Replies to Reviewer's and Editor's comments

Title: Genetics of Diabetes

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We are thankful to the editor and reviewers for providing very valued input. Based on these comments, the manuscript has been thoroughly revised. We believe including new suggestions has substantially improved the quality of this manuscript. Below we provide our point-by-point response to each comment in blue font and have included these changes in the revised manuscript (attached below starting from page 4) in yellow highlights.

Reviewer#2

Query 1: This is a well-written…..and its complications. However, the following point need to be considered: 1. In the Figure 1 by description of "Types of diabetes", the authors consider that "In T2D body's own immune system mistakenly destroys the insulin-producing pancreatic β-cells, thereby affecting insulin production". This statement is not correct.

Reply to Query 1: We are thankful to the reviewer for pointing out this mistake. This has been corrected in Figure 1 in the revised manuscript.

Reviewer#3

Query 1: I think this is a useful review at this point in time for personalized medicine for diabetes. However, this is a good description of MODY, but there is no mention of atypical diabetes. Need to check the literature and add it.

Reply to Query 1: This information regarding atypical diabetes has been added and highlighted in the revised manuscript on page number 7, 8, and 19.

Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Diabetes, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Query 1: Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference

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Reply to Query 1: As per the company editor-in-chief's suggestions, all the figures have been put separately in a power point in an editable manner. As the figures were generated by the authors, hence a copyright statement (Copyright ©The Author(s) 2023) has also been added at the bottom of each figure.

Invited Review#02863550

Genetics of Diabetes

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Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Abstract

Diabetes mellitus (DM) is a complicated disease characterized by a complex interplay of genetic, epigenetic, and environmental variables. It is one of the world's fastest-growing diseases, with 783 million adults expected to be affected by 2045. Devastating macrovascular consequences (cerebrovascular disease, cardiovascular disease, and peripheral vascular disease) and microvascular complications (like retinopathy, nephropathy, and neuropathy) increase mortality, blindness, kidney failure, and overall quality of life in individuals with diabetes. Clinical risk factors and glycemic management alone cannot predict the development of vascular problems; multiple genetic investigations have revealed a clear hereditary component to both diabetes and its related complications. In the twenty-first century, technological advancements (genome-wide association studies, next-generation sequencing, and exome-sequencing) have led to the identification of genetic variants associated with diabetes, however, these variants can only explain a small proportion of the total heritability of the condition. In this review, we address some of the likely explanations for this "missing heritability," for diabetes such as the significance of uncommon variants, gene-environment interactions, and epigenetics. Current discoveries clinical value, management of diabetes, and future research directions are also discussed.

Keywords: Type 1 diabetes, Type 2 diabetes, gestational diabetes mellitus, MODY, genome-wide association studies; common variants; rare variants

1.0 Introduction

Diabetes mellitus (DM) is a set of diverse metabolic illnesses characterized by disturbances in the metabolism of glucose, resulting in hyperglycemia and glucose intolerance. Diabetes can occur either by the failure of the body to produce insulin, resistance to the action of insulin, or both [1, 2]. Diabetes mellitus is one of the most common endocrinological disorders worldwide. Its prevalence is rising because of physiological risk factors such as socioeconomic level, stress, obesity, hyperlipidemia, and hypertension. In addition to these, changes in behavioral patterns such as unhealthy lifestyles and eating habits can contribute significantly to the pathogenesis of diabetes [3]. DM has a devastating effect on different organs of the body such as the heart, kidneys, nerves, and eyes, and can lead to the development of various long-term microvascular or macrovascular complications [4, 5]. The rapid global increase in instances of diabetes, which affects people's life expectancy and quality of life, places a significant public health burden on society [6].

2.0 Classification of Diabetes Mellitus

Diabetes Mellitus can be broadly classified into four types **(Figure 1)** i.e., type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and maturity-onset diabetes of young (MODY) [7]. Of these, T2DM is the most prevalent form of diabetes accounting for 90% of all cases worldwide.

2.1 Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus (T1DM) is also known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. T1DM is caused by the autoimmune destruction of pancreatic beta cells by a T-cell-mediated inflammatory response, resulting in reduced insulin production. T1DM accounts for around 5-10% of the individuals diagnosed with diabetes and approximately 80-90% of cases with diabetes among children and adolescents [8]. The interaction between T-lymphocytes and autoantigens causes beta-cell death. In newborns and children, the rate of beta cell loss is relatively variable with rapid progression. Adults are more likely to develop the slowly progressive form, commonly known as latent autoimmune diabetes in adults (LADA). At this stage, the body secretes little or no insulin, and patients frequently become dependent on insulin for survival [2, 9].

2.2 Type 2 Diabetes Mellitus (T2DM)

T2DM is the most common type of diabetes, accounting for almost 90% of all cases globally. T2DM is characterized by insulin insensitivity caused by insulin resistance, poor insulin production, and pancreatic beta-cell destruction. The increased demand for insulin in the target tissues caused by insulin resistance could not be met due to beta cell abnormalities, resulting in hyperglycemia [10]. T2DM is a complex condition characterized by a combination of genetic as well as environmental variables, such as stress, obesity, and lack of physical activity [11].

2.3 Gestational Diabetes Mellitus (GDM)

Gestational diabetes is most common in pregnant women and accounts for about 7% of all pregnancy cases. Females having a history of GDM are 10 times more likely to develop postpartum T2DM, cardiovascular disease, and metabolic perturbation in the future [12]. Furthermore, children of pregnant women with gestational diabetes are at risk of anomalies related to glucose metabolism and have a 40 to 60 percent chance of getting diabetes in adulthood [13]. Women with a family history of diabetes and obese women are more likely to develop gestational diabetes [14].

2.4 Maturity Onset Diabetes of Young (MODY)

MODY, a monogenic variant of type 2 diabetes, has an autosomal dominant inheritance pattern and is characterized mostly by insulin secretion abnormalities, however, with normal insulin action [15]. MODY generally occurs before the age of 25 years or during childhood [2]. Roughly 2-5% of type 2 diabetes patients have been estimated to have MODY. Different types of MODY are classified based on underlying genetic defect: MODY1 (*HNF4A*); MODY2 (*GCK*); MODY3 (*HNF1A*); MODY4 (*PDX1*); MODY5 (*HNF1B*); MODY6 (*NEUROD1*); MODY12 (*ABCC8*), and MODY13 (*KCNJ11*).

3.0 Atypical Diabetes Mellitus

There are two atypical types of diabetes mellitus: latent autoimmune diabetes of adults (LADA) and ketosis-prone diabetes mellitus (KPDM), both of which are prone to misdiagnosis, leading to ineffective management.

3.1 Latent Autoimmune Diabetes of Adults (LADA)

LADA is a kind of autoimmune diabetes that resembles T1DM but the onset is during adulthood and it progresses slowly toward absolute insulin insufficiency than classical childhood-onset T1DM, which requires prompt exogenous insulin therapy [16]. Approximately 2-12% of all diabetes mellitus patients may have LADA [17]. Most LADA patients do not require insulin at the time of diagnosis; nevertheless, they do have diabetes-specific autoantibodies (DAAs). As a result, they have characteristics of both T1DM and T2DM and are at risk of being misdiagnosed as having T2DM [18]. According to studies from China, Korea, India, and the United Arab Emirates, the prevalence of LADA is 5.7%, 4.4% to 5.3%, 2.6% to 3.2%, and 2.6%, respectively [19]. Usage of clinical risk tools (age of onset of diabetes <50 years, acute symptoms of hyperglycemia at the time of onset, body mass index <25kg/m^2, family history or personal history of autoimmune disease), and evaluation of C-peptide level can help identify individuals at higher risk of LADA in adults [19].

3.2 Ketosis-Prone Diabetes Mellitus (KPDM)

Diabetic ketoacidosis (DKA) is a potentially fatal but treatable complication of diabetes mellitus that is characterized by hyperglycemia, metabolic acidosis, and ketonemia as a result of absolute or relative insulin insufficiency [20]. Although the actual prevalence of KPDM is unknown, men have a higher prevalence than women [21]. Patients with KPDM typically show acute and very recent history (mostly <4 weeks) of hyperglycemic symptoms such as polyuria, polydipsia, and weight-loss [22, 23].

4.0 Global Prevalence of Diabetes Mellitus

Diabetes is one of the fastest-growing global health emergencies of the 21st century **(Figure 2)**. Diabetes affected around 537 million people in 2021, and this number is projected to reach 643 million by 2030 and 783 million by 2045, which is a nearly 46% increase in its prevalence [24]. Middle-income countries are expected to see the greatest percentage increase in the prevalence of diabetes, followed by high- and low-income countries. In 2021, there were approximately 8.4 million individuals worldwide with T1DM, of which 1.5 million were younger than 20 years of age. In 2040 the prevalence of T1DM has been predicted to increase to 13.5-17.4 million (60-107%

higher than in 2021) [25]. The frequency of the most common type of diabetes mellitus i.e., T2DM varies substantially by region, with low and middle-income countries accounting for almost 80% of all T2DM cases [26]. This variance in diabetes incidence across the globe may be attributable to environmental as well as lifestyle factors apart from underlying genetic components. Globally, the prevalence of GDM varies greatly (from 1% to 28%) depending on demographic variables (e.g., maternal age, socioeconomic status, race or ethnicity, or body composition), screening methods, and diagnostic criteria. The estimated prevalence of MODY is 1 in 10,000 for adults and 1 in 23,000 for children.

5.0 Pathogenesis of Diabetes Mellitus

The pathogenesis of type 2 diabetes mellitus is influenced by eight key abnormalities described collectively as "the ominous octet" [27] **(Figure 3)**. Reduced insulin secretion, decreased incretin action, increased lipolysis, increased glucose reabsorption, decreased glucose uptake, neurotransmitter dysfunction, increased hepatic glucose synthesis, and increased glucagon secretion are examples of these [27, 28]. Therapy options for T2DM should target these documented pathophysiological abnormalities while also using a patient-centered approach that incorporates aspects other than glycemic control, such as lowering overall cardiovascular risk [29, 30]. Recent research has indicated that during the progression of T2DM, pancreatic β-cells undergo dynamic compensation and decompensation processes, with metabolic stressors such as endoplasmic reticulum stress, oxidative stress, and apoptosis acting as major regulators of the β-cell dynamics [31].

T1DM is characterized by the autoimmune death of pancreatic beta cells produced by a T-cell-mediated inflammatory response, which results in decreased insulin production **(Figure 3)**. On the other hand, in gestational diabetes mellitus (GDM), glucose intolerance develops usually in the second trimester which results in adverse impacts on both mothers and offspring **(Figure 3)**. MODY is caused by mutations in the *GCK*, *HNF*, and *NEUROD1* genes, which are involved in glucose metabolism, insulin control, glucose transport, and fetal pancreas development.

Several pathways play a significant role in causing the microvascular and macrovascular complications associated with T2DM. Hexosamine biosynthetic pathway is implicated in the

development of insulin resistance and diabetic vascular problems. It has been reported that hyperglycemia increases the production of transforming growth factor-beta (TGF-beta1), a prosclerotic cytokine implicated in the development of diabetic nephropathy [32]. The polyol pathway is a two-step metabolic mechanism that converts glucose to sorbitol and then to fructose [33, 34]. It has long been assumed that the polyol pathway is almost silent under normal physiological conditions but becomes active and detrimental under hyperglycemic conditions. The protein kinase C pathway (PKC) in diabetes promotes vascular contractility in an endothelium-independent way through K^+ channel inactivation and Ca^{2+} sensitization of myofilaments in vascular smooth muscle cells [35]. The binding of advanced glycation end products (AGEs) to its receptor (RAGE) activates a range of signaling pathways, which further enhances oxidative stress, hence leading to nerve cell damage and apoptosis [36].

6.0 Identification of Diabetes Susceptibility Genes

Family and twin studies have reported 20-80% of heritability in diabetes. First-degree relatives of people with T2DM are three times more likely to get the disease than people without a positive family history [37]. Even though diabetes from both the maternal and paternal side increases the risk of acquiring diabetes, the Framingham Offspring research reported that offspring with maternal diabetes had a slightly higher risk of impaired glucose tolerance than those with paternal diabetes [24]. Multiple twin concordance studies in T2DM found that monozygotic twins had a greater concordance rate than dizygotic twins, indicating that the condition has a significant genetic component [37]. On the other hand for T1DM, monozygotic twins have a concordance rate of 40-50% in population-based twin studies [38]. The following methods have been used to identify the diabetes risk gene:

6.1 Genetic Linkage Studies

Linkage analysis is based on the principle that genetic sequences located on the same chromosome tend to be inherited together and are not separated during meiotic homologous recombination. It is typically used in family studies to determine the position of an associated variant(s) [39, 40]. Linkage studies have successfully uncovered genetic variations that cause monogenic diseases such as MODY [41]. In 1996, using linkage analysis, major histocompatibility complex loci (HLA)

on chromosome 6 were identified as the genetic susceptibility loci for T1DM [42]. In 2004, the calpain-10 gene (*CAPN10*) on chromosome 2 was identified as the cause of T2DM using genome-wide screening and positional cloning [43, 44]. *TCF7L2*, the now well-known T2DM gene, was mapped to chromosome 10 in a Mexican-American group in the year 1999 and has been replicated several times in T2DM GWAS [45, 46]. *TCF7L2* plays an important role in the Wnt/β-catenin signaling pathway and helps in regulating the expression of genes in lipid metabolism in adipocytes and glucose-induced insulin exocytosis.

6.2 Candidate Gene Association Studies

It is a hypothesis-driven method in which candidate genes are chosen based on prior knowledge such as a gene's biological function, position, or probable significance about a given phenotype [47]. This method is usually more suitable in studies where individuals are unrelated [48]. Candidate gene studies revealed an association between T2DM and insulin receptor substrate 1 (*IRS1*), peroxisome proliferator-activated receptor gamma (*PPARG*), and insulin receptor substrate 2 (*IRS2*), Wolfram syndrome 1 (wolframin) (*WFS1*), potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*), HNF1 homeobox A (*HNF1A*), and HNF1 homeobox B (*HNF1B*) [49]. By association studies for T1DM, four non-HLA genes with established risk loci [*HLA*, *INS* (insulin), *CTLA4* (cytotoxic T-lymphocyte antigen 4), *PTPN22*] [50] could be identified. Of all the genes identified for gestational diabetes mellitus; *TCF7L2*, *MTNR1B*, *CDKAL1*, *IRS1*, and *KCNQ1* candidate genes are the most common, whereas other identified genes are ethnic-specific. On the other hand, MODY is inherited in an autosomal dominant pattern and manifests itself as a result of mutations in transcription factor genes such as *HNF4* (hepatocyte nuclear factor), *HNF1*, *IPF1* (insulin promoter factor), and neuro-D1 [51, 52].

6.3 Genome-wide Association Studies (GWAS)

GWAS are large-scale hypothesis-free investigations that entail the fast scanning of genetic variants (SNPs on genotyping arrays) across the complete human genome to uncover unique genetic associations with a certain trait [53]. The initial T2DM-related GWAS studies identified hematopoietic expressed homeobox (*HHEX*), solute carrier family 30 member 8 (*SLC30A8*), cyclin-dependent kinase inhibitor 31 2A/2B (*CDKN2A/2B*), insulin-like growth factor 2 mRNA

binding protein 2 (*IGF2BP2*), CDK5 regulatory subunit associated protein 1 like 1 (*CDKAL1*), and FTO alpha-ketoglutarate (*FTO*) [54-58]. Approximately 250 significant susceptibility loci for T2DM have been identified to date (https://www.ebi.ac.uk/gwas/efotraits/MONDO_0005148). On the other hand, for T1DM by GWAS more than 60 loci have so far been discovered (https://www.ebi.ac.uk/gwas/efotraits/MONDO_0005147), revealing the pathways underlying the disease, and overlaps with autoimmune diseases [59]. GWAS in T1DM has not only verified the previously reported T1DM loci but also uncovered several novel variations, such as those near the *KIAA0350* (*CLEC16A* approved symbol) [60] gene and with *UBASH3A* (ubiquitin-associated and SH3 containing A) [61]. To our knowledge, to date, only three GWAS have been conducted for GDM [62-64]. Kwak et al. [62] identified two significant GDM variants, rs7754840 and rs10830962 in the intronic region of *CDKAL1*, and upstream of *MTNR1B*, respectively. On the other hand, Wu et al. [63] identified 23 SNPs in four genes: *CTIF*, *CDH18*, *PTGIS*, and *SYNPR* to be associated with GDM. Recently, Pervjakova et al. [64] through multi-ancestry meta-analysis reported five loci (mapping to/near *MTNR1B*, *TCF7L2*, *CDKAL1*, *CDKN2A-CDKN2B*, and *HKDC1*) through genome-wide association studies for GDM. Using a meta-analysis approach, the genetic architecture of T1DM and T2DM has been determined in many populations with different ethnic backgrounds [65-74].

There are many challenges to the GWAS approach. The current GWAS genotyping arrays are based on HapMap and the 1000 genome project dataset, and these are designed to target common SNPs (MAF>5%). As a result, the prior GWAS did not directly investigate rare variants for an association with the trait [75]. Also, the observed variants that are linked to the trait may not be the causal variations, but rather be in linkage disequilibrium with the causal variants. Furthermore, since the variant is often located outside the coding regions and may affect genes and regulatory elements at a distance, it is usually difficult to understand how the variant affects the trait.

6.4 Genome-wide Rare Variants Association Studies

The '*common disease, rare variant*' hypothesis, in contrast to the standard '*common disease, common variant*' paradigm, says that many rare genetic variations with relatively high penetrance play a significant influence in the elevated risk of common diseases [76]. Huyghe et al. [77] for the first time in 2013 investigated the significance of low-frequency variants (minor allele

frequency <5%) associated with the risk of T2DM or T2DM-related traits using the Illumina exome array technique. Two low-frequency variants in *SGSM2* and *MADD* were reported to be associated with fasting proinsulin concentrations and three novel variants in *TBC1D30*, *KANK1*, and *PAM* genes were reported with proinsulin or insulinogenic index. Later in 2014, Steinthorsdotter et al. [68] using an exome sequencing technique in the Icelandic population, reported three more T2DM-associated low-frequency variants in *CCND2*, *PAM*, and *PDX1*. In the following years, rare variants in *MTNR1B*, *HNF1*, and *G6PC2* genes were also reported to be associated with T2DM or T2D-related traits [78]. Nejentsev et al. [79] reported four rare variants (rs35667974, rs35337543, rs35732034, and rs35744605) in *IFIH1*, a gene previously discovered in T1DM GWAS. Additionally, a cluster of rare detrimental variations in *PTPN22* was identified for T1DM, comprising two novel frameshift mutations (ss538819444 and rs371865329) and two missense variants (rs74163663 and rs56048322) [80].

7.0 Epigenetic Alterations in T2DM

The term "epigenetics" refers to heritable alterations in gene function that occur without a change in the nucleotide sequence. Epigenetic changes can be inherited from one cell generation to the next and in some cases, can be inherited through the generations. Epigenetic changes can also develop during life, either randomly or in response to environmental stimuli, impacting the effects of genetic variants and so acting as a gene-environment interaction mechanism. Both DNA methylation and histone modifications can amend the response of our genome to the environment during life. The involvement of intrauterine DNA methylation and imprinting in the programming of diabetogenic effects later in life has received significant interest in the etiology of the T2DM [81]. An intriguing study by Dabelea et al. [82] found that intrauterine diabetes exposure increased the incidence of diabetes and obesity in offspring compared to siblings born before their mothers' diabetes onset. However, the precise mechanism underlying this maternal impact is unknown. Some studies have suggested a role of epigenetic regulation of genes involved in energy metabolism, appetite control, and -cell function, such as *PPARA* [83], *LEP* [84], and pancreatic and duodenal homeobox 1 (*PDX1*) [85].

8.0 MicroRNAs (miRNAs)

MicroRNAs (miRNAs) have emerged as promising novel biomarkers for T2DM and related problems due to their metabolic stability and abundance in various body fluids including blood and cerebrospinal fluid. MicroRNAs are a class of endogenous, small (18-25 nucleotide) RNA that regulates many cellular activities by suppressing gene expression [86]. According to recent research, differential concentrations of circulating miRNAs **(Table 1)** may offer the intriguing potential for diabetes (T1DM, T2DM, MODY, and GDM) diagnosis, prognosis, and treatment monitoring.

Table 1. List of various circulating miRNAs reported in Diabetes Mellitus individuals

Mechanism/pathway (diabetes type)	Expression of miRNAs	Reference
Endothelial dysfunction (T2DM)	↑ miR-28-3p	[87]
	↓ miR-24	
	↓ miR-21	
	↓ miR-20b	
	↓ miR-15a	
	↓ miR-126	
	↓ miR-191	
	↓ miR-197	
	↓ miR-223	
	↓ miR-320	
	↓ miR-486	
	↓ miR-150	
	↓ miR-29b	
	↓ miR-107	
	↓ miR-132	
	↓ miR-144	
Glucose metabolism (T2DM)	↑ miR-9	[88]
	↑ miR-29a	
	↑ miR-30d	
	↑ miR-34a	
	↑ miR-124a	
	↑ miR-146a	
	↑ miR-375	
Inflammation (T2DM)	↓ miR-146a	[89]
Glucose metabolism (T2DM)	↑ miR-27a	[90]
	↑ miR-320a	
Glucose metabolism (T2DM)	↓ miR-126	[91-93]
Inflammation (T2DM)	↓ miR-103b	[94]
Inflammation (T2DM)	↓ miR-126-3p	[95]
	↓ miR-21-5p	
Inflammation (T2DM)	↓ miR-126	[96]
Endothelial dysfunction (T2DM)	↓ miR-126	[97]
	↓ miR-26a	
Glucose metabolism (T2DM)	↓ miR-21	[98]
Inflammation (T2DM)	↓ miR-126-3p	[99]
Endothelial dysfunction (T2DM)	↓ miR-24	[100]
Platelet reactivity (T2DM)	↓ miR-223	[101]
	↓ miR-26b	

Mechanism/pathway (diabetes type)	Expression of miRNAs	Reference
	↓ miR-126	
	↓ miR-140	
Glucose metabolism (T2DM)	↑ miR-375	[102]
	↑ miR-9	
Glucose metabolism (T2DM)	↑ miR-30a-5p	[103]
	↑ miR-150	
	↓ miR-103	
	↓ miR-28-3p	
	↓ miR-29a	
	↓ miR-9	
	↓ miR-15a	
	↓ miR-126	
	↓ miR-145	
	↓ miR-375	
	↓ miR-223	
	↓miR-133	
	↓miR-107	
Endothelial dysfunction (miR-126); hypoxia (miR-210) (T2DM)	↓ miR-126	[104]
	↑ miR-210	
Angiogenesis (T2DM)	↑ miR-193b-3p	[105]
	↑ let-7i-5p	
	↑ miR-199a-3-5p	
	↑ miR-26b-5p	
	↑ miR-30b-5p	
	↑ miR-374a-5p	
	↑ miR-20a-3p	
	↑ miR-26a-5p	
	↑ miR-30c-5p	
	↓ miR-409-3p	
	↓ miR-95-3p	
Apoptosis (T1DM)	↑miR-21	[106, 107]
	↓miR-23a-3p	[108]
	↓miR-23b-3p	
	↓miR-149-5p	
Inflammation (T1DM)	↑miR-101a	[109]
	↑miR-30b	
β-cell dysfunction (T1DM)	↑miR-106b-5p	[110, 111]
	↑miR-222-3p	
	↑miR-181a	
T-cell dysfunction (T1DM)	↑miR-26a	[112]

Mechanism/pathway (diabetes type)	Expression of miRNAs	Reference
	↑miR-98	[113]
	↑miR-23b	
	↑miR-590-5p	
β-cell lymphopoiesis (T1DM)	↑miR-34a	[114]
DNA damage checkpoint (T1DM)	↑miR-200	[115]
Apoptosis (T1DM)	↓miR-144	[116]
Autoimmune imbalance (T1DM)	↓miR-146a	[117]
MODY	↑miR-103	[118]
MODY	↑miR-224	
Glucose metabolism (GDM)	↑miR-222	[119]
	↑miR-98	[120]
	↑miR-518d	[121]
	↑miR-340	[122]
	↑miR-130b, miR148a	[123]
β-cell dysfunction (GDM)	↑miR-33a-5p	[124]
	↑miR-330-3p	[125]
	↓miR-494	[126]
	↓miR-96	[127]
	↓miR-221	[128]

9.0 Polygenic Risk Scores for T2DM

Since, T2DM is the most common form of diabetes, hence most of the polygenic risk score (PRSs) studies have been performed on T2DM. GWAS investigations have enabled the development of polygenic risk scores or genotype risk score (GRS) that assess an individual's lifetime genetic risk for various diseases. Several studies on coronary artery disease have been reported [129-132], however, there is a scarcity of reports on the prediction models for diabetes (T1DM, T2DM, and GDM). The area under the receiver operating characteristics (ROC) curve (AUC) is a measure of the prediction accuracy of the constructed PRS [133]. One of the first research estimated a T2DM genotype risk score (GRS) using a combination of 18 loci and reported that genetic information only marginally improved risk prediction when paired with standard clinical risk factors such as age, gender, or diabetes family history [134-136] **(Table 2)**. There has been a rise of interest in GRS in recent years, utilizing many more loci reported from large-scale, multi-ancestry cohorts. T2DM GRS studies from large datasets [137-139] reported that GRS constructed from multi-ethnic computed weights indicated a marginal increase in predictive power as compared to single-

ancestry computed weights, the reason might be heterogeneity across different ancestries **(Table 2)**.

Table 2. Studies on PRS for T1DM and T2DM

Diabetes type	SNPs	AUC for PRS	Ethnicity	Reference
T1DM	41	0.87	Caucasian	[140]
T1DM	30	0.88	Caucasian	[141]
T1DM+T2DM	99	0.89	Caucasian	
T1DM	32	0.86	Caucasian	[142]
T1DM	32	0.90	Caucasian Hispanic	
T1DM	32	0.75	African-American	
T1DM	32	0.92	Asian-American	
T1DM	67	0.93	Caucasian	[143]
T2DM	3	0.58	Caucasian	[144]
T2DM	18	0.80	Caucasian	[136]
T2DM	16	0.75	Caucasian	[134]
T2DM	18	0.91	Caucasian	[135]
T2DM	22	0.74	Caucasian	[145]
T2DM	62	0.91	Caucasian USA population	[146]
T2DM	1000	0.79	Caucasian	[147]
T2DM	4	0.67	African	[148]
T2DM	7 million	0.73	Caucasian	[149]

SNP: single nucleotide polymorphisms, AUC: area under the curve; PRS: polygenic risk score; USA: Unites States of America

PRSs have also been demonstrated to predict pre-diabetes and T2DM in women with a history of GDM **(Table 3)**. Some studies have found that using a PRS in conjunction with traditional T2DM risk factors improves discrimination of the risk of pre-diabetes in women with prior GDM, potentially giving more accurate tools for the prediction of future T2DM.

Table 3. PRS studies for GDM

Diabetes type	SNPs	OR 95%CI	Reference
GDM	34 SNPs previously associated with T2DM	1.11 (1.08-1.14)	[150]
GDM	11 SNPs previously associated with T2DM	1.18 (1.10-1.27)	[151]
GDM	150 previously associated with T2DM	1.06 (1.01-1.10)	[152]
GDM	84 SNPs	6.15 (5.03-7.51) top 5%	[153]

PRS: polygenic risk score; OR: odds ratio; CI: confidence interval

GRS, on the other hand, may have a role in recognizing high-risk patients before clinical risk markers become apparent. It needs to be shown whether GRS data can drive preventive therapy to meaningfully reduce rates of future incident T2DM.

10.0 Lifestyle Modifications, Environmental Factors, and Management of Diabetes Mellitus

In the long term, the pharmacological strategy for treating diabetes may be only partially effective. Major changes in patients' lifestyles (change in physical activity, dietary alteration, stress management, and improved sleeping patterns), along with treatments through pharmacological techniques, are required to ensure optimal disease management. Self-monitoring of blood glucose (SMBG) is an excellent tool for monitoring glycemic status. Current American Diabetes Association (ADA) guidelines urge its use in all patients with T1DM, T2DM, or any other form of diabetes (e.g., gestational diabetes) that requires numerous subcutaneous insulin injections [154]. Continuous glucose monitoring (CGM) systems i.e., Dexcom G6, Frestyle Libre 1and 2, GlucoMen Day, Eversense, Eversense XL, S7 EasySense, Guardian, and Connect have been reported to be of great use to diabetics. Insulin pens are the most often utilized method of insulin administration in T2DM patients [155]. Users can track boluses, calculate remaining insulin, check insulin temperature, and receive dosage reminders using Bluetooth-enabled insulin pen caps and attachments that connect to smartphone apps [156]. The integration of insulin pumps with other diabetes technologies developed over the last decade has paved the way for techniques of optimally regulating blood glucose while minimizing user stress. For the management of LADA C-peptide levels should be monitored every 6 months. For KPDM patients lifestyle modifications as stated above have been proposed to successfully treat the disease.

In addition to the above-mentioned methods, the following steps can be taken to control blood sugar levels:

10.1 Physical Activity

Physical exercise is positively associated with controlled hyperglycemia levels among T2DM patients. Moderate physical activity (walking, gardening, regular household chores) on a regular basis has been shown to be an effective method to reducing the long-term symptoms of diabetes [157]. In women with type 2 diabetes, yoga practice is more beneficial than the same course of aerobic exercise in enhancing sleep quality, hence, yoga activity can thus be recommended to these patients [158]. The identification of cytokines such as irisin, osteocalcin, and adiponectin has led

to the assumption that they may be important hormonal mediators of exercise therapy for diabetes and metabolic illnesses, although the precise mechanism remains unknown [159-161].

10.2 Dietary Changes

Strict adherence to a restricted diet combined with adequate physical exercise is strongly linked to a lower incidence of diabetes [162]. The incorporation of a Paleolithic diet (a diet rich in lean meat, fish, fruits, and vegetables) into the daily routine of diabetic patients resulted in a significant improvement in glucose management [163]. Foods that are naturally abundant in dietary fiber also contain a variety of chemicals that may help decrease glycemia. For example, bioactive proteins, polyphenolic compounds, and other phytochemicals [164]. Additionally, according to current research, meal timing and frequency, missing meals, and fasting are all linked to metabolic syndrome. Eating frequently and in the morning may help to prevent metabolic syndrome. Understanding the impact of dietary choices on health is just as important as understanding the impact of nutrients on health.

10.3 Stress

The bulk of T2DM and T1DM-related parameters, including the release of glucose (and lipids) in circulation, the development of inflammatory cytokines, and raised blood pressure, are heavily influenced by psychological stress [165]. The underlying mechanisms entail a complex neuroendocrine structure that includes both the central nervous system and the peripheral nervous system. In one study, when type 2 diabetes patients were subjected to acute stress during the postprandial period, significant increases in blood glucose levels were seen [166]. Treatment options, including stress management therapies, appear to be a promising approach for effectively preventing or reducing type 2 diabetes incidence.

10.4 Sleep Patterns

Another modifiable lifestyle choice that has been shown to influence metabolic health and energy status is sleep. Sleeping pattern optimization is critical in the diabetes management [167]. According to a population-based study, short sleep (less than 5 hours) or insomnia is related to an elevated risk of T2DM [168]. Poor sleep was linked to increased HbA1c levels (>7%) and insulin

resistance in T2DM patients in previous research [167]. Similar results has been observed for T1DM also, where persons with T1DM who reported sleeping more than 6 hours had 0.24% lower A1C values than those who slept less than 6 hours [169].

10.5 One-step or Two-step Diagnosis for GDM

The One Step or Two Step techniques are used to diagnose gestational diabetes mellitus. The One Step method consists of a 2-hour oral glucose tolerance test with a 75-g glucose overload that examines plasma glucose concentration at fasting, 1 hour, and 2 hours following glucose delivery. A positive result is characterized as a number more than 92, 180, or 153 mg/dL [170-172]. The Two-Step method comprises a nonfasting oral 50-g glucose load followed by a glucose blood measurement 1 hour later. A positive result is defined as a blood glucose level greater than 130, 135, or 140 mg/dL; the most used number is 135 mg/dL. A diagnostic test is performed after a positive screening test [173].

11. Pharmacogenomics in Diabetes Mellitus

Pharmacogenomics is the process of developing a genetically personalized therapy strategy to obtain the best optimal individual response. Several polymorphisms in the genes i.e., *ABCC8*, *KCNJ11*, *TCF7L2*, *CYP2C9*, *IRS1*, *CDKAL1*, *CDKN2A*, *CDKN2B*, *KCNQ1*, *NOS1AP*, and *CAPN10* have been explored in recent years in relation to the therapeutic response of various anti-diabetic medicines [174]. The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) and the American Diabetes Association (ADA) in addition to metformin had proposed four oral options (sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 [DPP-4] inhibitor, sodium-glucose cotransporter 2 [SGLT2] inhibitor) and injectable agents (glucagon-like peptide-1 receptor agonist [GLP-1 RA] or basal insulin) for lowering blood glucose levels **(Figure 3)**. Although these drugs have important therapeutic effects on diabetes, their long-term impact has not been accomplished, and their responses in individuals also display variances [175, 176]. Moreover, some agents produce adverse side effects, such as hypoglycemia, weight gain, gastrointestinal discomfort, urogenital infections, discomfort at the injection site, and in some cases heart failure [177].

11.1 Potential Therapeutic Drugs with New Targets for Diabetes

It is important to identify and develop novel targets to improve the therapeutic efficacy of present anti-diabetic medications, reduce the risk of side effects, and even reverse the development of diabetes. Many potential antidiabetic drugs i.e., Dorzagliatin (glucokinase activators [GKAs]), BI 135585 (β-hydroxysteroid dehydrogenase-1 inhibitors [11-β-HSD1 inhibitors]), DS-8500a (G-protein-coupled receptor 119 agonists [GPR119 agonists]), and PF-06291874/LGD-6972 (glucagon receptor antagonists) with new targets are currently undergoing clinical trials. These drugs may become new diabetes treatment options and provide more therapeutic alternatives for diabetes patients.

There is growing evidence that vitamin D insufficiency may play a critical role in the T2DM etiology [178]. Thus, in a randomized controlled study, the oral daily doses of vitamin D supplementation with metformin significantly reduced HbA1c levels after 3 and 6 months of supplementation, compared to the metformin alone [179].

12. Phytoconstituents: An Alternative Option

In diabetic patients, monotherapies combined with herbal extracts or phytoconstituents demonstrated significant improvements in blood glucose levels. Plant-derived chemical compounds have also proven to be potential alternatives. **Table 4** shows the known effects of various phytoconstituents on diabetes. Diabetes can be managed using either nonpharmacological (reasonable diet and exercise) or pharmacological (drugs or insulin) techniques. However, T2DM medication is expensive for patients and has substantial adverse effects. Plants appear to offer an appealing alternative to traditional diabetes treatment. They comprise complex compounds including many natural bioactive principles with less adverse effects.

Table 4. List of phytochemicals used in the prevention and treatment of diabetes and its complications

Phytochemical	Source	Outcomes	Reference
Curcumin	Curcuma longa	↑Insulin sensitivity, ↓blood glucose levels, and hypoglycemia	[180]
Rutin	Buckwheat (Fagopyrum esculentum)	↓Hepatic glucose production, ↑glucose tolerance	[181]
Resveratrol	Grapes, plums, peanuts, nuts, red wine	Improved insulin signaling, ↑glucose-mediated insulin secretion	[182]

Phytochemical	Source	Outcomes	Reference
Quercetin	Apples, black tea, berries, capers, red wine, onions	↑Glucose uptake, ↓hepatic glucose production	[182, 183]
Genistein	Legumes	Improved lipid glucose metabolism and ↓fasting glucose	[184]
Hesperidin	Orange, lemon	↑Glucose uptake, ↓HbA1c, ↓oxidative stress	[185]
Naringin	Skin of grapefruit and orange	↓Hepatic glucose production, ↓oxidative stress, ↑Glucose uptake	[185]
Naringenin	Citrus fruits, tomatoes, cherries, grapefruit, cocoa	↑Glucose uptake, ↓glucose intolerance and reduced blood glucose levels	[186]
Vitamin A, D, and E	Eggs, yellow, red, and green (leafy) vegetables, such as spinach, carrots, sweet potatoes and red peppers. yellow fruit, such as mango, papaya and apricots	↓glucose intolerance, ↓hyperglycemia	[182]
Fisetin	Strawberry, apple, persimmon, grape, onion, and cucumber	↓Hepatic glucose and ↑glucose metabolism	[187]
Flavonoids	Coffee, guava tea, whortleberry, olive oil, propolis, chocolate, and cocoa	↓Glucose absorption, inhibition of advanced glycation end products	[188]
Isoflavones	Soybean	Improves Glucose metabolism	[189]
Catechins	Tea leaves and red wine	Promote insulin sensitivity	[190]
Hydroxycinnamic acids	Fruits and vegetables, especially the outer part of ripe fruits	Promote glucokinase activity	[191]
Caffeoylquinic	Potatoes, eggplants, peaches, prunes, and coffee beans	Promote insulin response	[192]
Anthocyanins and anthocyanidins	Berries, eggplants, avocado, oranges, olives, red onion, fig, sweet potato, mango, and purple corn	Promote blood glucose regulation	[193]
Stillbenoids	Grapevine, berries, and peanuts	Promote pancreatic β-cell and hepatoprotective activity	[194]

13. Conclusions

Diabetes pathogenesis encompasses genetic, epigenetic, and environmental variables and their interactions. To date, the examined common variations can explain just a small portion of the heritability of diabetes. Furthermore, the technique of integrating the associated variants as a type of genetic risk score (GRS) does not accurately predict diabetes risk. As a result, the trend for genetic risk factors for diabetes is shifting from common to rare variants. Aside from genetic variables, systemic data from other trans-omics such as epigenomics, transcriptomics, proteomics, metabolomics, and metagenomics will contribute to a better understanding of genetic determinants in the progression of metabolic illnesses like diabetes. Technological, computational, and

collaborative developments continue to uncover novel genetic diabetes risk factors. There are high prospects for tailored diabetes treatment in the future, based on increased knowledge of the molecular genetic profile of the patients.

Abbreviations

11-β-HSD1	β-hydroxysteroid dehydrogenase-1 inhibitors
AACE	American Association of Clinical Endocrinologists
ABCC8	ATP-binding cassette, subfamily C, member 8
ACE	American College of Endocrinology
ADA	American Diabetes Association
AGE	Advanced glycation end-products
AUC	Area under the curve
Ca^{2+}	Calcium ion
CAPN10	Calpain-10
CCND2	Cyclin D2
CDH18	Cadherin 18
CDKAL1	CDK5 regulatory subunit associated protein 1-like 1
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CDKN2B	Cyclin-dependent kinase inhibitor 2B
CGM	Continuous glucose monitoring
CI	Confidence interval
CLEC16A	C-type lectin domain containing 16A
CTIF	Cap-binding complex-dependent translation initiation factor
CTLA4	Cytotoxic T-lymphocyte antigen 4
CYP2C9	Cytochrome P450, subfamily IIC, polypeptide 9
DM	Diabetes Mellitus
DPP-4	Dipeptidyl peptidase-4
FTO	FTO alpha-ketoglutarate-dependent dioxygenase
G6PC2	Glucose-6-phosphatase, catalytic, 2
GCK	Glucokinase
GDM	Gestational Diabetes Mellitus
GKAs	Glucokinase activators
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GPR119	G-protein-coupled receptor 119 agonists
GRS	Genotypic risk score
GWAS	Genome-wide association study
HbA1c	Glycated hemoglobin
HHEX	Hematopoietically expressed homeobox
HKDC1	Hexokinase domain-containing protein 1
HLA	Histocompatibility complex loci
HNF	Hepatocyte nuclear factor
HNF1	Hepatocyte nuclear factor 1
HNF1A	Hepatocyte nuclear factor 1 homeobox A

HNF1B	Hepatocyte nuclear factor 1 homeobox B
HNF4	Hepatocyte nuclear factor 4
HNF4A	Hepatocyte nuclear factor 4-alpha
IDDM	Insulin-dependent diabetes mellitus
IFIH1	Interferon-induced helicase C domain-containing protein 1
IFN-γ	Interferon gamma
IGF2BP2	Insulin-like growth factor 2 mRNA-binding protein 2
IL-2	Interleukin-2
INS	Insulin
IPF1	Insulin promoter factor 1
IRS1	Insulin receptor substrate 1
IRS2	insulin receptor substrate 2
K^+	Potassium ion
KANK1	KN motif- and ankyrin repeat domain-containing protein 1
KCNJ11	Potassium inwardly-rectifying channel, subfamily J, member 11
KCNQ1	Potassium channel, voltage-gated, KQT-like subfamily, member 1
KPDM	Ketosis-prone Diabetes Mellitus
LADA	Latent autoimmune diabetes in adults
LEP	Leptin
MADD	MAP kinase-activating death domain
MAF	Minor allele frequency
miR	Micro RNA
MiRNA	Micro ribonucleic acid
MODY	Maturity Onset Diabetes of Young
MODY1	Maturity Onset Diabetes of Young Type 1
MODY12	Maturity Onset Diabetes of Young Type 12
MODY13	Maturity Onset Diabetes of Young Type 13
MODY2	Maturity Onset Diabetes of Young Type 2
MODY3	Maturity Onset Diabetes of Young Type 3
MODY4	Maturity Onset Diabetes of Young Type 4
MODY5	Maturity Onset Diabetes of Young Type 5
MODY6	Maturity Onset Diabetes of Young Type 6
MTNR1B	Melatonin receptor 1B
NEUROD1	Neurogenic differentiation 1
NOS1AP	Nitric oxide synthase 1 adaptor protein
OR	Odds ratio
PAM	Peptidylglycine alpha-amidating monooxygenase
PDX1	Pancreas/duodenum homeobox protein 1
PKC	Protein kinase C-pathway
PPARA	Peroxisome proliferator-activated receptor-alpha
PPARG	peroxisome proliferator-activated receptor-gamma
PRS	Polygenic risk score
PTGIS	Prostaglandin I2 synthase
PTPN22	Protein tyrosine phosphatase, nonreceptor-type 22
RAGE	Receptor for advanced glycation end products
RNA	Ribonucleic acid

ROC	Receiver operating curve
SGLT2	Sodium-glucose cotransporter 2
SGSM2	Small G protein signaling modulator 2
SLC30A8	Solute carrier family 30, member 8
SMBG	Self-monitoring of blood glucose
SNP	Single nucleotide polymorphism
SYNPR	Synaptoporin
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TBC1D30	TBC1 domain family, member 30
TCF7L2	Transcription factor 7-like 2
TGF	Transforming growth factor
UBASH3A	Ubiquitin-associated and SH3 domain-containing protein A
USA	United State of America
WFS1	Wolfram syndrome 1

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