Genetic environmental interactions with diabetes type 2: In-depth understanding of the literature.

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Abstract

The present review gives deep understanding of diabetes type 2 from the perspectives of genetic and environmental points of view. Diabetes type 2 is a story with multiple episodes that needs to be fully understood to observe the events and characters. The complications of diabetes depend on multi-factors such as obesity, energy expenditure, stress, and genetic predisposition. In this review, we expanded the concept of genetic more than it was thought. Taken together, targeting diabetes type 2 from one perspective is not a practical issue, and we should expand our horizon by taking all perspectives together to better understand and manage diabetes.

Keywords: Diabetes type 2, Genetic factors, Environmental factors, Diabetes complications, Obesity.

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Introduction

According to the World Health Organization, 422 million people worldwide have diabetes, with the majority living in low- and middle-income countries and the majority suffering from type 2 diabetes. For decades, as the population ages and gets less active and overweight, the prevalence has climbed rapidly (GBD 2019 Risk Factors Collaborators, 2020). Early detection is critical, especially because long-term consequences, such as referable diabetic retinopathy, can occur even before type 2 diabetes is diagnosed [1-4].

T2DM is the most common type of diabetes in adults, accounting for more than 90% of cases. In diabetic individuals, resistance to insulin action is the most common cause of chronic hyperglycemia. T2DM is the result of many pathways and variables associated in insulin resistance and cell dysfunction being activated. In addition, the genesis of T2DM is complicated by the interaction of genetics and environmental variables. To obtain improved diabetes management, lifestyle changes can effectively control this interplay Type 2 diabetes and obesity have been on the rise for decades and are predicted to continue to climb as the population ages and becomes more sedentary. Global health care is expected to be severely strained [5-7].

Insulin resistance and cell dysfunction are two of the most common symptoms of Type 2 Diabetes Mellitus (T2DM), both of which are caused by a disruption in homeostasis. The main physiological abnormalities are caused by a vicious triad of cell failure (80% of their cell function) and insulin resistance in muscles and the liver. T2DM, on the other hand, is traditionally thought of as an insulin deficiency and resistance condition, and new insights into the pathophysiology of T2DM point to the involvement of other critical players in insulin insufficiency and functional incapacity. Insulin-releasing cells (48%–59%), Glucagon-releasing cells (33%–46%), Somatostatin (SsT) releasing cells, and F cells that release polypeptides (PPs) in identical proportions make up pancreatic islets. Furthermore, paracrine connections occur in the following order: cell to cell, cells and PP-cells/F-cells. While the interaction of cells is currently the focus, the interaction of other cells in the pancreas is critical and must be investigated more to understand their involvement in glucose homeostasis [8-10]. Furthermore, fat cells (accelerated lipolysis), the gastrointestinal tract (incretin deficiency/resistance), cells (hyperglucagonemia), the kidneys (increased glucose reabsorption), and the brain (insulin resistance) all play a role in the development of glucose resistance in T2DM, as do complex interactions between these factors and T2DM associated genes. To enhance the overall health condition of T2DM patients, lifestyle changes are required in addition to medication therapies [11-15].

The Unfocused Aspects of Understanding the Diabetes Machinery

Pancreatic-cell function and amylin proteins

For their functions in glucose homeostasis in T2DM, cells are the most widely researched pancreatic cells. Islet amyloid PP (amylin) is a cell peptide hormone released in a 100:1 ratio with insulin. Diabetic patients' secretion is also affected. Amylin works as a satiety drug because it inhibits glucagon secretion and slows stomach emptying. Amylin's function is carried out by an area postrema (glucose-sensitive section of the brain stem) that works together to minimize overall insulin demand. Aside from these tasks, amylin is involved in the demise of the cell by forming amyloid aggregates and fibers [16-20]. Histopathological findings revealed an accumulation

of extracellular amyloid proteins, hyperphosphorylated tau proteins, ubiquitin, apolipoprotein E, apolipoprotein (a), cJun Nterminal Kinase (JNK1) and islet brain protein 1/JNK1 interaction 1 (IB1/JIP1) as an islet feature in individuals with type 2 diabetes, suggesting that amylin in combination with the endocrine system plays an important role in the physiology, pathology, and progression of diabetes remove type 2 sugar [21-24].

α-cells

α-cells are recognized to play an important part in T2DM pathogenesis. Glucagon secretion from the cell is controlled by a complex interaction of glucose, hormones, and other substrates. Any aberration in cells leads to a disruption in glucose homeostasis. Glucagon secretion is enhanced in T2DM patients during fasting and postprandial states with normal and raised glucose levels, as well as an altered hypoglycemic response [25-27]. T2DM, according to the bi-hormonal theory, is caused by insulin resistance/deficiency combined with an excess of glucagon secretion, resulting in a significantly faster rate of hepatic glucose synthesis than glucose utilization. Hyperglycemia arises because of this. Many clinical and experimental studies support the hypothesis. Under hyperglycemic conditions, decreased regulation of glucagon release is a contributing factor to postprandial hyperglycemia [28-30]. Interestingly, α-cells do not exhibit this behavior in the presence of appropriate insulin levels, implying that anomalies in glucagon release in T2DM are also caused by impairments in the insulin mechanism [31]. Furthermore, in T2DM patients treated with insulin, glucagon production has a significant impact on hypoglycemia. The secretory response of cells to low glucose concentrations is impaired in such patients, which increases the risk of severe hypoglycemia. Multiple errors in α-cells regulation have been associated to glucagon insufficiency in response to hypoglycemia [32]. Even in the case of islet allotransplantation, which allows diabetic patients to stay insulin-free for a long period, the delayed response of α-cells to hypoglycemia is frequently unchanged, showing that the treatment does not totally restore α-cells physiological capabilities. Defects in cell control and glucagon secretion, taken together, result in poor glucose sensing, α-cell dysfunction, and insulin resistance [33-36].

Pancreatic PP cells, SST, and F-cells (F-cells)

The stomach, intestine, neuroendocrine cells, and pancreas all include δ-cells. In response to changes in glucose levels, they release Somatostatin (SST) in a pulsatile manner. SST is a hormone that controls endocrine activities and is involved in the gut-brain axis. SST receptors are found on α-cells and β-cells, where they operate as inhibitory receptors for insulin and glucagon production. SST has a tonic inhibitory effect on insulin and glucagon release, as well as facilitating the islet response to cholinergic activation. SST is also implicated in the reduction of glucagon production induced by nutrients [37-39]. SST also affects glucose homeostasis and feedback loops in a substantial way). After food ingestion, pancreatic PP is released by F-cells in the pancreas. It inhibits stomach emptying, intestinal motility, exocrine pancreatic secretion, hepatic glucose generation, and gallbladder contraction in the postprandial period. Food intake and energy metabolism are greatly affected by PP's functional capacities. PP has an orexigenic (appetite stimulating) impact in the brain when injected intracerebroventricularly. Intraperitoneal injection of PP, on the other hand, reduces food intake and reduces body weight by increasing energy expenditure. Obesity and diabetes are linked to elevated PP levels in the blood [40-44].

Resistin and adipose tissue

Adipocytes, connective tissue matrix, nerve tissue, stromovascular cells, and immune cells are all found in adipose tissue. The importance of adipose tissue as an endocrine organ has long been recognized. Leptin, cytokines, adiponectin, complement components, plasminogen activator inhibitor-1, renin-angiotensin system proteins, and resistin are all released [45-47]. Aside from secreting hormones and components, adipose tissue collaborates with other hormone systems and the central nervous system. Under normal circumstances, adipose tissues function as a fat storage facility, but in metabolic diseases, they also produce Free Fatty Acids (FFAs). The increased release of FFAs and insulin resistance in adipose tissue has been linked to deterioration in the function of the β-cell in normal people. T2DM progression and development are substantially linked to resistin, an adipose tissue-specific secretory factor secreted from adipose tissue. It is an inhibitory hormone that causes insulin resistance. T2DM causes an increase in circulating resistin, which leads to oxidative stress, insulin resistance, and platelet activation. Resistin gene expression has been found in the pancreas islets, pituitary, and hypothalamus. Resistin is largely released by macrophages in humans, where it aids in the recruitment of immune cells and proinflammatory factors, but it also plays a role in hyperglycemia and insulin resistance. The activation of AMP-protein kinase and decreased expression of gluconeogenic enzymes in the liver cause resistin-induced hyperglycemia and obesity. Insulin resistance is induced in rodents after the administration of recombinant resistin, which is reversed when the immune system is neutralized [48-50].

Genetics

Obesity and diabetes are on the rise due to the contemporary obesogenic environment, which favors high-calorie diets and physical inactivity. Not everyone who is exposed to this environment, however, acquires weight or develops type 2 diabetes. People's responses to environmental circumstances are influenced by their genetic propensity to obesity and type 2 diabetes, at least in part. The heritability, which is a population-level estimate of how much of the variance in disease susceptibility is related to genetic variation, has traditionally been used to quantify the genetic contribution. The heredity of obesity and type 2 diabetes has been estimated to be moderate to high, ranging between 30% and 70%. The quest for contributing genes began in the 1990s, with early success limited to monogenic obesity and diabetes. Mutations that occur De Novo or in families have been discovered to

cause severe abnormalities in the function of the genes in which they are situated, bringing new insights into the pathophysiology of body weight regulation and glucose metabolism [51-54].

T2DM is known as "the geneticist's worst nightmare." Multiple gene changes occur because of the combined effects of hereditary and environmental factors. Multiple processes influence the development and progression of T2DM, either directly or in combination with other factors. Defects in pancreatic angiogenesis, innervation, and paternal imprinting are among them. The severity of both maternal and paternal insulin resistance and/or insulin sensitivity plays a role in T2DM etiology. According to one study, T2DM patients' first-degree relatives are more likely to develop the disease and have a considerable genetic propensity to β-cell failure. Furthermore, β-cell malfunction, autosomal dominance, and heterozygous alterations in β-cell transcription factors are also common reasons of T2DM onset early. Insulin promoter factor-1, Hepatocyte Nuclear Factor (HNF)-4, NeuroD1/BETA2, HNF-1, and HNF-1 are among the genes linked to early-onset T2DM [55-58]. T2DM or pre-diabetes in the offspring of women with gestational diabetes has also been linked to a hyperglycemic intrauterine environment. In addition, during gestational diabetes, the expression of insulin receptor-β, PI3K (Phosphatidylinositol 3-Kinase) with its subunit p85, and GLUT-4 in placental tissues declines, with a compensatory increase in the expression of GLUT-1 mRNA. Increased insulin resistance and, as a result, a higher risk of T2DM in offspring has been linked to a polymorphism in the resistin gene 299 (G>A) and an increase in serum resistin. Furthermore, offspring with the AA genotype or the combination GA and AA genotype are at a higher risk. Diabetes, on the other hand, can cause genetic changes that lead to comorbidities. Changes in genes involved in vitamin synthesis, for example, cause lowered riboflavin and glycaemia, microalbuminemia, and altered uric acid levels in T2DM patients, as well as the development of insulin resistance due to vitamin D insufficiency. Importantly, diabetics have polymorphisms in the vitamin D receptor and its binding protein genes, as well as CYP1 [59-62].

Gut

The gut is a vital link between the brain and the neurological system of the intestine. Following food consumption, the release of gastrointestinal hormones (incretin, Glucagon-Like Peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP) increases. These hormones help insulin and glucagon maintains glucose homeostasis while also improving glucose sensing in cells. GLP-1 enhances cell sensitivity to glucose and stimulates absorption of ingested nutrients by glucose-stimulated insulin release GLP-1 also induces satiety by suppressing glucose-dependent glucagon secretion, delaying stomach emptying, and suppressing glucose-dependent glucagon secretion [63-65]. GIP and GLP-1 enhance β-cell proliferation and apoptosis inhibition in the pancreas, resulting in an increase in pancreatic β-cell mass. In addition, GIP promotes fat deposition. GIP and GLP-1 are implicated in appetite control in the brain. GIP also reduces gastric acid output, whereas GLP-1 shortens the time it takes for the stomach to empty. Furthermore, in T2DM patients, the insulin tropic effects of GIP and GLP-1 differ, so that GLP-1 production is diminished but GIP secretion is unaltered. Increased gastrointestinal permeability is caused by changes in incretin function and related pathways in T2DM, and this is one of the primary underlying mechanisms for diabetes comorbidities in the latter stages. Other hormones released by the gut are engaged in multiple signaling pathways. Ghrelin, galanin, Cholecystokinin (CCK or pancreozymin), and leptin are just a few of them. In reaction to meals, enter endocrine cells (duodenal and jejunal I cells) and neurons produce and release CCK, which causes pancreatic acinar cells to secrete pancreatic digesting enzymes. CCK also improves digestion by decreasing gastric emptying. Through the feedback mechanism, vagus stimulates trypsin release from the pancreas, which hydrolyzes CCK to maintain homeostasis. CCK has a favorable relationship with leptin and insulin levels, which leads to a disruption in glucose homeostasis and diabetes complications in T2DM [66-69].

Gut microbiota

Diabetes is a gastrointestinal condition in which the gut microbiota plays an important role. Along the length of the gastrointestinal tract, the concentration of microflora rises distally. In general, the flora of the upper intestine accounts for about 105 cfu/mL of the overall microflora composition. Microflora concentrations rise to 107 cfu/mL in the mid-ileum, and the colon becomes densely populated. Firmicutes (60%–80%), Ruminiococcus, Clostridium, and Lactobacillus, Bacteroidetes (20%–30%): Bacteroides, Prevotella, and Xylanibacter, Actinobacteria (10%), Bifidobacterium, Proteobacteria (1%), Escherichia and Enterobacteriaceae and yeast Saccharomyces [70-72]. Obesity/adiposity is unquestionably a major contributor to T2DM. Interestingly, with obesity, the levels of Staphylococcus, Enterobacteriaceae, *Faecalibacterium prausnitzii* and *E. coli* rise, whereas Bacteroides levels fall. Firmicutes, *Lactobacillus gasseri*, *Streptococcus mutants* and *E. coli* are also increased in T2DM, whereas Proteobacteria, butyrate-producing bacteria, Bacteroidetes, Roseburia, *Eubacteria halii* and *Faecalibacterium prausnitzii* are significantly reduced. Insulin resistance and disease/metabolic syndrome are linked to changes in the gut microbiota/gut-brain microbiome. Obesity also has a significant impact on low-grade inflammation, which is linked to changes in gut-brain-microbiota connections, making T2DM an inflammatory condition. Increased intestinal permeability caused by inflammation is seen in obesity and diabetes, which can lead to leaky gut syndrome and allow gut microorganisms to enter the bloodstream [73-75]. This raises the level of circulating LPS, which triggers the development of inflammasomes. Furthermore, diabetes compromises vagal control due to persistent hyperglycemia, damaged Cajal interstitial cells, and gastroparesis (5%–12% of diabetic individuals). Increases in mucosal surface area, intestinal weight, and the number of goblet cells per villus cause esophageal peristalsis to be

interrupted and sphincter tone to be reduced. Overall, intestinal motor function problems lead to stasis and bacterial expansion, potentially disrupting the intestinal barrier and altering permeability, allowing microorganisms to enter. Furthermore, circulating LPS plays a role in insulin resistance and the progression of diabetes to comorbidities. Biologically active polyunsaturated fatty acids, chronic low-grade inflammation caused by the endotoxin axis TLR4 and impaired intestinal barrier function [76-79].

Lifestyle Changes, Environmental Factors, and Management of T2DM

Pharmacological approaches to treat T2DM are only partially ineffective in the long-term management of diabetes. Significant changes in a patient's lifestyle, coupled with pharmacological approach interventions, are important to ensure effective management of the disease. These include changes in physical activity, changes in diet, management of stress or related factors, and improvement in sleep patterns [80-83].

Physical activity

Physical activity is positively associated with blood sugar control in patients with type 2 diabetes but daily physical activity has been shown to be an effective means of controlling long-term manifestations of the disease. These include walking, gardening and doing routine household chores. Walking is the most effective physical activity in type 2 diabetes, because it allows significant glycemic control with limited physical load in patients who are already physically weak. Additionally, the most warranted lifestyle changes in patients with type 2 diabetes are changes in sedentary pattern. Sedentary behavior results in significantly low energy expenditure. Prolonged sedentary time in patients with type 2 diabetes is also associated with poor blood sugar control. Therefore, a reduction in sedentary time, being important in patients with diabetes, can be achieved by increasing physical labor. Furthermore, regular aerobic exercise has been shown to lower HbA1c levels in diabetic patients. Aerobic exercise improves patient health outcomes through a variety of pathways, including increased mitochondrial density, improved insulin sensitivity, improved blood vessel compliance, and improved lung functions with increased cardiac output [84-87].

Medical nutrition therapy and dietary changes

High sugar intake, fried food, and red meat consumption are all connected to insulin resistance and the development of T2DM. Intake of vegetables high in antioxidants, fiber, and other nutrients, on the other hand, is associated with a lower risk of T2DM development. Diabetes patients' average energy consumption varies depending on their obese status. An average energy intake of 1,500–2,500 calories per day is recommended for no obese diabetes patients, but the average calorie intake is reduced to 800–1,500 calories per day for obese diabetic patients. Diabetes patients' average energy consumption varies depending on their obese status. In T2DM patients, limiting refined sugar intake is highly suggested [88,89]. In such patients, non-nutritive sweeteners (aspartame, saccharine, etc.) can be effective sugar alternatives. Furthermore, foods high in saturated fats and cholesterol should be avoided, and those high in polysaturated fats should be substituted. Changes in eating habits, such as breaking meals into small fractions throughout the day rather than having one or two large meals, can also help to reduce postprandial blood glucose spikes. Strict adherence to a regulated diet combined with enough physical activity has been linked to a lower risk of diabetes. When diabetes patients incorporate a Paleolithic diet (a diet rich in lean meat, fish, fruits, and vegetables) into their daily routine, their glucose management improves significantly. It is also widely recommended that nutritional therapy be used in the treatment of diabetes. Nutritional therapy is a method of treating a disease by altering one's food and nutrition intake. Medical nutrition treatment is the application of evidence-based nutrition care therapy in ill patients by a qualified and certified dietician. Diabetes patients undergoing nutritional therapy have a lower dependency on oral hypoglycemic therapy [90-93].

Furthermore, diabetic patients who receive rigorous nutritional education from a qualified dietician have significantly better clinical results than those who receive basic nutrition information (BE). Taken together, simple but significant dietary adjustments in diabetic patients could be a promising strategy for reducing the disease's long-term consequences. Furthermore, the implementation of nutritional therapy in diabetic patients might be a lucrative strategy for better diabetes management and improved health outcomes [94].

Stress

In T2DM patients, higher levels of stress are linked to poor treatment adherence and glycemic control. Moderate/high levels of stress were found to be responsible for a multifold increase in diabetes occurrences in a longitudinal research. Furthermore, repeated exposure to stressors, poor mental health, and psychological stress has all been linked to an increased risk of T2DM. The key reason responsible for this higher risk of T2DM in such individuals is thought to be allosteric load (wear and tear in the body caused by prolonged psychological stress). Furthermore, chronic stress has been linked to a worsening of clinical outcomes in T2DM patients. Chronic stress is linked to a disruption in glucose metabolism and neuroendocrine function, as well as low-grade inflammation. The release of glucose (and lipids) in circulation, the development of inflammatory cytokines, and raised blood pressure are all variables implicated in T2DM that are substantially influenced by psychological stress. Significant increases in blood glucose levels were seen in type 2 diabetes patients subjected to acute stress during the postprandial period in one research [95-98].

Chronopharmacology and sleep patterns

Although physical activity and a consistent dietary pattern improve T2DM management, they cannot be considered the only cause of rising diabetes rates. Another modifiable lifestyle

choice that has been shown to influence metabolic health and energy levels is sleep. Sleeping habits must be optimized for diabetes control. Short sleep (less than 5 hours) or insomnia may be linked to an increased risk of T2DM, according to a population-based study. Poor sleep has been linked to higher HbA1c levels (>7%) and insulin resistance in T2DM patients in previous research. Diabetes onset, progression, and control are all influenced by disrupted circadian rhythms and sleep-wake patterns. Due to chronic sleep deprivation and a disrupted circadian rhythm, shift workers are more prone to metabolic problems. Furthermore, a developed proclivity for napping because of poor or insufficient nocturnal sleep is linked to a higher risk of T2DM [99-102].

Experimental manipulation of sleep and circadian pattern resulted in a considerable reduction in insulin sensitivity to a standardized meal in one study, which may be reversed with restored sleeping habits. Short sleep has been linked to changes in appetite-regulating hormones (leptin and ghrelin), resulting in an increased desire for carbohydrate-rich foods and higher calorie intake. Furthermore, a lack of sleep causes oxidative stress and the release of orexin or hypocretin, a neuropeptide that regulates sleep and appetite and causes sympathetic nervous system stimulation, increased cortisol release, and a decrease in growth hormone secretion, all of which contribute to significant hyperglycemia. Daily rhythms in physiology have a significant impact on Pharmacokinetics and Pharmacodynamics (PK-PD). Chronopharmacology is the name given to this phenomenon. Indeed, hormonal, and physiological homeostasis play a big role in diabetes pathogenesis. The use of Chronopharmacology in diabetes management should be considered. T2DM-affected -cells do not lose all their ability to respond to glucose. Insulin production is preserved in response to stimulation by amino acids or other hormones such Glucagon-like Peptide 1 (GLP-1). Between midnight and early morning, blood levels of leptin (the satiety hormone) are normally greater, possibly suppressing appetite during the night). Furthermore, the levels of ghrelin rise as sleep time increases. Furthermore, circadian variation affects the temporal reliance of GLUT4-mediated glucose absorption. Furthermore, meal durations can affect blood leptin levels' diurnal cycle. Ghrelin and leptin both function in feedback loops with other hormones and the HPA axis to influence psychophysiological pleasure in diabetic patients. As a result, Chronopharmacology may have a significant impact on diabetic pathophysiology and the PK-PD of medicines administered [103-105].

Genetics, Gut Microbiota, Lifestyle, and Environmental Factors All Play a Role

Several epidemiological studies have suggested that modifying lifestyle, eating patterns, and other linked environmental factors can reduce the effects of several T2DM-associated genes. The Ala12 PPAR variation, for example, has been linked to enhanced insulin sensitivity. Unsaturated fat appears to be more receptive to Ala12 carriers, while saturated fat appears to be less responsive. PPAR Pro12 variant carriers, on the other hand, are more sensitive to the harmful effects of saturated fat and impaired glucose homeostasis. Unsaturated fat appears to interact with the PPAR Ala12 variation and upregulate its activity TCF7L2 risk-variant (rs7903146) and lifestyle alterations may have potential Gene-Environment (GE) interactions (physical activity, MNT, and dietary changes). Lifestyle changes have a considerable impact on insulin resistance and risk reduction in TCF7L2 risk-variant carriers. T2DM risk is linked to a common SNP in the fat mass and obesity associated gene (FTO rs9939609). Increased physical activity lowers the incidence of T2DM and obesity caused by the FTO rs9939609 mutation. GCKRrs780094 is an insulin-raising allele caused by an SNP in the glucokinase regulatory protein gene. Its association with whole grains (increased whole grain intake) causes carriers to have lower fasting insulin levels [106-109].

In T2DM, KCNQ1 (potassium voltage-gated channel subfamily Q member 1) is a vulnerable gene. KCNQ1 mutations are linked to a reduction in insulin secretion. Reduced expression of the noncoding RNA Kcnq1ot1 in the Kcnq1 genetic region causes an increase in the expression of the Cyclic-dependent kinase inhibitor 1C (Cdkn1c), leading in decreased pancreatic cell mass and insulin secretion. The CCAAT sequence in the Cdkn1c gene's promoter region acts as a binding site for transcription factor C/EBP, which promotes Cdkn1c production. The expression of C/EBP causes endoplasmic reticulum stress, which leads to cell dysfunction. In the context of a high fat diet, the buildup of C/EBP in pancreatic cells increases, potentiating cell dysfunction in the sensitive population. Overall, growing research on gene-environment interactions suggests that dietary patterns, physical activity, and other lifestyle interventions have a significant impact on the expression of genes associated with the development of T2DM [110-112].

Environmental influences, in addition to gene expression, have the capacity to influence gut microbiota. A variety of factors influence the gut environment, including nutrition, pH, and nutrient absorption. While carbohydrates and simple sugar rich diets promote the growth of Firmicutes and Proteobacteria, saturated fats and animal protein-rich diets promote the growth of Bacteroidetes and Actinobacteria. Furthermore, a high-fat diet causes considerable changes in gut flora, including increased gram negative/gram positive bacteria ratio (*Bifidobacterium and Bacteroides*). This resulted in increased LPS secretion, lipid content, body weight, and T2DM-related inflammatory reactions. The loss of a strong intestinal barrier is mostly due to a reduction in butyrate. The proliferation of butyrate-producing Phytophthora is favored by an intestinal pH of 5.5, which begins to decline at a pH of 6.5. Furthermore, the hypoglycemic drugs used in anti-diabetic therapy have a significant impact on the gut microbiota. Metformin and acarbose have been shown to promote the growth of lactobacilli, Akkermansia, and other bacteria that have been shown to help people with diabetes. The makeup of the gut microbiota has an impact on the control of gene expression in T2DM [113]. Although research on potential interactions between gut microbes and T2DM-associated gene variations are few, available reports on the influence of gut microbes on

T2DM-related gene expression genes are strongly suggestive of a complex gene-microbe interaction in the etiology of T2DM. In addition, through modifying DNA methylation, the microbiome plays an important role in the epigenetic control of genes. A short-chain fatty acid-producing bacterium *F. prausnitzii* was discovered to be important in the epigenetic regulation of the FFA receptor gene in T2DM patients. In these patients, the presence of *F. prausnitzii* was significantly reduced. As a result, these people have very little methylation in the promoter region of the FFA receptor gene. T2DM is characterized by an increase in the secretion of pro-inflammatory cytokines. Microbes are commonly linked to increased inflammatory cytokine release by generating products like LPS, which induce low-grade inflammation and endotoxemia. On the other hand, several microbes, including *Roseburia intestinalis*, *Bacteroides fragilis*, *Akkermansia muciniphila*, *Lactobacillus plantarum*, and *Lactobacillus casei*, have been shown to induce the expression of anti-inflammatory cytokines such as IL-10 and IL-22, which have been shown to improve insulin sensitivity [114-116].

Bacteroides vulgatus and *Bacteroides dorei*, two other beneficial bacteria, have been found to boost the expression of tight junction genes in T2DM to compensate for the impaired gut permeability (leaky gut). In the case of glucose metabolism and homeostasis, probiotics play a significant role. *L. gasseri* BNR17, for example, has been shown to boost the expression of the GLUT-4 transporter gene. Another gut microbe, *L. casei,* has been found to boost the expression of T2DM-related genes such as ClC1-7, GlyR1, SLC26A3, SLC26A6, GABAA1, Bestrophin-3, and CFTR, resulting in a considerable reduction in hyperglycemia. It suggests that considering the potential interaction between several T2DM-related genes and these microorganisms is critical. Without a doubt, the absence of these microorganisms in the gut microbiota is a major contributor to the aberrant gene regulation seen in T2DM patients [117-119].

Conclusion

Diabetes type 2 is not a single event resulting from insulin deficiency, but rather it may serve as a theater that exhibits a play with various episodes, each episode has certain stars.

Genetic factors are important episodes, environmental factors are other important episodes, microbes are other important episodes, and possibly others. The deep understanding of these episodes and their interactions permits better management of the disease.

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