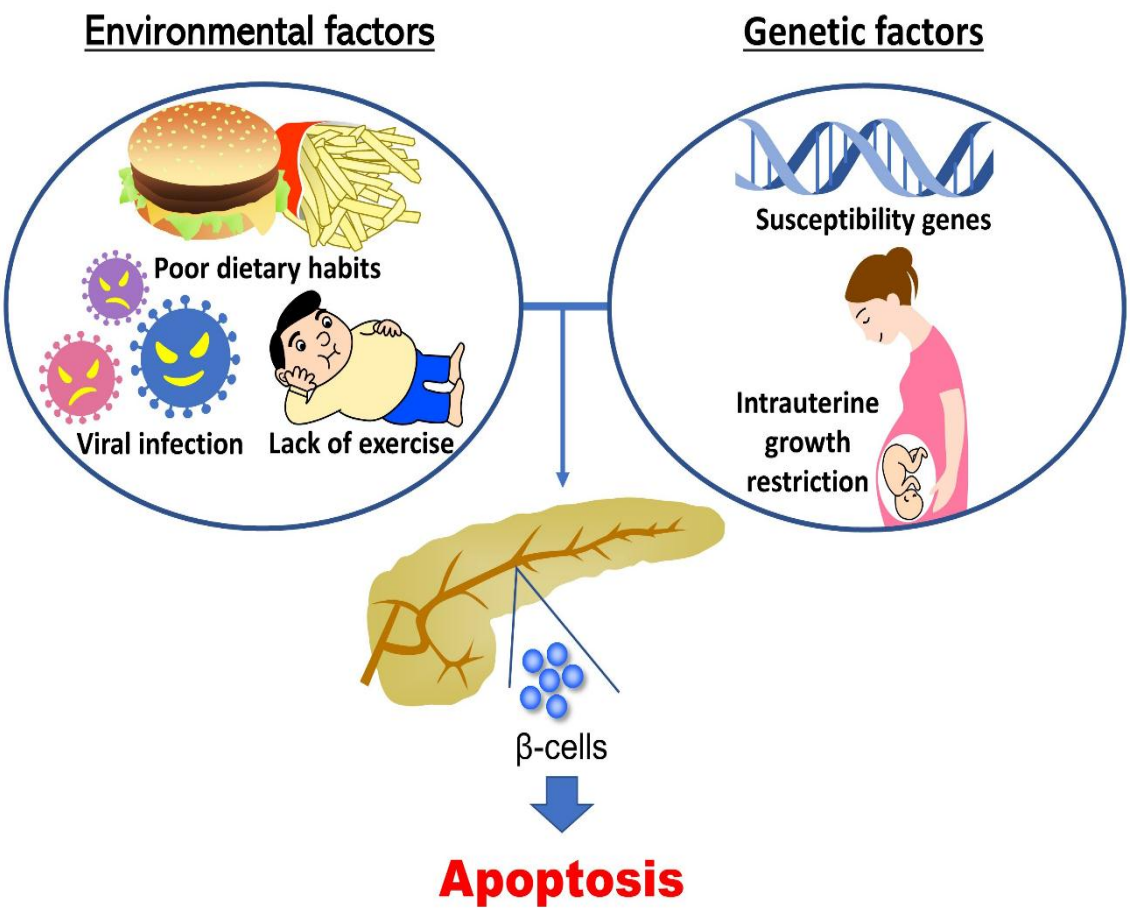


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Fig. 4

Our primary interest lies in genes that possess metastable in nature epialleles, imprinted DNA, and functional genes associated to diabetic. These genes may have a link between environmental influences during early development and the susceptibility to diseases as an adult as shown in Fig .3, 4 and 5[66-67].

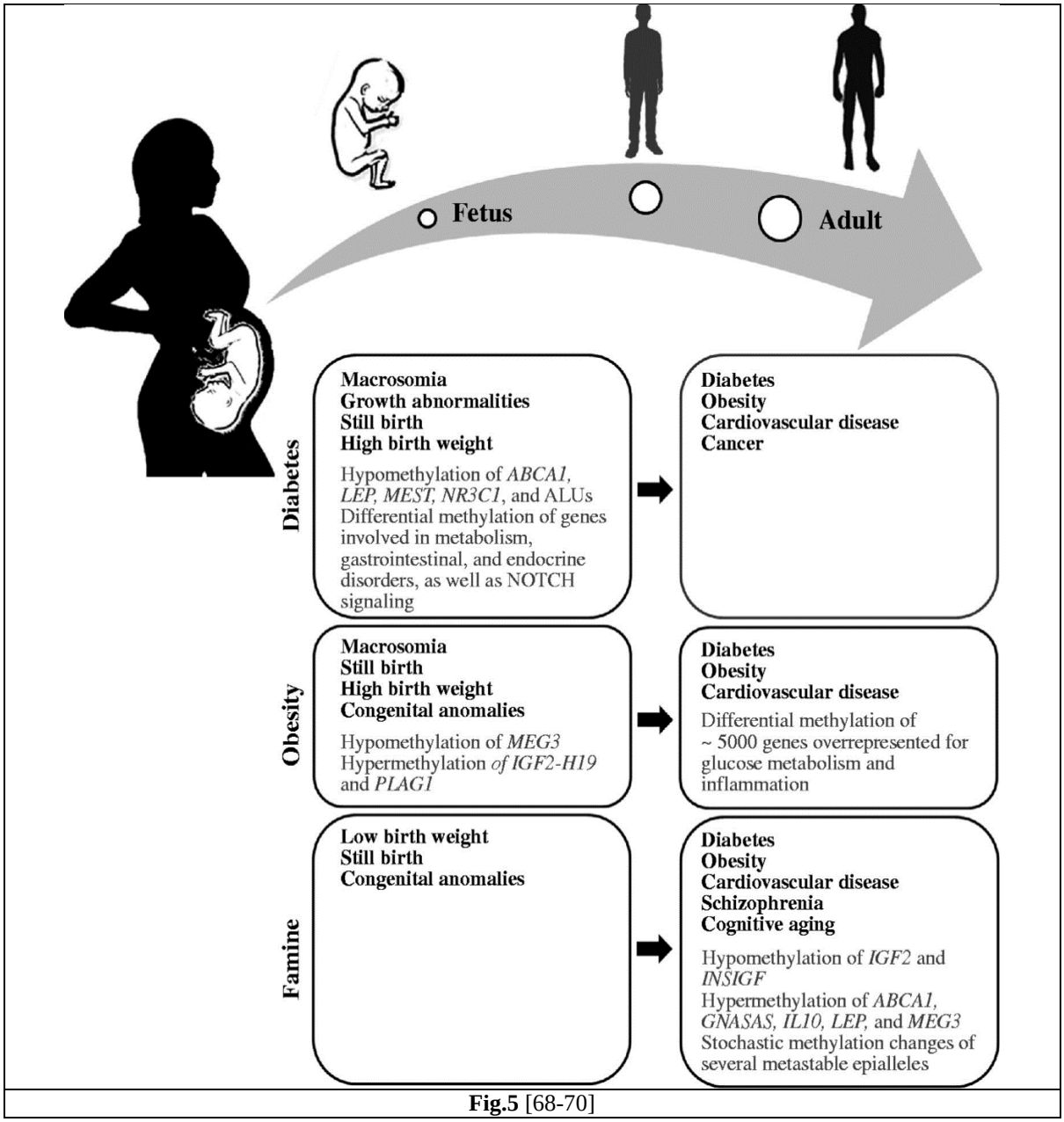

Fig.5 [68-70]

Metastable epiallele-containing genes

Reversible and changeable epigenetically changed loci are known as metastable epialleles. Transposable elements are invariably silenced by CpG methylation, with the exception of a tiny percentage whose methylation status is metastable and varies at random. Even in genetically similar individuals, nearby genes' expression can be influenced by the epigenetic state, resulting in cellular epigenetic mosaicism [71]. A typical example is the mouse allele known as agouti viable yellow, or any. An upstream intracisternal A-particle (IAP) retrotransposon is present in the loci as a metastable epiallele. Diabetes and a yellow coat color result from the abnormal expression of the agouti gene caused by an unmethylated retrotransposon. A rise in DNA methylation in the IAP retrotransposon has been linked to the color change of children's coat changing from yellow to brown when the mother supplements the diet with methyl-donor [72].

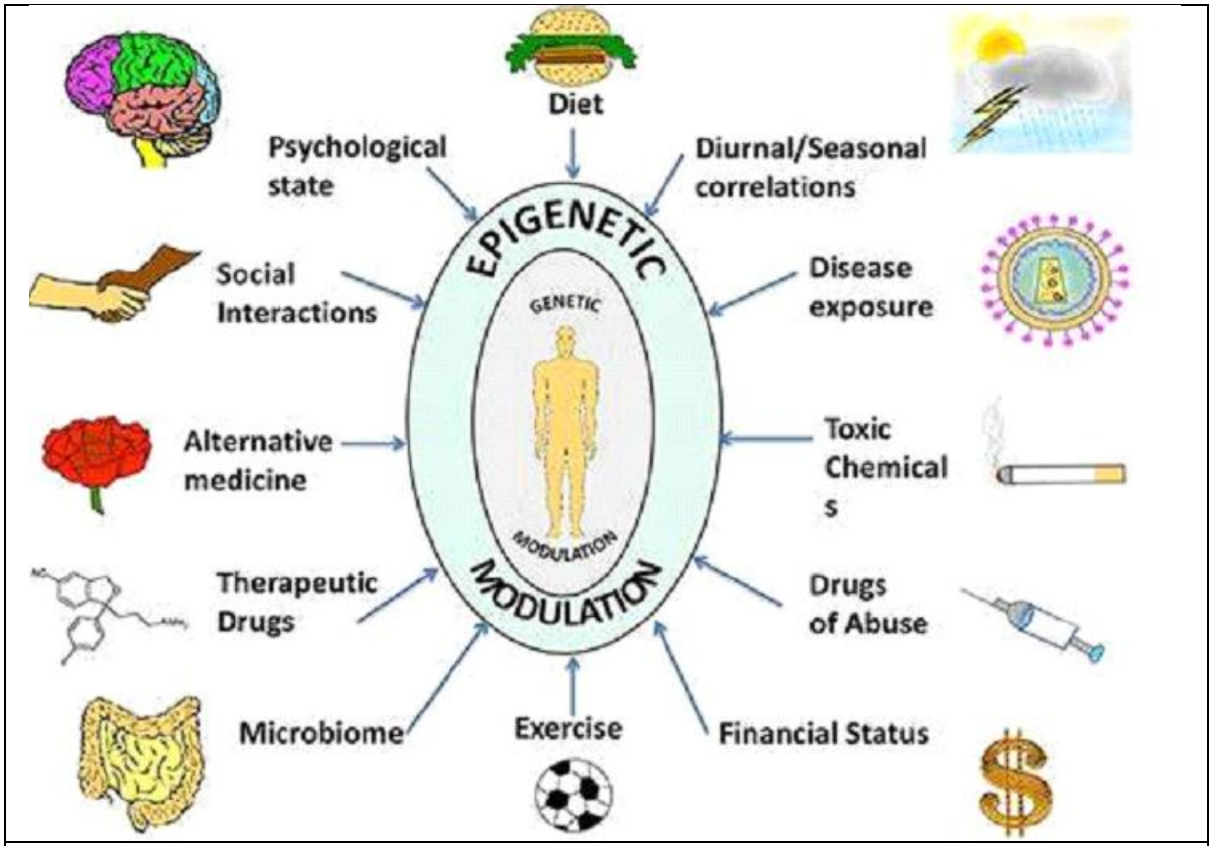

Fig. 6

The phenotypic changes in children were directly correlated with the epigenome alterations caused by the mother dietary environment Due to the high link between methylation patterns at IAP CpG sites in tissues generated from the three germ layers, it is probable that methylation in response to environmental stimuli is set earlier than embryonic stem cell differentiation. In addition to being stable, these epigenetic modifications are easily inherited through the germline and can pass from generation to generation. The issue under investigation pertains to the first stages of adult disorders and the significance of epigenetic alterations during early development. Transposable elements are a common feature of the human genome. Consequently, examining the biological significance of these modifications will be one task and whether they have an impact on a person's vulnerability to diabetes as discussed in Fig.6 and 7 [73].

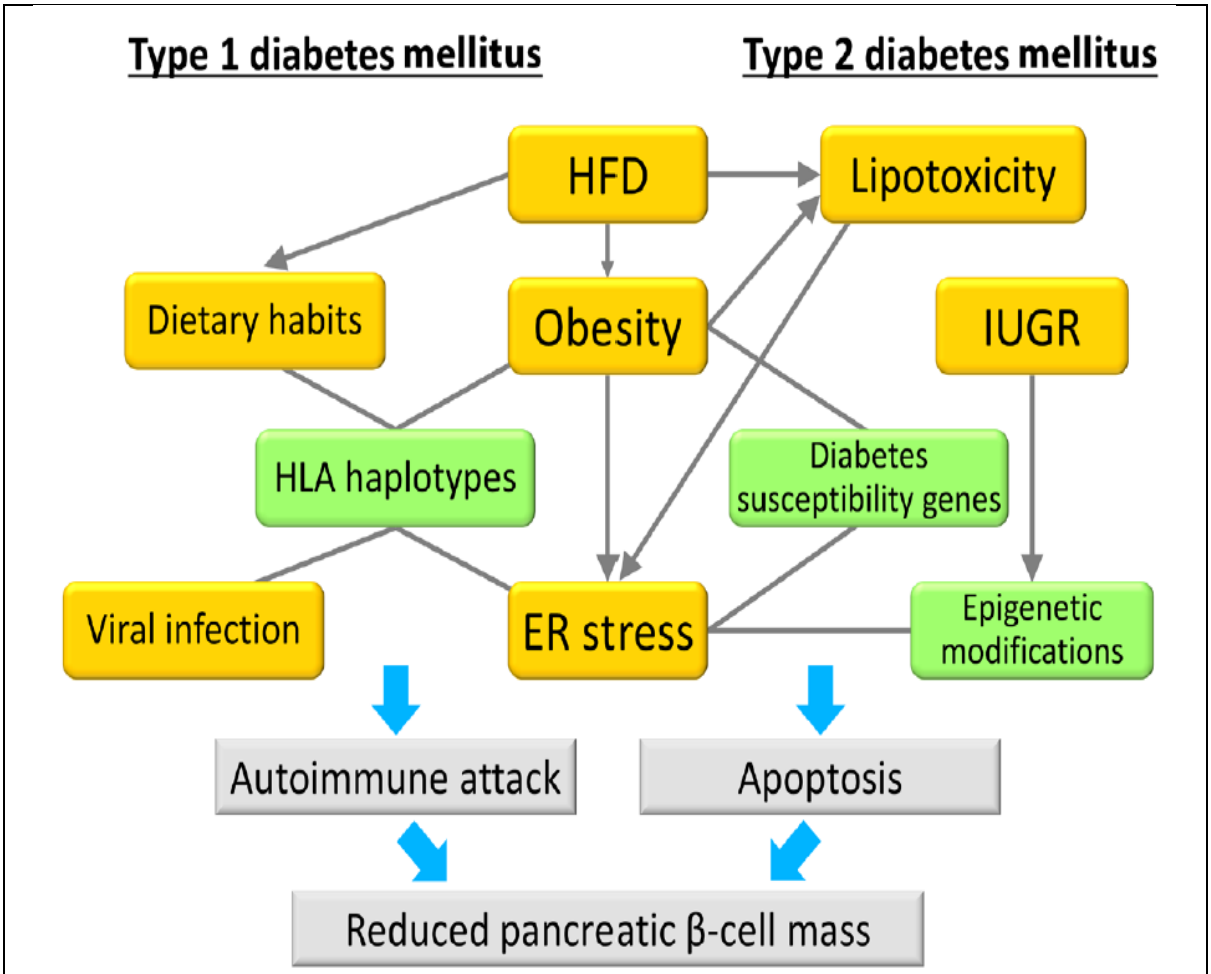

Fig. 7 Diagram showing the relationships underlying the mass of cell types in the pancreas and the interactions between genes and their surroundings. The pancreatic β-cell mass is reduced in people with type 1 diabetes as a consequence of an autoimmune response brought on by a confluence of lifestyle factors (overweight individuals, cellular endoplasmic reticulum [ER] tension, nutrition habits, and viral infection) and genetic (human leukocyte antigen [HLA] haplotypes). Pancreatic β-cell mass in type 2 diabetes mellitus is primarily controlled by the proliferation and death of these cells. Intrauterine growth restriction (IUGR) induces epigenetic alterations, which are a significant process involving genetic factors. In a synergistic way with hereditary variables, outside influences such fat toxicity, obesity, and ER stress from a fatty diet (HFD) feeding trigger pancreatic β-cell malfunction. Gene-specific variables are displayed in shaded green boxes (nonmodifiable parameters) and ecological variables (configurable aspects) are displayed in orange boxes [74-75].

Printed genetic material

Most autosomal genes are expressed by both paternal and maternal alleles; however, about 1% of autosomal genes are imprinted, indicating that the gene may be expressed by either or both of the parents' alleles. Gene imprinting is a non-Mendelian pattern of inheritance, characterized by traits that are both germline-inherited and epigenetically regulated [76]. Imprinted marks are created by parental gametes, and the parent of origin determines whether imprinted genes are expressed. Human imprinted genes are also impacted by environmental information that has been stored in the generation before them [77]. The basic idea that imprinting alters DNA suggests that impaired loci might be the epigenetic targets of the environmental aberrations that cause the disorders. Can rise to a range of disease phenotypes. Developmental abnormalities including Somatic or germline cells are the primary cause of Prader-Willi and Angelman syndromes. problems resulting from early-life imprinting of genes or regions. Several recent research have suggested that imprinting genes may have a role in different types of diabetes [78]. Plagl1, an imprinted gene that regulates Chromosome 6q24 is the location of both cell cycle arrest and pancreatic islet insulin synthesis. Approximately two thirds of cases of transient neonatal diabetes (TNDM) are shifted in

location. Both of them Diabetes type 2 (T2D) and type 1 (T1D) are associated with imprinted genes. A number of identified epigenetically imprinted genes have been linked to phenotypes related to metabolic syndrome and a parent-of-origin involved in transgenerational diabetes. These genes include Igf2 (insulin-like growth factor 2), Dlk1 (delta-like 1 homologue), Kcnq1 (potassium voltage-gated channel subfamily Q member), and Cdkn1c (cyclin-dependent kinase inhibitor 1C). DNA methylation is required for the parental-specific regulation of imprinted genes, especially during gametogenesis and early embryogenesis when the genome is demethylated and remethylated [79]. The environmental factors that influence DNA methylation can affect this process [80]. Consequently, imprinted genes might be significant loci for environmentally induced disorders with parental inheritance markers. It was found that the imprinted genes were tightly related.to organisms, indicating the need for a more appropriate animal model to evaluate its role in the human phenotype [81-85]

Genes that function but have different epigenetic modifications

Mature-onset diabetes of the young is a kind of early-onset diabetes mostly caused by changes in genes that encode transcription factors such IPF1/PDX1, HNF1A/ 4A/1B, and NEUROD1 [86]. One way that HNF1A promotes gene transcription is through the remodeling of chromatin in promoter regions PDX1 induced insulin expression in islet β cells affects glucose of the pancreas, a procedure that depends on PDX1 and histone H4 hyperacetylation at the insulin gene promoter TNDM is an additional kind of growth retardation in newborns. kind of diabetes that appears in the first six weeks of life Hypomethylation of chromosome 6q24 has been linked to TNDM. Surprisingly, TNDM and hypomethylation at chromosome 6q24 have been associated with ZFP57 mutations; this implies that PLAGL1 and HYMAI, two imprinted genes, are impacted. T1D is an autoimmune disease that causes destruction to the pancreatic β-cells [87]. Previous studies show that most histone modifications target genes that are associated with type 1 diabetes and are considered harmful. For example, in vitro research further corroborated the discovery that T1D patients had greater acetylation levels of H3K9Ac in their upstream regions for HLA-DRB1 and HLA-DQB1 [88]. The complex kind of diabetes known as type 2 diabetes (T2D) is brought on by a combination of reduced insulin production and insulin resistance. A growing amount of research has focused on epigenetic modifications in pancreatic islets model in humans and animals. Pancreatic islets from patients with diabetes mellitus showed decreased insulin production and increased DNA methylation of the insulin promoter regions. Furthermore, utilizing DNA methylation sequencing data from the pancreatic islets of T2D and healthy donors, a number of new target genes that are epigenetically regulated and linked to islet function have been discovered. For example, it has been demonstrated that the expression and methylation of TCF7L2, PPP2R4, SLC25A5, GRB10, CDKN1A, PDE7B, and SEPT9 varied in the pancreatic islets of T2D patients. Insulin and glucagon levels dropped as a result [89-92]. A further potential risk factor for type 2 diabetes is insulin resistance, a condition in which the main target tissues—the liver, adipose tissue, and skeletal muscle—react inadequately to insulin. Per a study, insulin-resistant individuals' visceral adipose tissue may have a different DNA methylation profile Naturally the insulin pathway accounted for the majority of the differentially methylated genes; 10% of these genes were found to be connected with diabetes, including IGF2BP1, GATA4, TET1, ZNF7L4, and ADCY9 [93-95].

EFFECTS DEPENDING ON DEVELOPMENTAL STAGE

The two primary phases of epigenome reprogramming in animals are gametogenesis and embryo-foetal development. Epigenetic alterations that take place during gametogenesis, early embryogenesis, and fertilization may impact a significant portion of the cells in an organ. Cell division and somatic maintenance intensify these alterations. Alterations in the epigenetic information that are acquired during early development may be retained throughout later life at certain genes and loci. Thus, the epigenome and the diabetes phenotype are influenced by environmental input differently depending on the embryonic stage [96-98].

Phase of gametogenesis

Oogenesis and spermatogenesis involve a worldwide reprogramming of the epigenome at distinct developmental schedules and magnitudes. Because genomic DNA methylation is erased and established in primordial germ cells as well as throughout germline cell differentiation and maturity, germ cells are sensitive to environmental stimuli even in adulthood. In male germ cells, 90% of the histones are replaced by protamine’s in particular. Following fertilizations, the first cell division restores the epigenetic markings and demethylates the paternal and maternal genomes once more [99]. For pluripotency and healthy embryonic development, there must be two significant rounds of reprogramming processes. Notably, throughout these processes, any changes in

germ cells' epigenetic makeup brought about by the environment likely have an impact on epigenomic reprogramming, which in turn affects the generation that follows [100]. A well-known instance is the paternal prediabetes model, wherein children were shown to have reduced insulin sensitivity and glucose tolerance, and transcriptome and epigenomic analysis Gene expression and DNA methylation were shown to be changed in pancreatic islets. Furthermore, sperm's general methylome patterns in F1 children were altered by the father's prediabetes status, which added to the transgenerational inheritance. According to recent research, there may be tRNAs implicated in the intergenerational inheritance passed down from father to son Evidence showed that a father's diet influenced the tRNAs in adult sperm, and that introducing tRNAs into viable zygotes resulted in the establishment of a diabetic phenotype and altered gene expression in the F1 offspring. Furthermore, recent studies have shown that adult male rats' pups that were exposed to environmental toxins like bisphenol A (BPA) through their dads had a worse glucose tolerance. Correlated with these alterations were decreased Igf2 expression in F1 pancreatic islets and increased Igf2 DMR2 methylation in F0 sperm. With no need for active transcription and translation, this presents a unique possibility the passing on of information from father sperm to the next generation [101-104]. Likewise, exposure to the environment may potentially alter the epigenetic markers in the mother's germline DNA methylation is the epigenetic mark most concerned about. This is in reality susceptible to external influences. Maternal obesity and high-fat diets (HFD) have the potential to cause hypomethylation of the paro promoter and hypermethylation of the Leptin promoter in mice. A prior study has demonstrated that gametes can transfer the diabetes phenotype that a mother's high-fat diet (HFD) has acquired to her children. It's unknown, nevertheless, how maternal germline transmission affects epigenetics. Additionally, recent studies have shown that F1 children of diabetic mothers are susceptible to reduced glucose tolerance. Reduced Tet3 levels in oocytes cause disruptions to paternal genome reprogramming in zygotes, which impacts the expression of several paternally hypermethylated diabetes-related genes This work provided an intriguing new explanation of the intricate biochemical mechanism by which oocytes transmitted information about epigenetic inheritance from the pregestational maternal hyperglycemia environment [105-107].

Stage of embryogenesis

Early stages of embryonic development seem to be more susceptible to environmental influences Mammals' early embryonic cells are rich in chromatin regulators and DNA methyltransferases, two types of epigenetic regulators Potential explanations for the stem cells' and early embryos' vulnerability to environmental cues include their abundance of regulatory machinery. On the other hand, most mature cells have stabilized epigenetic markers and are comparatively less active [108]. Both people and animal models, where assisted reproductive technology (ART) is widely employed, can be used to study the possible process [109]. Further research was done on the zygote and preimplantation embryo in vitro cultures in animals. Individual glucose metabolism and postnatal development may be impacted by the culture procedure and the nonphysiologically culture milieu, which may result in reduced glucose tolerance and fasting glucose levels. Freezing and thawing of the mouse preimplantation embryos may change the transcriptomics of the hepatocytes and affect the adult offspring's ability to withstand glucose and synthesize glycogen in the liver Three out of twelve ART-conceived offspring seemed to have hypomethylated KvDMR1 in response to the effects of ART on a single maternal imprinting-controlled area in humans [110]. The preimplantation environment of the mother can have an impact on the health of the baby in addition to ART itself [111]. The non physiological processes linked to DNA methylation changes in blastocysts, which have an intergenerational impact on child metabolism, are a part of ovarian stimulation therapy (ART). From the time of mating (Embryonic day 0) to implantation (E3.5), female mice in a different animal model were administered a low-protein diet. This brief maternal exposure at the Embryogenesis stage resulted in an increased adult metabolic illness with hypomethylated DNA. mature tissues have hypomethylation Thorough investigation would clarify the significance of this crucial time frame for personal metabolic planning and well-being [112].

Foetal phase

It has been indicated by several studies that epigenetic disruption can occur during the foetal period. Tissue differentiation, organogenesis, and foetal growth occur concurrently during the intrauterine developmental stage. In the Avy mouse model, maternal consumption of methyl-donor during pregnancy significantly affected the offspring's Avy methylation, while the mother's Avy methylation appeared to be unaffected. According to a common study on the Dutch Hunger Winter, peri-conceptional famine exposure resulted in the development of the diabetes phenotype in the progeny. There has been report of a small but

substantial change in the methylation of Igf2, Ins, and Gnas DNA [113]. There is also another type of diabetes that has foetal roots: gestational diabetes mellitus (GDM). An adult's chance of developing type 2 diabetes may increase if their mother had the disease, according to data gathered from Pima Indians. The chance of type 2 diabetes was 3.7 times higher in children conceived after the mother's diagnosis compared to siblings born prior to her diabetes diagnosis. DNA methylation changes in the exposed offspring's placenta and cord blood are linked to maternal gestational diabetes. There were discovered to be differently methylated CpG sites related to 29 genes and 10 intergenic regions in Pina Indian children whose mothers had diabetes. In mice, in utero hyperglycemia at the foetus stage may also lead to insulin insufficiency and an increased risk of adult-onset diabetes. In child pancreatic islets, aberrant Igf2/H19 DNA methylation alteration is linked to this adult phenotype Interestingly, feeding HFD to newborns after birth did not protect offspring receiving maternal insulin therapy for GDM, especially in male progeny Furthermore, hypermethylated areas were found in several genes that regulate insulin production, including Abcc8, Cav1.2, and Cav2. This information was obtained using DNA methylation profiling of pancreatic islets in progeny [114-115].

Exposure to environmental pollutants may influence the likelihood of developing diabetes, even though altering nutrition during the prenatal period has a considerable impact on the incidence of diabetes. It has been demonstrated that exposing pregnant rats to BPA increases the methylation of the glucokinase (GCK) promoter and reduces the expression of the GCK gene in the liver of the 3-week-old offspring. Another chemical found in the environment, phthalates, is also linked to diabetes. According to epidemiological evidence, exposure to phthalates during pregnancy is linked to both insulin resistance and aberrant insulin production. In the muscle of the offspring, Prenatal exposure to phthalates increased global DNA methylation and histone deacetylase 2 interaction with Glut4, according to a rat study [116].

According to recent studies, the placenta and embryo experience distinct impacts from environmental stimuli during the prenatal period. They identified a brand-new placenta-based method for transmission across generations. especially in male progeny. When there is an increase in placental superoxide dismutase 3 (SOD3) through the vitamin D receptor, the fetus is affected by maternal environmental factors. This causes the foetal offspring liver's AMPK/TET signaling axis to be activated, which changes the metabolic phenotype of the foetal offspring by demethylating its DNA. Future research is necessary to determine whether the aforementioned notable distinctions might be employed as possible biomarkers to indicate a person's vulnerability to diabetes [117].

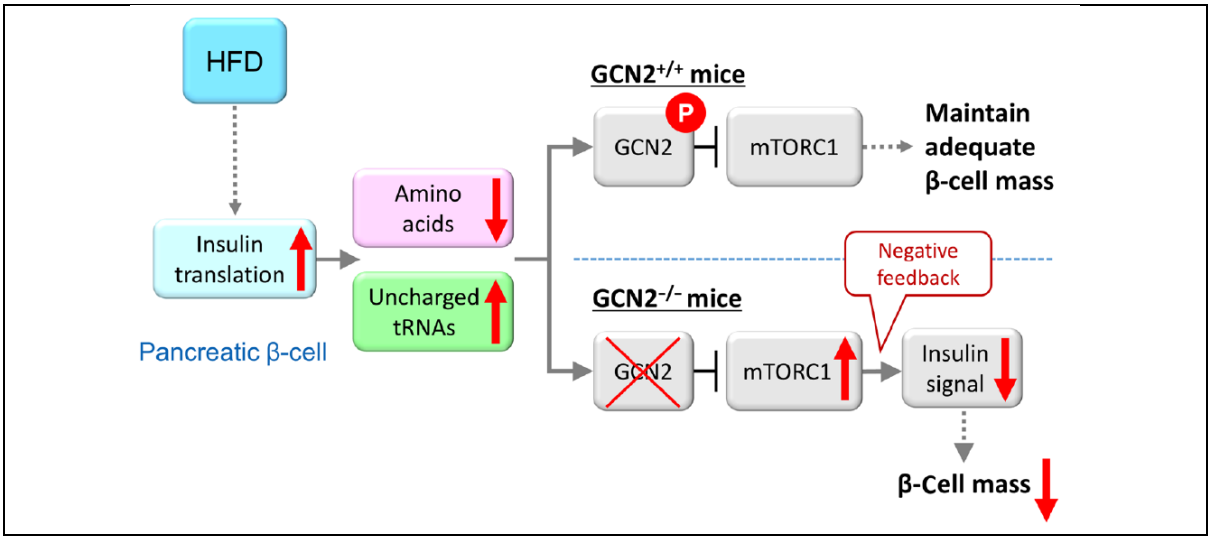

Fig. 8 An all-encompassing management paradigm HFD feeding-induced modulation of pancreatic β-cell mass via nonderepressible 2 (GCN2) being activated. Acquisition of amino acids by pancreatic β-cells lowers concentrations of amino acids as a consequence of increased insulin demand from high-fat diets. Through intrinsic increase of methodological domain of rapamycin complex 1 (mTORC1) owing to GCN2 inactivation, which HFD-fed GCN2 mutant mice experience hyperglycaemia and decreased pancreatic β-cell mass. The aetiology of pancreatic β-cell failure is a combination of genetic variables, including GCN2, and environmental ones, like a high-fat diet. GCN2 is phosphorylated, as indicated by the letter "P." modified from Kanno et al. with the American Society for Clinical Inspection's consent [118-120].

Postnatal phase

The postnatal stage is characterized by the development of the metabolic organs, including the muscles, liver, adipose tissue, and pancreas. The transition from umbilical to oral feeding occurs throughout the postnatal period due to environmental factors, especially nutritional ones [121-130]. Research on rats has demonstrated that under appropriate cross-fostering scenarios, young animals raised on the diets of fat or diabetic mothers were more likely to experience aberrant glucose metabolism in the future. Furthermore, the impact of in utero exposures on metabolic disorders may be amplified by exposures during the lactational stage [131]. For example, in rat offspring of obese mothers, overfeeding during lactation enhanced adiposity and glucose intolerance, indicating an autonomous role for the lactational stage in the development of metabolic syndrome [132-133]. These models focus more research on the transfer of micro-vesicle RNAs through milk rather than epigenetic markers. Furthermore, the postnatal epigenome is susceptible to environmental influences [134-136]. There is evidence that locus-specific interindividual DNA methylation changes occur partly after birth, according to data from research involving monozygotic twins. Increased Slc2a4 promoter methylation was seen in conjunction with a reduction in Glut4 transporter mRNA in the skeletal muscle of male newborns fed a high-carb diet. It has been suggested that nursing in humans may change the NYP and LEPTIN promoter DNA methylation, which is linked to obesity and diabetes. According to earlier animal research, an individual's epigenome may be impacted by their diet at this particular moment [137-140].

II. CONCLUSION

Considering there exists no appreciable or persistent modifications to hereditary variables, the recently observed exponential development of the international diabetes patient population is mostly the result of environmental changes. Genetic variables, however, are probably going to be impacted by modifications to the surroundings. We compiled the information supporting the connection between IUGR or diabetes-associated markers and responses to the environment in the present investigation. Nonetheless, it is thought that gene-environment interactions, particularly those pertaining to decreased β-cell mass, are broadly relevant to the modern pathophysiology of diabetes. Therefore, the secret to personalised therapy may lie in a more thorough examination of these gene-environment interactions. We anticipate more advancements in this area in future years.

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