Deciphering the complex interplay of risk factors in type 2 diabetes mellitus: A comprehensive review

Samradhi Singh [a], Mona Kriti [a], Anamika K.S. [b], Devojit Kumar Sarma [a], Vinod Verma [c], Ravinder Nagpal [d], Dheeraj Mohania [e], Rajnarayan Tiwari [a], Manoj Kumar [a,*]

[a] *ICMR- National Institute for Research in Environmental Health, Bhopal Bypass Road, Bhauri, Bhopal, 462030, Madhya Pradesh, India*
[b] *Christ Deemed to Be University Bangalore, Karnataka, India*
[c] *Stem Cell Research Centre, Department of Hematology, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, 226014, Uttar Pradesh, India*
[d] *Department of Nutrition & Integrative Physiology, College of Health & Human Sciences, Florida State University, Tallahassee, FL, 32306, USA*
[e] *Dr. R. P. Centre, All India Institute of Medical Sciences, New Delhi, India*

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ABSTRACT

The complex and multidimensional landscape of type 2 diabetes mellitus (T2D) is a major global concern. Despite several years of extensive research, the precise underlying causes of T2D remain elusive, but evidence suggests that it is influenced by a myriad of interconnected risk factors such as epigenetics, genetics, gut microbiome, environmental factors, organelle stress, and dietary habits. The number of factors influencing the pathogenesis is increasing day by day which worsens the scenario; meanwhile, the interconnections shoot up the frame. By gaining deeper insights into the contributing factors, we may pave the way for the development of personalized medicine, which could unlock more precise and impactful treatment pathways for individuals with T2D. This review summarizes the state of knowledge about T2D pathogenesis, focusing on the interplay between various risk factors and their implications for future therapeutic strategies. Understanding these factors could lead to tailored treatments targeting specific risk factors and inform prevention efforts on a population level, ultimately improving outcomes for individuals with T2D and reducing its burden globally.

1. Introduction

Type 2 Diabetes Mellitus (T2D) is a prevalent metabolic condition found globally, affecting over 90 % of diabetes cases [1]. It is marked by inadequate insulin production from pancreatic islet β-cells, resistance to insulin in tissues, and a deficient compensatory response in insulin secretion [1]. Attributed to these pathophysiological factors, the condition leads to hyperglycemia i.e. inability of insulin secretion to maintain glucose homeostasis and hence there is a continual increase in blood glucose level [2]. Various anthropological factors, including age, body weight, body fat percentage, Waist-to-Hip Ratio, and Body Mass Index (BMI), and, along with lifestyle factors such as sedentary behaviors, high-calorie diets, obesity, and demographic shifts towards an aging population, have been identified as associated with the onset and advancement of the condition [3,4]. Factors such as epigenetic modifications, genetic predisposition, environmental pollutants, gut microbiota, dietary habits, and organelle stress are significant contributors to the onset and progression of this disease.

As per the International Diabetes Federation (IDF), approximately 537 million people were living with diabetes in 2021. Projections suggest this number will increase to 643 million by 2030 and 783 million by 2045 [5]. Alarmingly, approximately 45 % of individuals with diabetes remain undiagnosed, with the majority having T2D [5]. HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) and HOMA-B (Homeostatic Model Assessment of Beta-Cell Function) are two commonly used indices for assessing insulin resistance and beta-cell function respectively [6]. HOMA-IR offers a quantitative assessment of insulin resistance, determined by fasting insulin and glucose levels. Elevated HOMA-IR values indicate decreased insulin sensitivity, indicating peripheral tissue resistance to insulin. Conversely, HOMA-B evaluates pancreatic beta-cell function, essential for insulin secretion. Particularly in T2D, it assesses the capacity of beta cells to counteract insulin resistance [7]. A deterioration in beta-cell function significantly contributes to disrupted glucose homeostasis, a defining characteristic of T2D. The interplay between HOMA-IR and HOMA-B offers a comprehensive understanding of T2D pathogenesis. Elevated HOMA-IR

coupled with impaired HOMA-B indicates a scenario where insulin resistance is not adequately compensated by beta-cell function, potentially leading to T2D [8]. Consequently, assessing glucose metabolism and insulin resistance using both HOMA indices is crucial for the primary prevention of T2D, given the relatively slow progression of metabolic abnormalities. Incorporating these assessments into routine clinical practice is essential, allowing clinicians to tailor individualized management plans for patients. Simultaneous assessment of HOMA-IR and HOMA-B can enhance risk stratification, helping identify individuals at higher risk for T2D and informing preventive strategies. Regular monitoring of both indices can guide population-level interventions. The use of HOMA can be helpful in normal populations as it allows comparisons of β-cell function and insulin sensitivity with subjects with abnormal glucose tolerance, as well as the collection of longitudinal data in subjects who go on to develop abnormal glucose tolerance. The HOMA model has proved to be a robust clinical and epidemiological tool in describing the pathophysiology of diabetes, and it has already become one of the standard tools in the armamentarium of clinical physiologists [9–11].

Traditional diabetes care strategy focuses on maintaining the blood sugar levels through dietary changes and medication, which is often unsuccessful and patients may require a combination of therapies to achieve an optimized state. For instance, personalized medicine in diabetes management encompasses innovative approaches like fecal microbiota transplantation (FMT) alongside traditional methods. FMT, which involves transferring fecal material from a healthy donor to a recipient, holds promise as a novel therapeutic avenue for T2D patients. Emerging research suggests that the gut microbiome plays a pivotal role in metabolic health, including glucose metabolism and insulin sensitivity. Individuals with T2D often exhibit dysbiosis in their gut microbiota, characterized by an imbalance in microbial composition and function. By restoring a healthy gut microbiota through FMT, it is possible to positively influence glucose homeostasis and potentially improve insulin sensitivity in diabetic patients. This approach aligns with the principles of personalized medicine by addressing the unique microbial profile of each individual, thereby offering a tailored therapeutic intervention. Furthermore, biomarkers related to glycemic control, beta-cell function, inflammation, genetics, and adipokines play a
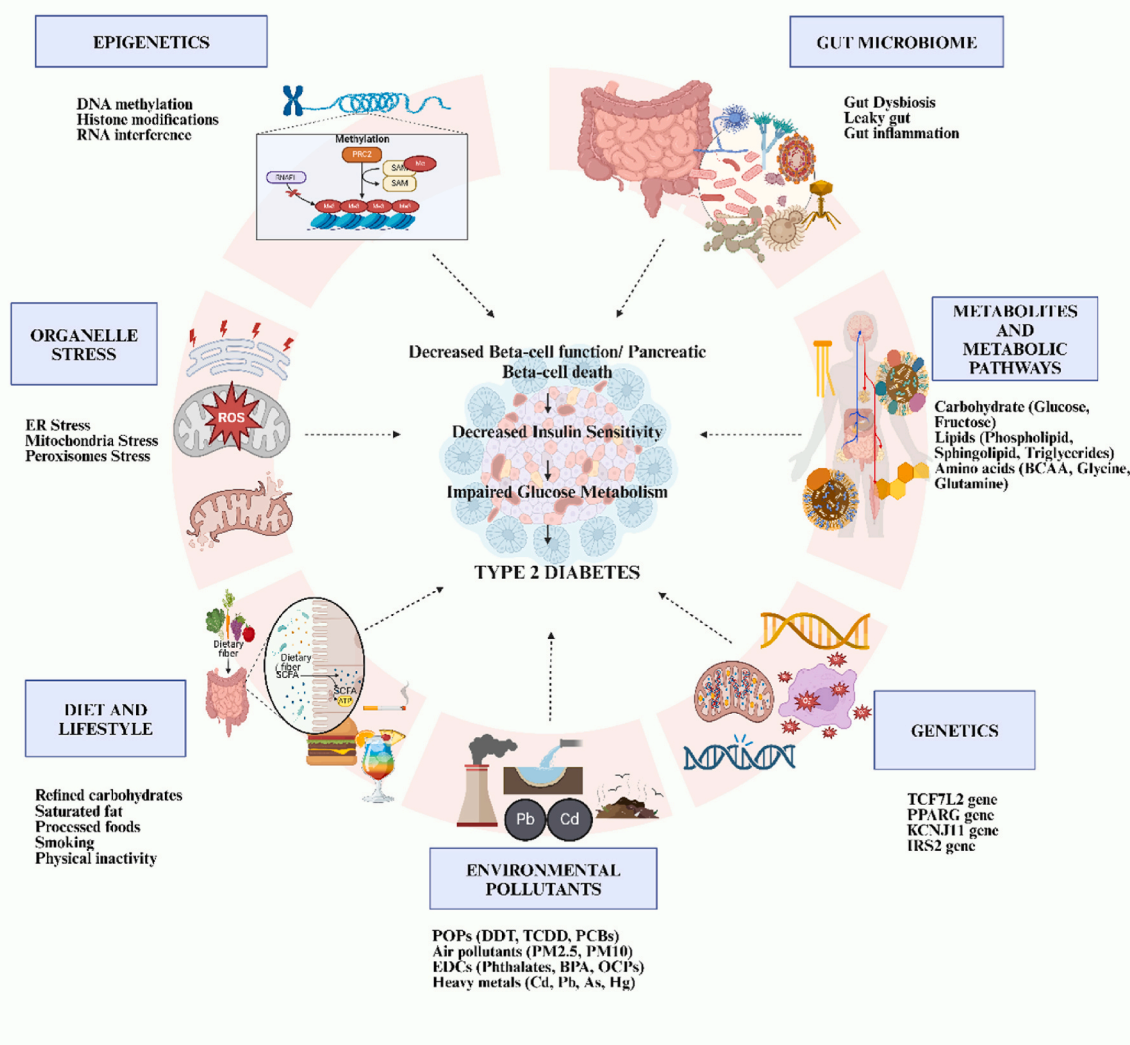

Fig. 1. The figure sheds light on the various factors that may contribute to the onset of Type 2 Diabetes and offers an understanding of the processes by which these factors work, making it easier to fully comprehend the intricate nature of the condition.

crucial role in predicting diabetes development and treatment outcomes. Integrating these biomarkers into predictive models enhances patient outcomes, improves treatment effectiveness, and establishes a more precise approach to managing diabetes. For example, personalized glycemic control—tailoring targets to individual patient needs—has been associated with favorable outcomes, including minimized hypoglycemia risk, improved quality of life, reduced diabetes complications, enhanced treatment adherence, and decreased healthcare costs [12–15]. Identifying biomarkers associated with health or disease poses an intriguing puzzle in tailoring personalized dietary plans. Clearly, when crafting a specific diet regimen, it becomes imperative to assess clinical indicators, genetic predispositions, and the microbiota composition to yield favorable outcomes, such as managing blood sugar levels in individuals with diabetes [15–17]. This article aims to delve into and analyze the current understanding of the factors contributing to the pathophysiology of T2D, with an emphasis on identifying potential areas for future research aimed at developing personalized treatments for individuals with T2D.

2. Factors leading to development of T2D

Several extrinsic and intrinsic variables contribute to the development of T2D. These factors encompass a wide range of genetic, environmental, lifestyle, and metabolic components that interact in a complex manner to predispose individuals to T2D. Understanding the intricate interplay of these factors is essential for developing effective therapeutic strategies for T2D management. By identifying the underlying mechanisms and pathways involved in T2D pathogenesis (Fig. 1), novel therapeutic targets can be elucidated.

2.1. Epigenetic regulation in the pathogenesis of T2D

Epigenetics refers to the process of altering gene expression without modifying the underlying DNA sequence. Although these epigenetic modifications can be reversed, they can be inherited through both mitotic and meiotic cell divisions [18]. DNA methylation, histone modification, and RNA interference are examples of epigenetic alterations that can occur naturally in response to environmental cues or genetic mutations that alter the enzymes that catalyze these modifications [19–21]. Epigenetic modifications usually interact and regulate each other, collectively forming a distinct epigenetic profile that alters genome function, notably gene expression, by modifying chromatin structure. This profile can either activate genes, by loosening chromatin and enabling transcription machinery access to DNA, or silence genes, by compacting chromatin and blocking DNA access [18]. Consequently, this epigenetic profile can impact gene expression across various cell types, developmental stages, and health conditions, including disease states [22].

When it comes to the development of complicated multifactorial diseases like T2D, environmental variables like nutrition and lifestyle can have a substantial impact on epigenetic consequences [23]. This is because environmental stimuli can activate or repress gene transcription by influencing pre-existing epigenetic marks in genes. The role of epigenetics in the development of T2D has been extensively studied, and several mechanisms have been implicated in its pathogenesis. One such mechanism is metabolic memory, which implies that target cells may be negatively impacted by prior glucose exposures for a considerable amount of time [24]. Epigenetic changes such as DNA methylation and histone modifications can alter gene accessibility by inducing either a condensed or open chromatin state, respectively [21]. Non-coding RNAs, such as miRNAs, can regulate gene expression and epigenetics. Epigenetic changes can occur at any stage during its lifetime and may even be inherited by future generations. Therefore, it is crucial to understand the role of epigenetics in T2D pathogenesis and identify potential therapeutic targets [24].

DNA methylation, which involves the addition of a methyl group to a cytosine residue in DNA [25], is an epigenetic modification that has been extensively studied concerning its role in the development of T2D. Various studies have demonstrated that the DNA methylation patterns are altered in individuals with T2D compared to healthy individuals, with specific CpG sites identified as differentially methylated in T2D patients [26]. For instance, Chambers et al. conducted a large-scale epigenome-wide association study (EWAS) that identified differential methylation of genomic DNA at five genetic loci associated with incident T2D in both Indian Asians and Europeans [27]. Similarly, Dayeh et al. found altered DNA methylation at CpG sites and genes, including TCF7L2, FTO, and KCNQ1, in human T2D Islets, which contribute to perturbed insulin and glucagon secretion [28]. Another study in the Botnia prospective cohort identified DNA methylation at two CpG sites in ABCG1 and PHOSPHO1 as being associated with future T2D risk. In control subjects, methylation of DNA at both loci in blood DNA was found to be correlated with various T2D clinical markers. Additionally, these altered DNA methylation were also found to be present in the T2D target cells namely pancreatic beta cells, skeletal muscles, liver, and adipose tissue [26].

Further research has revealed a link between the risk of T2D and DNA methylation at the PGC-1α gene, which is essential for energy metabolism and mitochondrial biogenesis [29]. Furthermore, pancreatic Islets from T2D donors were found to have enhanced DNA methylation and reduced expression of key genes such as INS, PDX1, PPARGC1A, and GLP1R, which were associated with impaired insulin secretion. High glucose and glycated haemoglobin (HbA1c) appeared to directly increase the DNA methylation of these genes [30–32]. Using the Illumina arrays, the DNA methylation of human adipose tissue, skeletal muscle, and liver from T2D patients and non-diabetic controls has also been investigated [33–38]. Globally, some genes like GLUT4, PPARγ, and IRS-1 have been observed to be hypermethylated and hypo-methylated in T2D subjects. Hypomethylation and hypermethylation are critical processes in which the former overexpresses and the latter represses the expression of specific genes; in concern with T2D the former is linked to insulin resistance and other aspects meanwhile the latter is linked to the dysregulation of insulin sensitivity, glucose metabolism and pancreatic function [33–38].

In general, hypo and hypermethylation of the promoter CpG island is correlated with transcriptional activation and silencing respectively. For example, hypermethylation of the promoter region of the PDX1 gene, which encodes a transcription factor critical for insulin secretion, has been associated with impaired insulin secretion and increased risk of T2D [39]. Additionally, the FTO gene, which is involved in the regulation of energy homeostasis, lipolysis, and nucleic acid demethylation displayed trivial but significant hypomethylation at a CpG site located in the very first intron of the gene in T2D patients compared with controls [40]. Taken together, these studies have identified various CpG sites with distinguished DNA methylation in T2D target cells, supporting the fact that epigenetics can play a key role in the pathogenesis of T2D. Although the exact mechanisms by which DNA methylation contributes to the development of T2D are not revealed completely, the DNA methylation patterns may lead to changes in gene expression that affect insulin signaling, glucose metabolism, β-cell function, and other key biological processes involved in the same.

Proteins called histones are essential for organizing DNA into chromosomes. Modifications of histones can alter gene expression by altering the structure of chromatin, which can make genes either more or less accessible to the transcriptional machinery. The nature of these modifications can be either activating, repressive, or inheritable. In individuals with T2D, if the balance of histone modifications is altered, it leads to changes in gene expressions that can further contribute to the advancement of the disease [41]. One of the main histone modifications associated with T2D is histone acetylation, which is an activating modification linked to increased gene expression. Histone acetylation is essential for insulin signaling and glucose metabolism. Insulin resistance and poor glucose homeostasis result from a reduction in histone

acetylation in T2D [42].

Histone methylation is another important histone modification associated with T2D. Histone methylation can either activate or repress gene expression, depending on the specific site and degree of methylation. In T2D, repressive histone methylation is increased at genes responsible for glucose metabolism, resulting in decreased gene expression and impaired glucose homeostasis [43]. According to a study, reduced global liver histone H3K9 and H3K23 acetylation, elevated levels of H3K4 mono-methylation, and elevated levels of H3K9 di-methylation are associated with the advancement of T2D [44]. The use of specific histone-modifying enzyme inhibitors might present a novel strategy to prevent and treat T2D. Other histone modifications, such as phosphorylation and ubiquitination, have also been associated with T2D [45]. For instance, histone phosphorylation is linked to increased gene expression responsible for inflammation and oxidative stress, both of which are associated with T2D [46]. It is therefore essential to comprehend the significance of epigenetic alterations in T2D in order to create novel techniques for the prevention and treatment of this disease, as there is a wealth of data confirming their involvement in the onset and progression of the condition.

A biological process known as RNA interference (RNAi) targets and destroys particular mRNA molecules to control gene expression. Research carried out across diverse ethnicities has revealed a correlation between polymorphisms in miRNA genes and T2D and its consequences [47]. One potential mechanism by which RNAi may contribute to the development of T2D is through the regulation of insulin signaling. Certain microRNAs (miRNAs), small non-coding RNAs regulating gene expression post-transcriptionally, are pivotal in RNAi, modulating proteins in insulin signaling, thereby influencing insulin resistance and glucose metabolism, as well as contributing to the development of pancreatic islets and the differentiation of insulin-producing cells [47, 48]. It has been demonstrated that downregulating IRS1 by miRNA-29a affects insulin signaling and plays a role in the emergence of insulin resistance [49]. The control of pancreatic beta cell function, whose abnormalities might result in altered insulin secretion, is another possible mechanism by which RNAi may contribute to the onset and progression of T2D. hsa-miR-126, found mainly in endothelial cells and important for blood vessel formation and wound healing, has been extensively studied as a potential biomarker. In people with T2D, levels of hsa-miR-126 are lower compared to those without diabetes or with impaired glucose tolerances [50–54]. This decrease in hsa-miR-126 levels can worsen with diabetes-related complications. However, with six months of treatment involving insulin, diet control, and exercise, the levels of hsa-miR-126 can increase [55].

Recent research has shown that certain miRNAs, such as miRNA-124a and miRNA-375, can regulate beta cell function by targeting genes involved in insulin secretion and glucose metabolism [56]. For example, downregulation of Mtpn by miRNA-375 has been shown to impair beta cell function and contribute to the development of T2D [56]. In β cells of pancreas, miR-29a is needed for normal exocytosis, but an enhanced levels are often associated with altered β-cell function [49]. In contrast, pancreatic β cell microRNA-26a alleviates T2D by improving peripheral insulin sensitivity and preserving β cell function [57]. One such classical study was done on type 2 diabetic mice and glucose intolerant patients where gene miR-21 was found to induce islet cells and promotes insulin secretion, thus supporting its role in the regulation of pancreatic β cell function in T2D [58]. Eight circulating miRNAs (miR-29a, miR-34a, miR-103, miR-107, miR-132, miR-142-3p, miR-144, and miR-375) were discovered to be potential biomarkers and to control functions like insulin secretion, signaling, and adipogenesis as a consequence of a meta-analysis of T2D miRNA expression profiling studies [59]. Reduced insulin production and secretion ability caused by increased exposure of these factors to β cells can lead to progressive β cell malfunction as several regulatory miRNAs are themselves controlled by changed glucose and fatty acid levels. High glucose levels boost the expression of miR-9, miR-15a, miR-133a, and miR-30d

while adversely regulating the expression of miR-375 [60–63]. For example, the expression of miR-146 and miR-34a is induced by higher fatty acid concentrations [56,64,65]. Although the role of RNAi in the development of T2D is still being studied, current research suggests that RNAi may regulate insulin signalling and beta cell functions thereby ensuring the potential of RNAi to be used therapeutically in T2D treatment. Abnormalities in the miRNA network may be significant in the aetiology of diabetes, as T2D has been associated with genetic variations in miRNA-encoding genes and miRNA binding sites in the 3′-UTR of mRNA-encoding genes [65]. Recently, researchers have found a cell-to-cell communication between beta-cells where exosomal miRNAs released by beta-cells is absorbed by neighbouring beta-cells thereby affecting their survival and activity [66].

Epigenetic information has the potential to be inherited across generations, suggesting that environmental factors may impact individuals not just directly but also indirectly through their parents, via intergenerational (IEI) and transgenerational epigenetic inheritance (TEI). Studies have shown that parental influence from nutritional imbalances can compromise the metabolic health of their offspring, potentially leading to obesity [67], through alterations in small RNA and DNA methylation in human spermatozoa [68]. However, detailed research on the exact mechanisms of TEI or IEI is constrained by ethical considerations and future implications in humans. The underlying processes through which IEI or TEI exerts its consequences encompass the modulation of offspring's pancreatic and adipose tissue programming via the epigenetic reduction of microRNA and DNA methylation levels in reproductive cells during developmental and functional differentiation [69]. Progress in comprehending the significance of epigenetics in T2D is expected to lead to improved interventions and treatments, potentially reducing the global prevalence of T2D. The question of whether the epigenetic alterations induced by today's sedentary lifestyle can be passed on to subsequent generations and reversed remains unanswered. In the pursuit of novel therapies for managing T2D, scientists have investigated the possibility of utilizing the reversibility of epigenetic modifications to restore healthy glucose metabolism. Recently, a diverse array of small molecules exhibiting both epigenetic and anti-diabetic properties have emerged. These compounds, often referred to as epigenetic drugs (or epidrugs), can be categorized based on their epigenetic effects. At present, extensive research is underway to investigate various inhibitors that target critical enzymes engaged in epigenetic alterations. These inhibitors include histone deacetylase inhibitors (HDACi), HDAC activators, histone acetyltransferase inhibitors (HATi), and inhibitors of microRNAs [70].

2.2. The genetics of T2D

T2D has a significant genetic component, with inheritance estimated between 20 % and 80 % whose evidences are recovered from various population, family, and twin-based studies [71,72]. More than 100 genetic loci linked to an elevated risk of T2D have been identified and reported through Genome-wide association studies (GWAS) [73]. These loci account for approximately 10%–15 % of the genetic predisposition to the disease and participate in various biological pathways which include beta-cell function, insulin secretion, and insulin resistance. The risk of T2D attributed to genetics does not stem from a single specific region but instead arises from the interaction of numerous genes distributed throughout the genome. Various genes have been identified in association with the development and progression of T2D, including TCF7L2, PPARG, KCNJ11, CAPN10, IRS-1, IRS-2, HNF1A, HNF1B, and HNF4A [74–77]. Different aspects of glucose metabolism, lipid metabolism, insulin sensitivity, and insulin secretion are influenced by these genes [76].

The other significant genetic component of T2D involves extranuclear inheritance. People with a family history of diabetes are more likely to develop the condition than those without it. Numerous studies have examined the relationship between maternal and paternal ancestry

and the onset of insulin resistance; individuals with a maternal family history of type 2 diabetes are more likely to develop the illness compared to those with a paternal family history. Numerous studies have examined the relationship between maternal and paternal ancestry and the onset of insulin resistance; individuals with a maternal family history of T2D are more likely to develop the illness compared to those with a paternal family history [71,78,79]. This is attributed to mitochondrial inheritance, where mitochondrial DNA (mtDNA) is passed from the mother to her offspring. Although the exact mechanism is still unknown, several studies have suggested that mtDNA has a direct role in insulin resistance via regulating energy metabolism [80].

The currently known genetic variants associated with T2D account for only a small portion of its heritability, indicating that other factors such as epigenetics, metabolites, and gut microbiome may also play a role in its development. A deeper understanding of the genetic mechanisms involved in T2D could pave the way for more effective treatments for this widespread and debilitating condition.

2.3. Metabolites implicated in the development of T2D

Metabolites are vital to many biological activities, such as energy production, signal transduction, and gene expression regulation. Research indicates that individuals with pre-diabetes or diabetes exhibit elevated levels of various metabolites compared to control subjects. These include carbohydrate metabolites like glucose and fructose, lipid metabolites such as phospholipids, sphingomyelins, and triglycerides, as well as amino acid metabolites like branched-chain amino acids (BCAAs), aromatic amino acids, glycine, and glutamine [81]. Gluconeogenesis, glycolysis, pentose phosphate, and the tricarboxylic acid cycle are among the metabolic pathways associated with T2D. Modifications to these pathways result in differences in glucose metabolism, including increased glucose production and decreased glucose utilization in T2D patients. It is not unexpected that patients with T2D have higher levels of fat-derived metabolites such as phosphatidylethanolamine (PE), phosphatidylcholine (PC), diacylglycerol (DAG), and lysophosphatidylcholine (LPC) because obesity is a risk factor for T2D [82].

Elevated levels of membrane sphingomyelin and sphingolipids especially ceramides are found to be positively correlated with fasting insulin and insulin resistance thus playing a vital role in the development and progression of T2D via modulating the pathways associated with insulin resistance, β-cell dysfunction, and inflammation [83,84]. They promote insulin resistance by the activation of anabolic enzyme Akt/PKB and inhibition of signals transmitted through phosphatidylinositol-3 kinase (PI3K) [85]. Ceramides also interfere with glucose uptake, alter the storage of nutrients like glycogen or triglyceride [86], activate protein phosphatase 2A (PP2A) [87,88], thereby activating and releasing proinflammatory cytokines [66]. The higher level of sphingolipids and VLDL particles [89,90] also impairs lipid metabolism, specifically in the liver, by impeding oxidation and encouraging fatty acid uptake [86], leaving behind an increased concentration of circulating fatty acids into the bloodstream and an amplified risk of T2D. In contrast, higher concentrations of n-6 fatty acids, particularly linoleic acid and HDL are associated with a reduced risk of T2D [89,91].

An elevated risk of T2D is associated with the concentration of apolipoproteins, the structural proteins of lipoprotein particles. One of the most reliable markers is the ratio of apolipoprotein B to apolipoprotein A1. Liposomal changes are a strong predictor of future poor insulin resistance and glucose intolerance [92]. In addition to alterations in lipoprotein metabolism, metabolic indicators linked to inflammation (GlycA) and lipolysis (glycerol) are also predictive biomarkers, showing that many pathways are impacted well before the start of T2D [93,94]. The long-term decline in insulin sensitivity and compromised post-load glucose levels were more clearly predicted by these metabolic abnormalities than by an increased likelihood of fasting hyperglycemia [89].

The BCAAs (isoleucine, leucine, and valine) and aromatic amino acids (phenylalanine and tyrosine) have consistently been identified as metabolite biomarkers for T2D [95]. Studies on the effects of BCAA supplementation in humans and animals have revealed that elevated circulating amino acid levels may cause insulin resistance by interfering with insulin signaling in skeletal muscle, which can lead to T2D. Furthermore, pancreatic accessory cell malfunction may arise from the combination of BCAAs and hyperinsulinemia. On the other hand, the TCA cycle may provide intermediates through BCAA catabolism, which could improve energy output [82].

A distinct viewpoint on the relationship between genes and environment in the development of T2D is provided by metabolomics. Studies on metabolomics have revealed changes in purine and pyrimidine metabolites involved in energy metabolism and DNA synthesis, which could contribute to the development and progression of T2D by impairing cellular function and altering energy metabolism [96–98]. It offers a useful tool for deciphering the disease's fundamental pathophysiology and locating prospective biomarkers and treatment targets. Subsequent research and thorough metabolic profile aid in clarifying the part metabolites play in T2D and in identifying new medications to focus preventative care on young, asymptomatic people who are at higher risk. To identify the underlying cause of T2D, it is crucial to concentrate on the application and implementation of metabolomics.

2.4. Contribution of environmental pollutants to the pathogenesis of T2D

Environmental pollutants are increasingly recognized as probable contributors to the risk of developing T2D in addition to genetic predisposition and lifestyle choices. These substances are anthropogenic and can persist and accumulate, leading to long-term exposure in humans and wildlife. Persistent organic pollutants (POPs), air pollution, and heavy metals are among the classes of environmental pollutants that have been linked to the development of T2D [99–101] (Fig. 2). Studies have also established associations between air pollution, residential noise levels, and area-level socio-economic deprivation with an enhanced risk of T2D [102–104], while neighborhood walkability and greenery are usually associated with a decreased risk of T2D [105].

A prominent environmental contaminant is persistent organic pollutants (POPs), which are manmade molecules that are resistant to degradation and capable of accumulating in the food chain. Stockholm Convention on persistent organic pollutants, 2001 identified and categorized some POPs namely PCBs, DDT, Dioxin, Heptachlor, Chlordane, and Aldrin as "Dirty Dozens". Reduced glucose uptake by adipose tissue, the liver, and the pancreas has been linked to TCDD, or 2,3,7,8-tetrachlorodibenzo-p-dioxin, an extremely toxic POP. This results in decreased insulin generation and release by the pancreatic beta cells [106–108]. Furthermore, pancreatic nitric oxide synthase (NOS) activity may be impacted by the beta cell dysfunction brought on by TCDD, which might potentially impair insulin secretion and metabolism [109]. Organochlorine pesticides and polychlorinated biphenyls (PCBs) are other types of POPs that have been linked to an enhanced risk of T2D due to their disruption of insulin signaling and impaired glucose metabolism [110,111].

Air pollutants, such as PM10, PM2.5, and NO2, have been extensively researched due to their detrimental impact on glucose metabolism and insulin resistance, with long-term exposure associated with a heightened risk of T2D [112,113]. PM2.5 exposure, in particular, has been associated with glucose homeostasis abnormalities, which are attributed to inflammation, insulin resistance, mitochondrial alterations, and other cardio-metabolic disorders that may contribute to the development of T2D [113]. The relationship between air pollution and inflammation is well-established in both in vivo and in vitro studies [103,114,115]. Moreover, a growing body of epidemiologic evidence indicates short-, medium-, and long-term exposure to air pollutants has been linked to increased inflammation, autonomic nervous system disturbances, oxidative stress, endoplasmic reticulum stress, apoptosis, and metabolic derangements such as glucose intolerance, decreased insulin
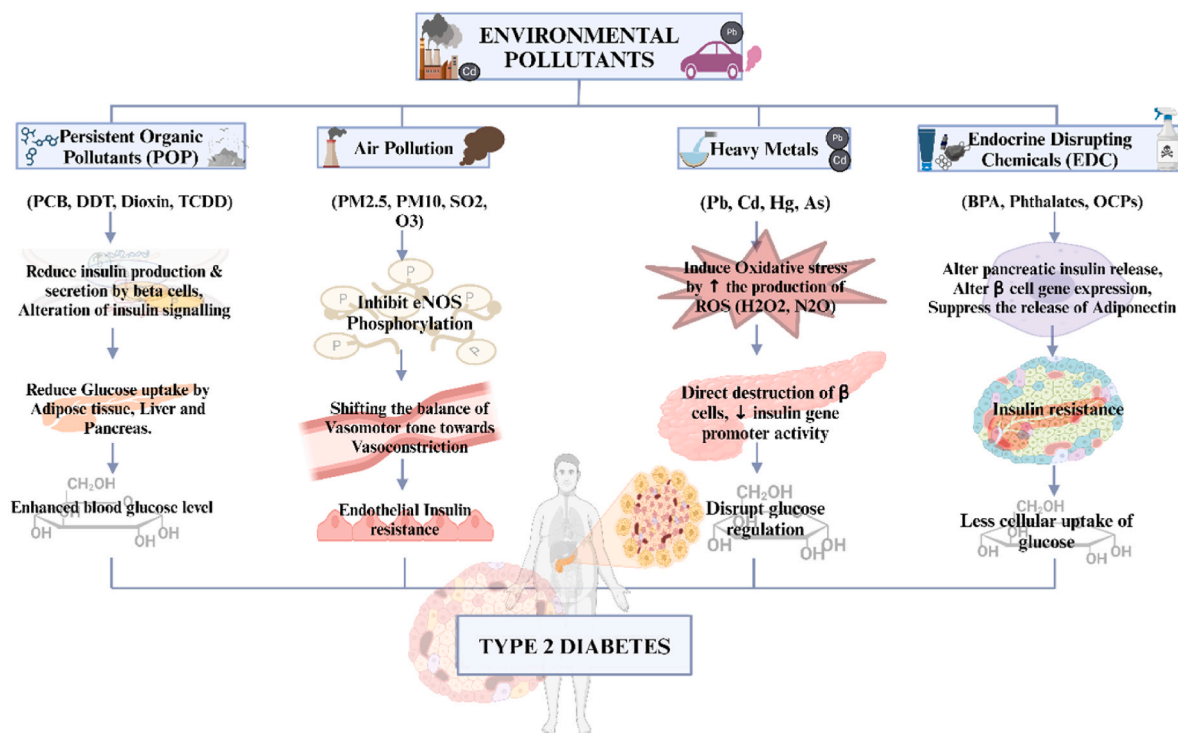
Fig. 2. Diagram showing how environmental pollutants like Persistent Organic Pollutants (POPs), air pollution, heavy metals, and Endocrine Disrupting Chemicals (EDCs) contribute to Type 2 Diabetes (T2D) development. Mechanisms include oxidative stress, inflammation, insulin resistance, and β-cell dysfunction, leading to T2D onset.

sensitivity, impaired insulin secretion, and elevated blood lipid concentrations [103,115–117].

There is proof that exposure to specific metals, such as arsenic (As), mercury (Hg), cadmium (Cd), and lead (Pb), causes T2D. This exposure can occur through contaminated food and water, inhalation of polluted air, and occupational exposure [99,118,119]. As, Cd, Hg, and Pb are among the hazardous metals that can cause oxidative stress by boosting the generation of reactive oxygen species (ROS), which include nitric oxide, hydrogen peroxide, and superoxide radicals. The destruction or malfunction of pancreatic islet β-cells and the disruption of glucose control caused by these ROS can directly result in T2D. Toxic metals can cause oxidative stress in pancreatic islet β-cells, reducing insulin gene promoter activity and mRNA expression, hence altering the associated molecular pathways governing glucose regulation and the kinetics and functions of the cell [120]. This can reduce insulin release, impair insulin receptors and glucose uptake, decrease peripheral glucose utilization, induce gluconeogenesis, and increase pancreatic glucagon release and hepatic glycolysis all of which could contribute to the pathophysiology of T2D [120–123]. Heavy metal exposure can also lead to impaired liver and kidney function, reduced pancreatic and muscle function, and elevated blood glucose levels. Certain heavy metals, both toxic (e.g., Cd, As, Pb, Hg) and essential (e.g., Cu, Co, Cr, Ni, Se), known as metalloestrogens, can alter enzyme structure, induce hormonal imbalance by harming the pancreas and adrenal glands, thereby potentially escalating diabetes risk through endocrine disruption [124]. Balanced levels of essential metals are crucial for healthy glucose metabolism, as deficiencies or excesses can damage pancreatic islet cells and contribute to diabetes development; additionally, essential trace metals, with their antioxidant properties, can mitigate the harmful effects of toxic metals, safeguarding pancreatic islet β-cells from harm, highlighting the vital role of their antagonistic interaction in preserving insulin balance and lowering the likelihood of T2D [125].

Endocrine-disrupting chemicals (EDCs) such as bisphenol A (BPA), phthalates, and organochlorine pesticides (OCPs) are a group of chemicals, either natural or man-made, that can interact with estrogen, androgen and progesterone receptors due to their structural similarity to steroid hormones. This can interfere with various aspects of the endogenous hormone's roles, including synthesis, metabolism, transport, elimination, and receptor binding [126]. Such interference can raise the risk of metabolic and endocrine illnesses in both people and animals, including T2D [127]. Studies have shown that BPA, a xenoestrogen [128] which is commonly found in plastic products, regulates the physiological pathways involved in the development of T2D [126]. It has the ability to control the production and release of pancreatic insulin, as well as modify the electrical activity, gene expression, and survival of β-cells [129]. It has also been shown to inhibit adiponectin secretion and stimulate proangiogenic effects on the endothelial cells. Adiponectin has insulin-sensitizing, anti-inflammatory and anti-atherogenic characteristics, and low levels of adiponectin have been associated to insulin resistance and T2D [129].

Phthalates, another class of chemicals widely used as plasticizers, may elevate the possibility of T2D by triggering oxidative stress, elevating inflammatory markers, impairing adiponectin levels, and inducing β-cell dysfunction. activating peroxisome proliferator-activated receptors [130]. These receptors regulate lipid and glucose homeostasis and, when activated by phthalates, they impair the development of pancreatic β-cells [131]. Human studies suggest that phthalates cause insulin resistance by activating PPARγ and increasing oxidative stress levels. These chemicals cause oxidative stress in hepatocytes and adipocytes, which disrupts glucose and lipid metabolism and eventually leads to insulin resistance [132,133].

Exposure to OCPs can disrupt the endocrine system, potentially increasing the risk of developing diabetes by affecting glucose metabolism, insulin resistance, and β-cell destruction. Exposure to both individuals and a mixture of OCPs has been associated with an elevated risk of T2D. Testosterone levels and androgen receptor methylation (ARm) act as mediators and moderators in the relationship between OCP exposure and T2D [134,135].

Perfluoroalkyl substances (PFAS) are chemicals usually present in various consumer products, such as non-stick cookware and waterproof

clothes; which is associated with the increased risk of T2D [136]. The precise mechanism by which PFAS contributes to diabetes risk is not fully understood, but it is thought to be involved in the disruption of glucose metabolism and insulin signaling. Further studies could shed light on the involvement of EDCs and other pollutants in the pathogenesis of T2D, as well as suggest measures to attenuate their effects on T2D.

The potential interventions or policy measures to mitigate exposure to harmful environmental factors, which can be used as a preventive strategy against T2D includes conducting detailed longitudinal observational studies to assess environmental exposures over time, considering factors beyond residential settings and activity space of individuals. Also, the study of mobility pattern combined with behavioural insights on use of food retailers and food delivery services could provide valuable information regarding the exposure and effect of environmental pollutants on the health of an individual. Additionally, the exposure assessment in cohorts could be improved using regression calibration techniques or the assessment should be improved by incorporating relevant exposure measures in follow-up questionnaires. Furthermore, addressing methodological challenges in the social environment research, such as inconsistent conceptualizations of the environment, long time lag between exposure and impact on T2D development, structural interventions, difficulty in distinguishing various social phenomena and risk accumulation over the life course can enhance our understanding of the link between social factors and risk of T2D. These studies will contribute to urban planning efforts aimed at creating a healthier living environment [137]. Additionally, five complementary activities like-awareness, adjustment, assistance, alignment, and advocacy can be implemented for better integration of social care into health care delivery [138].

2.5. Understanding organelle stress and its impact on T2D development

Recent studies have highlighted the involvement of organelle stress and dysfunction in the development of T2D [139,140]. Some organelles, responsible for energy production, protein synthesis, and signaling such as endoplasmic reticulum (ER), mitochondria, and lysosomes, have crucial roles in cellular metabolism and homeostasis [141]. Their stress and dysfunction can result in cellular impairment and contribute to T2D development. Although the mechanism behind organelle stress and dysfunction in T2D are intricate and not fully understood, several factors such as oxidative stress, inflammation, and intracellular signaling disruption have been suggested for the same.

The ER is an essential organelle involved in calcium homeostasis, lipid synthesis, and protein synthesis and folding [142]. "ER stress," which is caused by an increase in the need for protein synthesis or by the build-up of misfolded proteins, also known as harmful conformations, in the ER, sets off a cascade of events known as the unfolded protein response (UPR). By reducing global protein synthesis, accelerating the breakdown of misfolded proteins, encouraging chaperone synthesis, raising ER membrane volume, and inducing cell death, the conserved transcriptional and translational pathway known as the UPR helps the body deal with ER stress. Pancreatic beta-cell survival, inflammation, insulin resistance, and lipogenesis are all correlated with ER stress and UPR [142]. ER stress and UPR have the potential to impact both peripheral insulin resistance and faulty insulin secretion, the two main pathophysiological characteristics of T2D [142].

The mitochondrion is an organelle that plays an important role in energy production and fatty acid oxidation. It is also a master regulator of insulin secretion and mutations in mitochondrial DNA that have been linked to the development of T2D. Insulin resistance and type 2 diabetes are frequently accompanied by decreased fatty acid β-oxidation and mitochondrial phosphorylation in the liver and skeletal muscle [142, 143]. Furthermore, these people typically have lower expression levels of genes linked to oxidative phosphorylation and mitochondrial biogenesis [144–146]. Defective mitochondria can result in increased

superoxide production and buildup of triglycerides and fatty acid intermediates (DAG, ceramides) in skeletal muscle, and liver, activating PKC-θ, a serine/threonine kinase that attenuates insulin signaling [147, 148].

Peroxisomes are organelles that work with other metabolic organelles like mitochondria and endoplasmic reticulum to manage ROS and lipid metabolism [149]. According to recent research, peroxisomes are essential for maintaining energy homeostasis, and impairment of peroxisomal activity raises the risk of obesity and related metabolic diseases, such as T2D. Investigating the role of peroxisomal ROS production and other metabolic processes might lead to the development of novel methods for diagnosing and treating obesity and diabetes. Furthermore, Lysosomes are responsible for breaking down and recycling cellular components; whose dysfunction can lead to the accumulation of damaged cellular components and impaired autophagy, which can contribute to the development of T2D [150]. Further research is necessary to appreciate the mechanisms by which organelle dysfunction leads to T2D development and to discover potential interventions to mitigate their effects.

2.6. Gut microbiome and T2D pathogenesis

The gut microbiome, which is comprised of microorganisms that reside in the human gut, interacts with host metabolism through various mechanisms, such as the production of metabolites, regulation of energy homeostasis, and modulation of host immune responses [151]. Dysbiosis, or alterations in gut microbiota composition and function, can disrupt these interactions, leading to metabolic dysfunction. These changes have been associated with increased inflammation, impaired gut barrier function, altered incretin secretion, and bile acid metabolism [152]. Ultimately, these changes can result in obesity, metabolic syndrome, and T2D by impairing glucose tolerance and promoting insulin resistance. Changes in the composition of the gut microbiota have been shown to be strongly associated with the development of T2D in numerous studies [153,154]. In particular, an imbalance in the Bacteroidetes/Firmicutes ratio has been associated with an altered production of butyrate. This butyrate acts as a histone deacetylase (HDAC) inhibitor and have a significant role in β-cell differentiation and proliferation thereby improving insulin secretion and sensitivity. Also, these HDAC controls the expression of glucose-6-phosphate thus alleviating hyperglycemia. Additionally, butyrate plays a crucial role in glucogenesis by stimulating the release of glucagon-like peptides (GLP-1 and GLP-2) from the intestinal L-cells which induces regeneration of pancreatic β-cells, subsequently activating G protein-coupled receptors (GPCRs) in β-cells, thereby inhibiting inflammation and enhancing gut permeability [155,156]. On the other hand, it has been discovered that certain bacteria offer protection by lowering the risk of diabetes by maintaining gut barrier integrity and decreasing proinflammatory indicators. Among them are *Bacteroides fragilis, Lactobacillus fermentum, Roseburia intestinalis, L. plantarum, L. casei,* and *Akkermansia muciniphila* [156]. Several studies have indicated that the gut microbiota may impact the effectiveness of some anti-diabetic drugs either by enhancing or reducing the efficacy. As a result, there is rising interest in personalized medicine strategies that take into account each patient's unique gut microbiota composition when creating T2D therapy regimens It is significant because certain drugs have been shown to affect the gut microbiota, such as metformin, a drug that is frequently used to treat diabetes. By altering inflammation, glucose metabolism, gut permeability, and the quantity of bacteria that produce short-chain fatty acids (SCFAs), metformin appears to interact with the gut microbiota [156]. Additionally, this increases the ability of individuals with diabetes-related gut dysbiosis to catabolize amino acids by encouraging the formation of butyrate and propionate [157]. These modifications may help to enhance the effects of metformin on glucose metabolism and homeostasis, combined with an increase in the number of *Akkermansia muciniphila* in the gut [158].

The relationship between gut microbiota dysbiosis, chronic low-grade inflammation, oxidative stress, and T2D appears to involve common metabolic factors. Studies have indicated that the gut microbiome can affect host metabolism by producing certain metabolites, including trimethylamine-N-oxide (TMAO), SCFAs, and metabolites derived from tryptophan. The changes in the levels of these metabolites have been associated with the pathogenesis of T2D [159]. Previous studies have shown that diabetic patients have lower levels of SCFAs, including acetate, propionate, and butyrate, compared to healthy individuals [160]. SCFAs may affect T2D through various mechanisms, such as promoting insulin secretion, improving insulin sensitivity, activating intestinal gluconeogenesis, increasing energy expenditure, and reducing fat accumulation and inflammation [159]. Additionally, SCFAs can also bind to Free Fatty Acid Receptor FFAR2 or FFAR3 present on the intestinal cells thereby stimulating the release of glucagon-like peptide-1 (GLP-1) and peptide YY, which are known to promote insulin secretion and reduce glucagon release [161]. The gut microbiota also plays a significant role in bile acid (BA) metabolism. Microbial enzymes can transform conjugated BAs in the intestine into secondary BAs, such as deoxycholic acid (DCA), lithocholic acid (LCA), and ursodeoxycholic acid (UDCA) [162]. These secondary bile acid binds to the farnesoid X receptor and release fibroblast growth factor, FGF19/15, which further promote insulin sensitivity and glucose tolerance [161]. While, according to a study, altered BAs in diabetic rats showed detrimental effects on glucose metabolism, indicating that BA metabolism may play a role in the development of T2D [163]. Another bacterial component Lipopolysaccharide (LPS), is well documented to induce low-grade inflammation. Numerous studies have reported an enhanced levels of LPS in the peripheral circulation of T2D patients. LPS binds to Toll-like receptor 4 (TLR4), prompting macrophage clustering and activation of the NF-κB signaling pathway thereby promoting the secretion of inflammatory factors and ultimately inhibiting insulin secretion [161, 164]. The synthesis of TMAO by gut bacteria from dietary choline and L-carnitine has been documented in a number of studies [165,166]. This molecule is also associated with lower hepatic glucose transport, insulin resistance, adipose tissue inflammation, hepatic gluconeogenesis, and poor glucose tolerance. Additionally, it might decrease the amount of hepatic glycogen and the mRNA expression of anti-inflammatory cytokines while raising the HOMA-IR index and pro-inflammatory cytokine mRNA expression [167].

A higher risk of T2D has also been associated with a number of other microbial metabolites, including xanthurenate, creatine, urate, xanthine, 2-hydroxyhippurate, 3-(4-hydroxyphenyl)lactate, and 2-hydroxybutyrate [168]. But further research is needed to determine the precise processes by which these metabolites impact T2D and the connection that exists between them and the disease. There is growing evidence that the metabolites and composition of the gut microbiota can be influenced by dietary practices, which can have an impact on human health and disease. For example, a diet high in fiber can dramatically raise levels of butyric acid by favorably promoting the growth of specific bacteria that make SCFAs. This increase in butyric acid has been linked to higher levels of GLP-1, a decrease in HbA1c, improved glucose homeostasis, and the inhibition of pro-inflammatory microorganisms. These effects can promote metabolic control in patients with T2D [159].

By focusing on the gut microbiota and microbial metabolites, randomized controlled trials (RCTs) have shown the advantageous benefits of probiotics, prebiotics, or synbiotics in ameliorating T2D. Through the synthesis of SCFAs or SBAs, these effects include improving glucose homeostasis, decreasing inflammation, and increasing insulin sensitivity, indicating their potential as adjuvant therapy in addition to pharmaceutical treatments for improving glycemia and insulinemia [159,169–171]. Research on animals has demonstrated that the use of probiotics such as *Lactobacillus, Bifidobacterium, Clostridium,* and *Akkermansia* leads to noteworthy enhancements in insulin resistance metrics. These interventions also ameliorate lipid profile, inflammatory and oxidative markers, SCFAs production and microbiota composition

[172]. In a clinical trial, supplementation with the multiprobiotic "Symbiter" (a concentrated biomass of 14 probiotic bacterial genera including *Bifidobacterium, Lactobacillus, Lactococcus, and Propionibacterium*) for 8 weeks resulted in a significant reduction of HOMA-IR and HbA1c, and modestly improved insulin resistance in patients with T2D [173].

Moreover, promising results have been observed in fecal microbiota transplantation (FMT) for improving metabolic diseases. In T2D patients, FMT has shown to alleviate hyperglycemia, improve insulin resistance, attenuate pancreatic β-cell apoptosis, inhibit chronic inflammation of pancreatic tissue, and increase the levels of SCFA-producing bacteria [159]. Since the efficacy of FMT relies on donor's profile, there are strong chances of development of other related disorders by the recipient. In a case study [174], FMT lead to the onset of obesity in female CDI patient post procedure when the donor exhibited corpulence. Fecal filtrate transplantation (FFT) also called fecal virome transplantation (FVT) a refined method that removes fecal bacteria and reduces the FMT associated risks can be used alternatively. Additionally, phage therapy also holds the potential and offers a targeted approach for the modification of individual bacterial species in the gut. However, different parameters regarding phage selection, administration, resistance, dosage, pharmacokinetics and pharmacodynamics needs to be studied more.

2.7. Role of diet and lifestyle in T2D pathogenesis

The development of T2D is highly influenced by dietary factors and nutrient deficiencies. Epidemiological studies have consistently shown that dietary patterns high in refined carbohydrates, saturated fats, and processed foods, and low in fiber, antioxidants, and micronutrients, are linked with an enhanced risk of developing T2D [175,176]. On the other hand, a high intake of whole grain products and total fiber has been linked with a decreased incidence of T2D, supported by high and moderate-quality of evidence, respectively. Whole grain and cereal fiber intake have been linked to greater insulin sensitivity, lower fasting insulin concentrations, lower concentrations of inflammatory markers such as CRP, and higher concentrations of the cytokine adiponectin, which is associated with a reduced incidence [177].

Micronutrients, such as vitamins and minerals, are essential for maintaining homeostasis, regulating enzymes, and influencing the development and progression of chronic diseases like diabetes. These malfunctions can include dysfunction of pancreatic β-cells, B-cell death, decreased islet cell populations, impaired tyrosine kinase activity, and oxidative stress. Additionally, deficiencies can cause decreased lean body mass, defective insulin signaling, and enhanced protein kinase C activity. Vitamins A, C, D, E, and B vitamins are of chief importance in the onset and pathogenesis of T2D [178]. Vitamin A enhances β-cell formation and glucose metabolism. B-vitamins supplementation can improve metabolic control by reducing homocysteine levels, which prevents oxidative stress, endothelial dysfunction, β-cell dysfunction, and peripheral insulin resistance [178]. Vitamin D can prevent auto-immunity and promote insulin uptake in cells and systems and its deficiency is a risk factor for the development of diabetes due to its function in insulin secretion and sensitivity [179]. Vitamin E can reduce free radicals and CRP, prevent lipid peroxidation, and improve insulin function. Deficiencies in these vitamins can result in β-cell abnormalities, insulin resistance, and insulin insufficiency [180]. The prolonged use of Metformin, the first-line drug for uncomplicated diabetes, can decrease the absorption of folic acid and vitamin B12, leading to deficiencies that may need to be supplemented regularly [181]. In addition, minerals such as zinc, magnesium, and selenium may have a protective effect against T2D by reducing oxidative stress and inflammation [182].

Trace elements are necessary for the body's growth, development, and metabolic processes. It has been demonstrated that trace element nanoparticles, particularly those based on Cu, Cr, Se, Mg, Zn, and Fe can

effectively manage diabetes through a variety of mechanisms, including lowering blood sugar levels, increasing insulin secretion, enhancing insulin sensitivity and glucose tolerance, optimizing lipid profiles, and producing anti-inflammatory and antioxidant effects [183]. Effective treatments for diabetes may be provided by using trace element nanoparticles as dietary supplements or nanomedicines.

In addition to these dietary habits and nutrition deficiencies, lifestyle choices make a significant difference in the development and advancement of this disease. Smoking is a significant contributor to T2D, with smokers being 30%–40 % more likely to develop the condition compared to non-smokers [184,185]. Those with diabetes who smoke often experience challenges in insulin management. Research shows elevated insulin levels and varying degrees of insulin resistance among smokers, while quitting smoking significantly improves insulin sensitivity [185]. Cigarette smoking induces rapid changes in glucose regulation in young healthy adults. The risk of developing T2D increases by 16 % for every additional 10 cigarettes smoked per day. While the risk remains elevated for those who quit smoking within the past 5 years, it gradually decreases with longer periods of cessation. After 10 years of not smoking, the risk level becomes comparable to that of individuals who have never smoked [186]. The relationship between smoking and insulin resistance is frequently reported but the underlying mechanisms are not fully understood. However, studies show that nicotine stimulates catecholamine-mediated glucagon release from the adrenal medulla, which further increases gluconeogenesis thus causing hyperglycemia [187]. In another cell culture study, it was recapitulated that nicotine stimulated p44/p42 MAPK and mTOR signaling pathway thereby causing insulin resistance and glucose intolerance. Additionally, it was found that smokers had greater IRS-1[ser636] phosphorylation as compared to non-smokers which may be implicated in the insulin resistance of smoking [188]. On the contrary, some studies have found no notable association between smoking and insulin resistance in healthy individuals suggesting that smoking may result in transitory stimulation of these pathways or are both the outcomes of underlying pathophysiological mechanisms that are not entirely elucidated thus challenging the prevailing notion of smoking as a key risk factor for insulin resistance [187,188].

Being overweight, often indicated by a BMI of 25 or higher, significantly heightens the risk of developing T2D. Even individuals with a normal BMI can face increased risks if they have a large waist circumference, as it correlates with higher fat levels in the abdomen and is associated with diabetes and heart disease [189]. To mitigate these risks, individuals with overweight or obesity can consider weight loss and increased physical activity to prevent or delay the onset of T2D. Regular aerobic exercise aids in blood glucose management, while resistance exercise enhances insulin sensitivity, particularly in individuals with T2D. Breaking up prolonged sitting with movement throughout the day benefits both blood glucose levels and insulin. Engaging in physical activity following meals helps lower blood glucose levels. Additionally, exercising later in the day can improve glycemic control and insulin sensitivity [190]. According to The American College of Sports Medicine and the American Diabetes Association, it is beneficial to walk moderately for at least 150 min/wk to vigorous physical activity for patients with T2D to improve glycemic control and reduce the mortality. Additionally, walking for at least 30 min per day is reported to reduce the risk of T2D by approximately 50 % and significantly improve glucose tolerance. While, a normal walking pace (3.2–4.8 km/h) is associated with an approximate 20%–30 % reduction in the risk of T2D in women who are not engaged in vigorous physical activities [191,192]. Similarly, walking at least 10000 steps/d combined with diet therapy in obese patients with T2D can improve their insulin sensitivity. Furthermore, the way of walking also holds significance with respect to glycemic control. For example, free-living interval-walking improve maximal oxygen consumption, decreased fat mass and visceral fat and fasting insulin, whereas no changes were reported in the continuous-walking group [193]. Additionally, the most common physical activities such as walking, housework, and gardening can improve the health-related quality of life [194]. Adopting a balanced diet and healthy lifestyle choices, coupled with appropriate medication, can effectively manage T2D, akin to managing other aspects of one's life.

3. Interconnected factors contributing to the development of T2D

Although various factors including epigenetics, genetics, metabolites, and gut microbiome have been linked to the onset of T2D, it is now apparent that these factors do not operate independently. In fact, their interactions are complex and contribute to the development and advancement of the disease that is not yet comprehended. Epigenetic changes can be affected by genetic, environmental, and metabolic factors, while genetic variations can affect gene expression and protein function, leading to metabolic changes and altered gut microbiome composition. Metabolites can modulate epigenetic changes, gene expression and gut microbiome composition, which in turn, can influence host metabolism. For instance, epigenetic changes can affect gene expression in detoxification pathways, immune function that cause insulin resistance and dysbiosis respectively [195]. Genetic variations can impact an individual's vulnerability to the harmful consequences of environmental pollutants while epigenetic modifications can modify the effects of both genetics and environmental factors [196]. Moreover, gut microbiota dysbiosis can alter epigenetic marks, further exacerbating the effects of genetic and epigenetic factors [197,198]. For example, variations in the amount of SCFAs, which are produced by gut bacteria, as a result of gut dysbiosis can cause epigenetic modifications in the host that affect lipid and glucose metabolism. In addition to having physiological and epigenome-regulatory impacts in a variety of tissues, SCFAs are essential for supplying the daily energy needs of tissues. They play a mediating role in the relationship between the commensal microbiota and the host genome's epigenetic alteration, which causes illnesses like T2D [199]. In comparison to acetate and propionate, which selectively inhibit HDAC2 and HDAC3, respectively, butyrate is a very strong natural HDACi that selectively suppresses HDAC1/2 activity [200,201]. Obese and T2D patients have lower microbiota diversity and a shortage of *Faecalibacterium prausnitzii*, which results in considerably lower methylation on the promoter area of the SCFA receptor GPR41/FFAR3 in individuals [202]. Inflammation induced by dysbiosis can also cause epigenetic modifications that affect insulin sensitivity and glucose metabolism [203].

Environmental factors like infectious pathogens, endocrine disruptors, heavy metals, Polycyclic aromatic hydrocarbons (PAHs), outdoor pollutants, and indoor allergens can induce epigenetic alterations through exposure or as a consequence of illness. Environmental pollutants can modify DNA methylation patterns, miRNA levels, or cause histone modifications, which can alter gene expression patterns involved in glucose and lipid metabolism, leading to the development of T2D [204]. Environmental pollutants can have a detrimental impact on organelle function, including mitochondrial dysfunction, which can disrupt the balance of reactive oxygen species and energy regulation [205]. This organelle stress can worsen the toxic effects of environmental pollutants and contribute to the development of insulin resistance and T2D. For example, the correlation between ER stress indicators and OCPs indicates that genetic susceptibility and environmental exposure interact. Increased OCP in visceral adipose tissue may cause ER stress-related genes to become active [206]. This study underscores the possible involvement of OCPs in the onset of T2D by disturbing the ER stress pathway. Additionally, these pollutants can disrupt the gut microbiota and contribute to dysbiosis, which can alter the metabolism of environmental pollutants and exacerbate their toxic effects, leading to an enhanced risk of developing T2D. Dysbiosis can also increase intestinal permeability, or "leaky gut," allowing environmental pollutants to move into the bloodstream and cause systemic inflammation and insulin resistance [207]. This, in turn, can further induce

organelle stress and contribute to elevated insulin resistance and glucose intolerance. Conversely, organelle stress can lead to alteration in gut microbiota composition and function, which can further exacerbate metabolic dysfunction [208]. In addition, epigenetic modifications can also play a role in causing organelle stress in diabetes. For example, alteration in DNA methylation in genes that regulate mitochondrial function and the endoplasmic reticulum stress response can lead to their dysfunction and the possible onset of the disease [209]. Additionally, the gut microbiome may act as an indicator of exposure to environmental pollutants and the likelihood of T2D development [210]. Thus, it could serve as a valuable diagnostic tool for evaluating T2D risk in individuals exposed to environmental pollutants.

4. Conclusion and future prospects

Diabetes is a high-concern disease which is prevalent all over the world. Even though other diabetes is there, the intertwined connection of diabetes to factors other than genetics paves a new way to seize them. Due to numerous factors of which some are obscure, it is quite hard to tackle the disease. Researchers are trying to realize the underlying mechanism and the interplay that differs from person to person. Genetics, epigenetics, exercise, food, gut microbiota, metabolites, and lifestyle all play a part in the complex and multidimensional character of T2D. To create novel treatments and preventative measures for T2D, this research is essential.

The hypothesis that a microbiome-gene-environment interaction underlies the development of T2D suggests that personalized interventions targeting the microbiome, genetics, and environmental factors may be more effective than traditional one-size-fits-all approaches. Conventional approaches to diagnosis and treatment have shown limited effectiveness, failing to consider the inherent complexity and heterogeneity of these disorders. In recent years, personalized medicine has emerged as a transformative approach, aiming to customize medical interventions based on an individual's distinct genetic, molecular, and clinical characteristics. To achieve this, interdisciplinary team-based interventions can be implemented, exercise plans, customized nutrition and diet recommendations, tailored medication choices, individualized health equity considered, and regular monitoring and feedback provided. By combining evidence-based approaches with personalized care, we can optimize T2D management and improve patient outcomes. Dietary factors that need to be adjusted for in microbiome analysis can be found by comprehending how nutrition affects drug metabolism mediated by the microbiota. To improve medication efficacy, individualized food advice may be suggested during pharmacological treatment.

Leveraging advanced omics technologies, personalized medicine offers an in-depth understanding of metabolic disorders and has the potential to revolutionize their treatment. To facilitate the integration of omics-based personalized diabetes therapies into clinical practice, it is essential to develop comprehensive algorithms and guidelines validated through clinical trials. Moreover, artificial intelligence (AI), particularly machine learning (ML) and deep learning (DL), can significantly enhance personalized medicine in diabetes by supporting clinical decision-making processes and optimizing therapeutic regimens for individual patients. These technologies can analyze complex datasets to predict patient responses to treatments, thereby enabling more precise and effective management of diabetes. AI provides for precision diabetes medicine by generating risk prediction models that incorporate individual variations and integrate diverse data sources to comprehensively assess an individual's health status, predisposition, and response to treatment. These tailored treatments consider a range of factors, including genomic variations, omics-based tests, and various contributing elements such as age, gender, race, family history, geography, immune profile, metabolic profile, gut microbiome, and environmental vulnerability. This approach prioritizes the unique biological makeup of the individual over the generalized population biology throughout the patient's medical journey. Additionally, biomarkers like protein expression, gut microbiome composition, and metabolic profiles are integrated with ML to enhance the precision of tailored treatments.

The combination of omics technologies and AI algorithms holds significant promise for advancing the treatment of T2D. These advanced methodologies can lead to more personalized and effective management strategies. However, before these approaches can be widely adopted in clinical practice, several key questions must be addressed. It will require collaborative efforts among researchers, clinicians, and policymakers to tackle these challenges and ensure the safe and effective implementation of these innovations. With continued development and refinement, omics-based personalized medicine has the potential to revolutionize the diagnosis, treatment, and prevention of T2D, leading to improved patient outcomes and more efficient healthcare delivery.

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Not applicable.

Consent for publication

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CRediT authorship contribution statement

Samradhi Singh: Writing – original draft, Visualization, Conceptualization. **Mona Kriti:** Writing – review & editing, Validation, Data curation. **Anamika K.S.:** Writing – review & editing, Data curation. **Devojit Kumar Sarma:** Writing – review & editing. **Vinod Verma:** Writing – review & editing. **Ravinder Nagpal:** Writing – review & editing. **Dheeraj Mohania:** Writing – review & editing. **Rajnarayan Tiwari:** Writing – review & editing. **Manoj Kumar:** Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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