**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 82701

**Manuscript Type:** REVIEW

**Genetics of diabetes**

Goyal S *et al*. Genetics of diabetes

Shiwali Goyal, Jyoti Rani, Mohd Akbar Bhat, Vanita Vanita

**Shiwali Goyal,** Department of Ophthalmic Genetics and Visual Function Branch, National Eye Institute, Rockville, MD 20852, United States

**Jyoti Rani, Vanita Vanita,** Department of Human Genetics, Guru Nanak Dev University, Amritsar 143005, Punjab, India

**Mohd Akbar Bhat,** Department of Ophthalmology, Georgetown University Medical Center, Washington DC, DC 20057, United States

**Author contributions:** Goyal S, Rani J, Bhat MA, Vanita V contributed data collection; Goyal S, Rani J, Bhat MA, Vanita V contributed manuscript writing; Vanita V contributed to edit the manuscript; All the authors have read and approved the final version of this manuscript.

**Corresponding author: Vanita Vanita, PhD, Professor,** Department of Human Genetics, Guru Nanak Dev University, GT Road, Amritsar 143005, Punjab, India. vanita.humangenetics@gmail.com

**Received:** December 26, 2022

**Revised:** March 13, 2023

**Accepted:** April 17, 2023

**Published online:**

**Abstract**

Diabetes mellitus 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.

**Key Words:** Type 1 diabetes; Type 2 diabetes; Gestational diabetes mellitus; Maturity-onset diabetes of young; Genome-wide association studies; Common variants; Rare variants

Goyal S, Rani J, Bhat MA, Vanita V. Genetics of diabetes. *World J Diabetes* 2023; In press

**Core Tip:** 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 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 transomics 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.

**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]. DM 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].

**Classification of Diabetes Mellitus**

DM can be broadly classified into four types (Figure 1) *i.e.*, type 1 DM (T1DM), type 2 DM (T2DM), gestational DM (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.

***Type 1 diabetes mellitus***

T1DM is also known as insulin-dependent DM (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].

***Type 2 diabetes mellitus***

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].

***Gestational diabetes mellitus***

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].

***Maturity onset diabetes of young***

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*).

**Atypical Diabetes Mellitus**

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

***Latent autoimmune diabetes of adults***

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 DM patients may have LADA[17]. Most LADA patients do not require insulin at the time of diagnosis; nevertheless, they do have diabetes-specific autoantibodies. 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 < 25 kg/m2, 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].

***Ketosis-prone diabetes mellitus***

Diabetic ketoacidosis is a potentially fatal but treatable complication of DM 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 wk) of hyperglycemic symptoms such as polyuria, polydipsia, and weight-loss[22,23].

**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 DM *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 10000 for adults and 1 in 23000 for children.

**Pathogenesis of Diabetes Mellitus**

The pathogenesis of type 2 DM 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 b-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 b-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 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, 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 in diabetes promotes vascular contractility in an endothelium-independent way through K+ channel inactivation and Ca2+ sensitization of myofilaments in vascular smooth muscle cells[35]. The binding of advanced glycation end products to its receptor activates a range of signaling pathways, which further enhances oxidative stress, hence leading to nerve cell damage and apoptosis[36].

**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.

***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 genome-wide association studies (GWAS)[45,46]. *TCF7L2* plays an important role in the Wnt/b-catenin signaling pathway and helps in regulating the expression of genes in lipid metabolism in adipocytes and glucose-induced insulin exocytosis.

***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 DM; *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].

***Genome-wide association studies***

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.

***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 (rs538819444 and rs371865329) and two missense variants (rs74163663 and rs56048322)[80].

**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].

**MicroRNAs**

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. miRNAs 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)[87-128]may offer the intriguing potential for diabetes (T1DM, T2DM, MODY, and GDM) diagnosis, prognosis, and treatment monitoring.

**Polygenic Risk Scores for T2DM**

Since, T2DM is the most common form of diabetes, hence most of the polygenic risk scores (PRSs) studies have been performed on T2DM. GWAS investigations have enabled the development of PRSs or genetic 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 curve is a measure of the prediction accuracy of the constructed PRS[133]. One of the first research estimated a T2DM 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)[140-149].

PRSs have also been demonstrated to predict pre-diabetes and T2DM in women with a history of GDM (Table 3)[150-153]. 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.

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.

**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 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 systems *i.e.*, Dexcom G6, Frestyle Libre 1 and 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 mo. 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.

***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].

***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.

***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.

***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 h) or insomnia is related to an elevated risk of T2DM[168]. Poor sleep was linked to increased glycated hemoglobin (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 h had 0.24% lower A1C values than those who slept less than 6 h[169].

***One-step or two-step diagnosis for GDM***

The one step or two step techniques are used to diagnose gestational DM. The one step method consists of a 2-h oral glucose tolerance test with a 75-g glucose overload that examines plasma glucose concentration at fasting, 1 h, and 2 h 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 h 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].

**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/American College of Endocrinology and the ADA in addition to metformin had proposed four oral options (sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, sodium-glucose cotransporter 2 inhibitor) and injectable agents (glucagon-like peptide-1 receptor agonist 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].

***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), BI 135585 [b-hydroxysteroid dehydrogenase-1 inhibitors (11-b-HSD1 inhibitors)], DS-8500a (G-protein-coupled receptor 119 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 mo of supplementation, compared to the metformin alone[179].

**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[180-194] 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.

**CONCLUSION**

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 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.

**REFERENCES**

1 **Zimmet P**, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; **414**: 782-787 [PMID: 11742409 DOI: 10.1038/414782a]

2 **American Diabetes Association**. Standards of medical care in diabetes--2009. *Diabetes Care* 2009; **32** Suppl 1: S13-S61 [PMID: 19118286 DOI: 10.2337/dc09-S013]

3 **Kutsuma A**, Nakajima K, Suwa K. Potential Association between Breakfast Skipping and Concomitant Late-Night-Dinner Eating with Metabolic Syndrome and Proteinuria in the Japanese Population. *Scientifica (Cairo)* 2014; **2014**: 253581 [PMID: 24982814 DOI: 10.1155/2014/253581]

4 **Fowler MJ.** Microvascular and macrovascular complications of diabetes. *Clin Diabetes 1* 2008; **26**: 77–82 [DOI: 10.2337/diaclin.26.2.77]

5 **Kwak SH**, Park KS. Genetic Studies on Diabetic Microvascular Complications: Focusing on Genome-Wide Association Studies. *Endocrinol Metab (Seoul)* 2015; **30**: 147-158 [PMID: 26194074 DOI: 10.3803/EnM.2015.30.2.147]

6 **Kirigia JM**, Sambo HB, Sambo LG, Barry SP. Economic burden of diabetes mellitus in the WHO African region. *BMC Int Health Hum Rights* 2009; **9**: 6 [PMID: 19335903 DOI: 10.1186/1472-698X-9-6]

7 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20**: 1183-1197 [PMID: 9203460 DOI: 10.2337/diacare.20.7.1183]

8 **Dabelea D**, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD, Merchant AT, Lawrence JM, Reynolds K, Dolan L, Liu LL, Hamman RF; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 2014; **311**: 1778-1786 [PMID: 24794371 DOI: 10.1001/jama.2014.3201]

9 **Sena CM**, Bento CF, Pereira P, Seiça R. Diabetes mellitus: new challenges and innovative therapies. *EPMA J* 2010; **1**: 138-163 [PMID: 23199048 DOI: 10.1007/s13167-010-0010-9]

10 **Druet C**, Tubiana-Rufi N, Chevenne D, Rigal O, Polak M, Levy-Marchal C. Characterization of insulin secretion and resistance in type 2 diabetes of adolescents. *J Clin Endocrinol Metab* 2006; **91**: 401-404 [PMID: 16291705 DOI: 10.1210/jc.2005-1672]

11 **Wolfs MG**, Hofker MH, Wijmenga C, van Haeften TW. Type 2 Diabetes Mellitus: New Genetic Insights will Lead to New Therapeutics. *Curr Genomics* 2009; **10**: 110-118 [PMID: 19794883 DOI: 10.2174/138920209787847023]

12 **Lemos Costa TMR,** Detsch JM, Pimazoni-Netto A, de Almeida ACR, Sztal-Mazer S, de Oliveira LMT, Nascimento DJ, Réa RR. Glycemic variability and mean weekly glucose in the evaluation and treatment of blood glucose in gestational diabetes mellitus; evidence for lower neonatal complications. *J Diabetes Metab*,2011; **2**: [DOI: 10.4172/2155-6156.1000137]

13 **Philips JC**, Emonts P, Pintiaux A, Kirkpatrick C, Scheen AJ. [Management of gestational diabetes]. *Rev Med Liege* 2013; **68**: 489-496 [PMID: 24180206]

14 **Buchanan TA**, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. *Nat Rev Endocrinol* 2012; **8**: 639-649 [PMID: 22751341 DOI: 10.1038/nrendo.2012.96]

15 **McDonald TJ**, Colclough K, Brown R, Shields B, Shepherd M, Bingley P, Williams A, Hattersley AT, Ellard S. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. *Diabet Med* 2011; **28**: 1028-1033 [PMID: 21395678 DOI: 10.1111/j.1464-5491.2011.03287.x]

16 **Guglielmi C**, Palermo A, Pozzilli P. Latent autoimmune diabetes in the adults (LADA) in Asia: from pathogenesis and epidemiology to therapy. *Diabetes Metab Res Rev* 2012; **28** Suppl 2: 40-46 [PMID: 23280865 DOI: 10.1002/dmrr.2345]

17 **Naik RG**, Brooks-Worrell BM, Palmer JP. Latent autoimmune diabetes in adults. *J Clin Endocrinol Metab* 2009; **94**: 4635-4644 [PMID: 19837918 DOI: 10.1210/jc.2009-1120]

18 **Buzzetti R**, Tuomi T, Mauricio D, Pietropaolo M, Zhou Z, Pozzilli P, Leslie RD. Management of Latent Autoimmune Diabetes in Adults: A Consensus Statement From an International Expert Panel. *Diabetes* 2020; **69**: 2037-2047 [PMID: 32847960 DOI: 10.2337/dbi20-0017]

19 **Patil SP**. Atypical Diabetes and Management Considerations. *Prim Care* 2022; **49**: 225-237 [PMID: 35595479 DOI: 10.1016/j.pop.2021.11.003]

20 **Nyenwe EA**, Kitabchi AE. The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. *Metabolism* 2016; **65**: 507-521 [PMID: 26975543 DOI: 10.1016/j.metabol.2015.12.007]

21 **Kitabchi AE**. Ketosis-prone diabetes--a new subgroup of patients with atypical type 1 and type 2 diabetes? *J Clin Endocrinol Metab* 2003; **88**: 5087-5089 [PMID: 14602730 DOI: 10.1210/jc.2003-031656]

22 **Umpierrez GE**, Casals MM, Gebhart SP, Mixon PS, Clark WS, Phillips LS. Diabetic ketoacidosis in obese African-Americans. *Diabetes* 1995; **44**: 790-795 [PMID: 7789647 DOI: 10.2337/diabetes.44.7.790]

23 **Vellanki P**, Umpierrez GE. DIABETIC KETOACIDOSIS: A COMMON DEBUT OF DIABETES AMONG AFRICAN AMERICANS WITH TYPE 2 DIABETES. *Endocr Pract* 2017; **23**: 971-978 [PMID: 28534682 DOI: 10.4158/EP161679.RA]

24 **Sun H**, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Magliano DJ. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022; **183**: 109119 [PMID: 34879977 DOI: 10.1016/j.diabres.2021.109119]

25 **Gregory GA**, Robinson TIG, Linklater SE, Wang F, Colagiuri S, de Beaufort C, Donaghue KC; International Diabetes Federation Diabetes Atlas Type 1 Diabetes in Adults Special Interest Group, Magliano DJ, Maniam J, Orchard TJ, Rai P, Ogle GD. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. *Lancet Diabetes Endocrinol* 2022; **10**: 741-760 [PMID: 36113507 DOI: 10.1016/S2213-8587(22)00218-2]

26 **Deshmukh C,** Jain A, Nahata BR. Diabetes Mellitus: A Review. *Indian J. Pure Appl. Biosci* 2015; **3:** 224-230

27 **Defronzo RA**. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; **58**: 773-795 [PMID: 19336687 DOI: 10.2337/db09-9028]

28 **Schwartz SS**, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell-Centric Classification Schema. *Diabetes Care* 2016; **39**: 179-186 [PMID: 26798148 DOI: 10.2337/dc15-1585]

29 **Garber AJ**, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, Dagogo-Jack S, DeFronzo RA, Einhorn D, Fonseca VA, Garber JR, Garvey WT, Grunberger G, Handelsman Y, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Rosenblit PD, Umpierrez GE. Consensus statement by the american association of clinical endocrinologists and american college of endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary. *Endocr Pract* 2017; **23**: 207-238 [PMID: 28095040 DOI: 10.4158/EP161682.CS]

30 **Inzucchi SE**, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; **38**: 140-149 [PMID: 25538310 DOI: 10.2337/dc14-2441]

31 **Lv C**, Sun Y, Zhang ZY, Aboelela Z, Qiu X, Meng ZX. β-cell dynamics in type 2 diabetes and in dietary and exercise interventions. *J Mol Cell Biol* 2022; **14** [PMID: 35929791 DOI: 10.1093/jmcb/mjac046]

32 **Schleicher ED**, Weigert C. Role of the hexosamine biosynthetic pathway in diabetic nephropathy. *Kidney Int Suppl* 2000; **77**: S13-S18 [PMID: 10997685 DOI: 10.1046/j.1523-1755.2000.07703.x]

33 **HERS HG**. The mechanism of the transformation of glucose in fructose in the seminal vesicles. *Biochim Biophys Acta* 1956; **22**: 202-203 [PMID: 13373872 DOI: 10.1016/0006-3002(56)90247-5]

34 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820 [PMID: 11742414 DOI: 10.1038/414813a]

35 **Kizub IV**, Klymenko KI, Soloviev AI. Protein kinase C in enhanced vascular tone in diabetes mellitus. *Int J Cardiol* 2014; **174**: 230-242 [PMID: 24794552 DOI: 10.1016/j.ijcard.2014.04.117]

36 **Kay AM**, Simpson CL, Stewart JA Jr. The Role of AGE/RAGE Signaling in Diabetes-Mediated Vascular Calcification. *J Diabetes Res* 2016; **2016**: 6809703 [PMID: 27547766 DOI: 10.1155/2016/6809703]

37 **Ali O**. Genetics of type 2 diabetes. *World J Diabetes* 2013; **4**: 114-123 [PMID: 23961321 DOI: 10.4239/wjd.v4.i4.114]

38 **Kyvik KO**, Green A, Beck-Nielsen H. Concordance rates of insulin dependent diabetes mellitus: a population based study of young Danish twins. *BMJ* 1995; **311**: 913-917 [PMID: 7580548 DOI: 10.1136/bmj.311.7010.913]

39 **Ott J**, Wang J, Leal SM. Genetic linkage analysis in the age of whole-genome sequencing. *Nat Rev Genet* 2015; **16**: 275-284 [PMID: 25824869 DOI: 10.1038/nrg3908]

40 **Hattersley AT**, Turner RC, Permutt MA, Patel P, Tanizawa Y, Chiu KC, O'Rahilly S, Watkins PJ, Wainscoat JS. Linkage of type 2 diabetes to the glucokinase gene. *Lancet* 1992; **339**: 1307-1310 [PMID: 1349989 DOI: 10.1016/0140-6736(92)91958-B]

41 **Vaxillaire M**, Froguel P. Genetic basis of maturity-onset diabetes of the young. *Endocrinol Metab Clin North Am* 2006; **35**: 371-384, x [PMID: 16632099 DOI: 10.1016/j.ecl.2006.02.009]

42 **She JX**, Marron MP. Genetic susceptibility factors in type 1 diabetes: linkage, disequilibrium and functional analyses. *Curr Opin Immunol* 1998; **10**: 682-689 [PMID: 9914216 DOI: 10.1016/S0952-7915(98)80089-7]

43 **Song Y**, Niu T, Manson JE, Kwiatkowski DJ, Liu S. Are variants in the CAPN10 gene related to risk of type 2 diabetes? A quantitative assessment of population and family-based association studies. *Am J Hum Genet* 2004; **74**: 208-222 [PMID: 14730479 DOI: 10.1086/381400]

44 **Tripathy D**, Eriksson KF, Orho-Melander M, Fredriksson J, Ahlqvist G, Groop L. Parallel manifestation of insulin resistance and beta cell decompensation is compatible with a common defect in Type 2 diabetes. *Diabetologia* 2004; **47**: 782-793 [PMID: 15114470 DOI: 10.1007/s00125-004-1393-8]

45 **Duggirala R**, Blangero J, Almasy L, Dyer TD, Williams KL, Leach RJ, O'Connell P, Stern MP. Linkage of type 2 diabetes mellitus and of age at onset to a genetic location on chromosome 10q in Mexican Americans. *Am J Hum Genet* 1999; **64**: 1127-1140 [PMID: 10090898 DOI: 10.1086/302316]

46 **Grant SF**, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 2006; **38**: 320-323 [PMID: 16415884 DOI: 10.1038/ng1732]

47 **Teare MD**. Candidate gene association studies. *Methods Mol Biol* 2011; **713**: 105-117 [PMID: 21153614 DOI: 10.1007/978-1-60327-416-6\_8]

48 **Kwon JM**, Goate AM. The candidate gene approach. *Alcohol Res Health* 2000; **24**: 164-168 [PMID: 11199286]

49 **Barroso I**, Luan J, Middelberg RP, Harding AH, Franks PW, Jakes RW, Clayton D, Schafer AJ, O'Rahilly S, Wareham NJ. Candidate gene association study in type 2 diabetes indicates a role for genes involved in beta-cell function as well as insulin action. *PLoS Biol* 2003; **1**: E20 [PMID: 14551916 DOI: 10.1371/journal.pbio.0000020]

50 **Rich SS**. Genetics and its potential to improve type 1 diabetes care. *Curr Opin Endocrinol Diabetes Obes* 2017; **24**: 279-284 [PMID: 28509690 DOI: 10.1097/MED.0000000000000347]

51 **American Diabetes Association**. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004; **27** Suppl 1: S5-S10 [PMID: 14693921 DOI: 10.2337/diacare.27.2007.S5]

52 Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes* 1979; **28**: 1039-1057 [PMID: 510803 DOI: 10.2337/diab.28.12.1039]

53 **Bush WS**, Moore JH. Chapter 11: Genome-wide association studies. *PLoS Comput Biol* 2012; **8**: e1002822 [PMID: 23300413 DOI: 10.1371/journal.pcbi.1002822]

54 **Frayling TM**, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007; **316**: 889-894 [PMID: 17434869 DOI: 10.1126/science.1141634]

55 **Dina C**, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougnères P, Kovacs P, Marre M, Balkau B, Cauchi S, Chèvre JC, Froguel P. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat Genet* 2007; **39**: 724-726 [PMID: 17496892 DOI: 10.1038/ng2048]

56 **Saxena R**, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S, Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* 2007; **316**: 1331-1336 [PMID: 17463246 DOI: 10.1126/science.1142358]

57 **Sanghera DK**, Ortega L, Han S, Singh J, Ralhan SK, Wander GS, Mehra NK, Mulvihill JJ, Ferrell RE, Nath SK, Kamboh MI. Impact of nine common type 2 diabetes risk polymorphisms in Asian Indian Sikhs: PPARG2 (Pro12Ala), IGF2BP2, TCF7L2 and FTO variants confer a significant risk. *BMC Med Genet* 2008; **9**: 59 [PMID: 18598350 DOI: 10.1186/1471-2350-9-59]

58 **Zeggini E**, Weedon MN, Lindgren CM, Frayling TM, Elliott KS, Lango H, Timpson NJ, Perry JR, Rayner NW, Freathy RM, Barrett JC, Shields B, Morris AP, Ellard S, Groves CJ, Harries LW, Marchini JL, Owen KR, Knight B, Cardon LR, Walker M, Hitman GA, Morris AD, Doney AS; Wellcome Trust Case Control Consortium (WTCCC), McCarthy MI, Hattersley AT. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* 2007; **316**: 1336-1341 [PMID: 17463249 DOI: 10.1126/science.1142364]

59 **Cerosaletti K**, Hao W, Greenbaum CJ. Erratum. Genetics coming of age in type 1 diabetes. Diabetes Care 2019;42:189-191. *Diabetes Care* 2019; **42**: 987 [PMID: 30885949 DOI: 10.2337/dc19-er05]

60 **Hakonarson H**, Grant SF, Bradfield JP, Marchand L, Kim CE, Glessner JT, Grabs R, Casalunovo T, Taback SP, Frackelton EC, Lawson ML, Robinson LJ, Skraban R, Lu Y, Chiavacci RM, Stanley CA, Kirsch SE, Rappaport EF, Orange JS, Monos DS, Devoto M, Qu HQ, Polychronakos C. A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. *Nature* 2007; **448**: 591-594 [PMID: 17632545 DOI: 10.1038/nature06010]

61 **Concannon P**, Onengut-Gumuscu S, Todd JA, Smyth DJ, Pociot F, Bergholdt R, Akolkar B, Erlich HA, Hilner JE, Julier C, Morahan G, Nerup J, Nierras CR, Chen WM, Rich SS; Type 1 Diabetes Genetics Consortium. A human type 1 diabetes susceptibility locus maps to chromosome 21q22.3. *Diabetes* 2008; **57**: 2858-2861 [PMID: 18647951 DOI: 10.2337/db08-0753]

62 **Kwak SH**, Kim SH, Cho YM, Go MJ, Cho YS, Choi SH, Moon MK, Jung HS, Shin HD, Kang HM, Cho NH, Lee IK, Kim SY, Han BG, Jang HC, Park KS. A genome-wide association study of gestational diabetes mellitus in Korean women. *Diabetes* 2012; **61**: 531-541 [PMID: 22233651 DOI: 10.2337/db11-1034]

63 **Wu NN**, Zhao D, Ma W, Lang JN, Liu SM, Fu Y, Wang X, Wang ZW, Li Q. A genome-wide association study of gestational diabetes mellitus in Chinese women. *J Matern Fetal Neonatal Med* 2021; **34**: 1557-1564 [PMID: 31269844 DOI: 10.1080/14767058.2019.1640205]

64 **Pervjakova N**, Moen GH, Borges MC, Ferreira T, Cook JP, Allard C, Beaumont RN, Canouil M, Hatem G, Heiskala A, Joensuu A, Karhunen V, Kwak SH, Lin FTJ, Liu J, Rifas-Shiman S, Tam CH, Tam WH, Thorleifsson G, Andrew T, Auvinen J, Bhowmik B, Bonnefond A, Delahaye F, Demirkan A, Froguel P, Haller-Kikkatalo K, Hardardottir H, Hummel S, Hussain A, Kajantie E, Keikkala E, Khamis A, Lahti J, Lekva T, Mustaniemi S, Sommer C, Tagoma A, Tzala E, Uibo R, Vääräsmäki M, Villa PM, Birkeland KI, Bouchard L, Duijn CM, Finer S, Groop L, Hämäläinen E, Hayes GM, Hitman GA, Jang HC, Järvelin MR, Jenum AK, Laivuori H, Ma RC, Melander O, Oken E, Park KS, Perron P, Prasad RB, Qvigstad E, Sebert S, Stefansson K, Steinthorsdottir V, Tuomi T, Hivert MF, Franks PW, McCarthy MI, Lindgren CM, Freathy RM, Lawlor DA, Morris AP, Mägi R. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. *Hum Mol Genet* 2022; **31**: 3377-3391 [PMID: 35220425 DOI: 10.1093/hmg/ddac050]

65 **Strawbridge RJ**, Dupuis J, Prokopenko I, Barker A, Ahlqvist E, Rybin D, Petrie JR, Travers ME, Bouatia-Naji N, Dimas AS, Nica A, Wheeler E, Chen H, Voight BF, Taneera J, Kanoni S, Peden JF, Turrini F, Gustafsson S, Zabena C, Almgren P, Barker DJ, Barnes D, Dennison EM, Eriksson JG, Eriksson P, Eury E, Folkersen L, Fox CS, Frayling TM, Goel A, Gu HF, Horikoshi M, Isomaa B, Jackson AU, Jameson KA, Kajantie E, Kerr-Conte J, Kuulasmaa T, Kuusisto J, Loos RJ, Luan J, Makrilakis K, Manning AK, Martínez-Larrad MT, Narisu N, Nastase Mannila M, Ohrvik J, Osmond C, Pascoe L, Payne F, Sayer AA, Sennblad B, Silveira A, Stancáková A, Stirrups K, Swift AJ, Syvänen AC, Tuomi T, van 't Hooft FM, Walker M, Weedon MN, Xie W, Zethelius B; DIAGRAM Consortium; GIANT Consortium; MuTHER Consortium; CARDIoGRAM Consortium; C4D Consortium, Ongen H, Mälarstig A, Hopewell JC, Saleheen D, Chambers J, Parish S, Danesh J, Kooner J, Ostenson CG, Lind L, Cooper CC, Serrano-Ríos M, Ferrannini E, Forsen TJ, Clarke R, Franzosi MG, Seedorf U, Watkins H, Froguel P, Johnson P, Deloukas P, Collins FS, Laakso M, Dermitzakis ET, Boehnke M, McCarthy MI, Wareham NJ, Groop L, Pattou F, Gloyn AL, Dedoussis GV, Lyssenko V, Meigs JB, Barroso I, Watanabe RM, Ingelsson E, Langenberg C, Hamsten A, Florez JC. Genome-wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type 2 diabetes. *Diabetes* 2011; **60**: 2624-2634 [PMID: 21873549 DOI: 10.2337/db11-0415]

66 **Ahlqvist E**, Ahluwalia TS, Groop L. Genetics of type 2 diabetes. *Clin Chem* 2011; **57**: 241-254 [PMID: 21119033 DOI: 10.1373/clinchem.2010.157016]

67 **Tabassum R**, Chauhan G, Dwivedi OP, Mahajan A, Jaiswal A, Kaur I, Bandesh K, Singh T, Mathai BJ, Pandey Y, Chidambaram M, Sharma A, Chavali S, Sengupta S, Ramakrishnan L, Venkatesh P, Aggarwal SK, Ghosh S, Prabhakaran D, Srinath RK, Saxena M, Banerjee M, Mathur S, Bhansali A, Shah VN, Madhu SV, Marwaha RK, Basu A, Scaria V, McCarthy MI; DIAGRAM; INDICO, Venkatesan R, Mohan V, Tandon N, Bharadwaj D. Genome-wide association study for type 2 diabetes in Indians identifies a new susceptibility locus at 2q21. *Diabetes* 2013; **62**: 977-986 [PMID: 23209189 DOI: 10.2337/db12-0406]

68 **Steinthorsdottir V**, Thorleifsson G, Sulem P, Helgason H, Grarup N, Sigurdsson A, Helgadottir HT, Johannsdottir H, Magnusson OT, Gudjonsson SA, Justesen JM, Harder MN, Jørgensen ME, Christensen C, Brandslund I, Sandbæk A, Lauritzen T, Vestergaard H, Linneberg A, Jørgensen T, Hansen T, Daneshpour MS, Fallah MS, Hreidarsson AB, Sigurdsson G, Azizi F, Benediktsson R, Masson G, Helgason A, Kong A, Gudbjartsson DF, Pedersen O, Thorsteinsdottir U, Stefansson K. Identification of low-frequency and rare sequence variants associated with elevated or reduced risk of type 2 diabetes. *Nat Genet* 2014; **46**: 294-298 [PMID: 24464100 DOI: 10.1038/ng.2882]

69 **Go MJ**, Lee Y, Park S, Kwak SH, Kim BJ, Lee J. Genetic-risk assessment of GWAS-derived susceptibility loci for type 2 diabetes in a 10 year follow-up of a population-based cohort study. *J Hum Genet* 2016; **61**: 1009-1012 [PMID: 27439680 DOI: 10.1038/jhg.2016.93]

70 **Fuchsberger C**, Flannick J, Teslovich TM, Mahajan A, Agarwala V, Gaulton KJ, Ma C, Fontanillas P, Moutsianas L, McCarthy DJ, Rivas MA, Perry JRB, Sim X, Blackwell TW, Robertson NR, Rayner NW, Cingolani P, Locke AE, Tajes JF, Highland HM, Dupuis J, Chines PS, Lindgren CM, Hartl C, Jackson AU, Chen H, Huyghe JR, van de Bunt M, Pearson RD, Kumar A, Müller-Nurasyid M, Grarup N, Stringham HM, Gamazon ER, Lee J, Chen Y, Scott RA, Below JE, Chen P, Huang J, Go MJ, Stitzel ML, Pasko D, Parker SCJ, Varga TV, Green T, Beer NL, Day-Williams AG, Ferreira T, Fingerlin T, Horikoshi M, Hu C, Huh I, Ikram MK, Kim BJ, Kim Y, Kim YJ, Kwon MS, Lee J, Lee S, Lin KH, Maxwell TJ, Nagai Y, Wang X, Welch RP, Yoon J, Zhang W, Barzilai N, Voight BF, Han BG, Jenkinson CP, Kuulasmaa T, Kuusisto J, Manning A, Ng MCY, Palmer ND, Balkau B, Stančáková A, Abboud HE, Boeing H, Giedraitis V, Prabhakaran D, Gottesman O, Scott J, Carey J, Kwan P, Grant G, Smith JD, Neale BM, Purcell S, Butterworth AS, Howson JMM, Lee HM, Lu Y, Kwak SH, Zhao W, Danesh J, Lam VKL, Park KS, Saleheen D, So WY, Tam CHT, Afzal U, Aguilar D, Arya R, Aung T, Chan E, Navarro C, Cheng CY, Palli D, Correa A, Curran JE, Rybin D, Farook VS, Fowler SP, Freedman BI, Griswold M, Hale DE, Hicks PJ, Khor CC, Kumar S, Lehne B, Thuillier D, Lim WY, Liu J, van der Schouw YT, Loh M, Musani SK, Puppala S, Scott WR, Yengo L, Tan ST, Taylor HA Jr, Thameem F, Wilson G Sr, Wong TY, Njølstad PR, Levy JC, Mangino M, Bonnycastle LL, Schwarzmayr T, Fadista J, Surdulescu GL, Herder C, Groves CJ, Wieland T, Bork-Jensen J, Brandslund I, Christensen C, Koistinen HA, Doney ASF, Kinnunen L, Esko T, Farmer AJ, Hakaste L, Hodgkiss D, Kravic J, Lyssenko V, Hollensted M, Jørgensen ME, Jørgensen T, Ladenvall C, Justesen JM, Käräjämäki A, Kriebel J, Rathmann W, Lannfelt L, Lauritzen T, Narisu N, Linneberg A, Melander O, Milani L, Neville M, Orho-Melander M, Qi L, Qi Q, Roden M, Rolandsson O, Swift A, Rosengren AH, Stirrups K, Wood AR, Mihailov E, Blancher C, Carneiro MO, Maguire J, Poplin R, Shakir K, Fennell T, DePristo M, de Angelis MH, Deloukas P, Gjesing AP, Jun G, Nilsson P, Murphy J, Onofrio R, Thorand B, Hansen T, Meisinger C, Hu FB, Isomaa B, Karpe F, Liang L, Peters A, Huth C, O'Rahilly SP, Palmer CNA, Pedersen O, Rauramaa R, Tuomilehto J, Salomaa V, Watanabe RM, Syvänen AC, Bergman RN, Bharadwaj D, Bottinger EP, Cho YS, Chandak GR, Chan JCN, Chia KS, Daly MJ, Ebrahim SB, Langenberg C, Elliott P, Jablonski KA, Lehman DM, Jia W, Ma RCW, Pollin TI, Sandhu M, Tandon N, Froguel P, Barroso I, Teo YY, Zeggini E, Loos RJF, Small KS, Ried JS, DeFronzo RA, Grallert H, Glaser B, Metspalu A, Wareham NJ, Walker M, Banks E, Gieger C, Ingelsson E, Im HK, Illig T, Franks PW, Buck G, Trakalo J, Buck D, Prokopenko I, Mägi R, Lind L, Farjoun Y, Owen KR, Gloyn AL, Strauch K, Tuomi T, Kooner JS, Lee JY, Park T, Donnelly P, Morris AD, Hattersley AT, Bowden DW, Collins FS, Atzmon G, Chambers JC, Spector TD, Laakso M, Strom TM, Bell GI, Blangero J, Duggirala R, Tai ES, McVean G, Hanis CL, Wilson JG, Seielstad M, Frayling TM, Meigs JB, Cox NJ, Sladek R, Lander ES, Gabriel S, Burtt NP, Mohlke KL, Meitinger T, Groop L, Abecasis G, Florez JC, Scott LJ, Morris AP, Kang HM, Boehnke M, Altshuler D, McCarthy MI. The genetic architecture of type 2 diabetes. *Nature* 2016; **536**: 41-47 [PMID: 27398621 DOI: 10.1038/nature18642]

71 **Wang X**, Strizich G, Hu Y, Wang T, Kaplan RC, Qi Q. Genetic markers of type 2 diabetes: Progress in genome-wide association studies and clinical application for risk prediction. *J Diabetes* 2016; **8**: 24-35 [PMID: 26119161 DOI: 10.1111/1753-0407.12323]

72 **Scott RA**, Scott LJ, Mägi R, Marullo L, Gaulton KJ, Kaakinen M, Pervjakova N, Pers TH, Johnson AD, Eicher JD, Jackson AU, Ferreira T, Lee Y, Ma C, Steinthorsdottir V, Thorleifsson G, Qi L, Van Zuydam NR, Mahajan A, Chen H, Almgren P, Voight BF, Grallert H, Müller-Nurasyid M, Ried JS, Rayner NW, Robertson N, Karssen LC, van Leeuwen EM, Willems SM, Fuchsberger C, Kwan P, Teslovich TM, Chanda P, Li M, Lu Y, Dina C, Thuillier D, Yengo L, Jiang L, Sparso T, Kestler HA, Chheda H, Eisele L, Gustafsson S, Frånberg M, Strawbridge RJ, Benediktsson R, Hreidarsson AB, Kong A, Sigurðsson G, Kerrison ND, Luan J, Liang L, Meitinger T, Roden M, Thorand B, Esko T, Mihailov E, Fox C, Liu CT, Rybin D, Isomaa B, Lyssenko V, Tuomi T, Couper DJ, Pankow JS, Grarup N, Have CT, Jørgensen ME, Jørgensen T, Linneberg A, Cornelis MC, van Dam RM, Hunter DJ, Kraft P, Sun Q, Edkins S, Owen KR, Perry JRB, Wood AR, Zeggini E, Tajes-Fernandes J, Abecasis GR, Bonnycastle LL, Chines PS, Stringham HM, Koistinen HA, Kinnunen L, Sennblad B, Mühleisen TW, Nöthen MM, Pechlivanis S, Baldassarre D, Gertow K, Humphries SE, Tremoli E, Klopp N, Meyer J, Steinbach G, Wennauer R, Eriksson JG, Mӓnnistö S, Peltonen L, Tikkanen E, Charpentier G, Eury E, Lobbens S, Gigante B, Leander K, McLeod O, Bottinger EP, Gottesman O, Ruderfer D, Blüher M, Kovacs P, Tonjes A, Maruthur NM, Scapoli C, Erbel R, Jöckel KH, Moebus S, de Faire U, Hamsten A, Stumvoll M, Deloukas P, Donnelly PJ, Frayling TM, Hattersley AT, Ripatti S, Salomaa V, Pedersen NL, Boehm BO, Bergman RN, Collins FS, Mohlke KL, Tuomilehto J, Hansen T, Pedersen O, Barroso I, Lannfelt L, Ingelsson E, Lind L, Lindgren CM, Cauchi S, Froguel P, Loos RJF, Balkau B, Boeing H, Franks PW, Barricarte Gurrea A, Palli D, van der Schouw YT, Altshuler D, Groop LC, Langenberg C, Wareham NJ, Sijbrands E, van Duijn CM, Florez JC, Meigs JB, Boerwinkle E, Gieger C, Strauch K, Metspalu A, Morris AD, Palmer CNA, Hu FB, Thorsteinsdottir U, Stefansson K, Dupuis J, Morris AP, Boehnke M, McCarthy MI, Prokopenko I; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans. *Diabetes* 2017; **66**: 2888-2902 [PMID: 28566273 DOI: 10.2337/db16-1253]

73 **Onengut-Gumuscu S**, Chen WM, Burren O, Cooper NJ, Quinlan AR, Mychaleckyj JC, Farber E, Bonnie JK, Szpak M, Schofield E, Achuthan P, Guo H, Fortune MD, Stevens H, Walker NM, Ward LD, Kundaje A, Kellis M, Daly MJ, Barrett JC, Cooper JD, Deloukas P; Type 1 Diabetes Genetics Consortium, Todd JA, Wallace C, Concannon P, Rich SS. Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers. *Nat Genet* 2015; **47**: 381-386 [PMID: 25751624 DOI: 10.1038/ng.3245]

74 **Spracklen CN**, Horikoshi M, Kim YJ, Lin K, Bragg F, Moon S, Suzuki K, Tam CHT, Tabara Y, Kwak SH, Takeuchi F, Long J, Lim VJY, Chai JF, Chen CH, Nakatochi M, Yao J, Choi HS, Iyengar AK, Perrin HJ, Brotman SM, van de Bunt M, Gloyn AL, Below JE, Boehnke M, Bowden DW, Chambers JC, Mahajan A, McCarthy MI, Ng MCY, Petty LE, Zhang W, Morris AP, Adair LS, Akiyama M, Bian Z, Chan JCN, Chang LC, Chee ML, Chen YI, Chen YT, Chen Z, Chuang LM, Du S, Gordon-Larsen P, Gross M, Guo X, Guo Y, Han S, Howard AG, Huang W, Hung YJ, Hwang MY, Hwu CM, Ichihara S, Isono M, Jang HM, Jiang G, Jonas JB, Kamatani Y, Katsuya T, Kawaguchi T, Khor CC, Kohara K, Lee MS, Lee NR, Li L, Liu J, Luk AO, Lv J, Okada Y, Pereira MA, Sabanayagam C, Shi J, Shin DM, So WY, Takahashi A, Tomlinson B, Tsai FJ, van Dam RM, Xiang YB, Yamamoto K, Yamauchi T, Yoon K, Yu C, Yuan JM, Zhang L, Zheng W, Igase M, Cho YS, Rotter JI, Wang YX, Sheu WHH, Yokota M, Wu JY, Cheng CY, Wong TY, Shu XO, Kato N, Park KS, Tai ES, Matsuda F, Koh WP, Ma RCW, Maeda S, Millwood IY, Lee J, Kadowaki T, Walters RG, Kim BJ, Mohlke KL, Sim X. Identification of type 2 diabetes loci in 433,540 East Asian individuals. *Nature* 2020; **582**: 240-245 [PMID: 32499647 DOI: 10.1038/s41586-020-2263-3]

75 **Visscher PM**, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J. 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet* 2017; **101**: 5-22 [PMID: 28686856 DOI: 10.1016/j.ajhg.2017.06.005]

76 **Schork NJ**, Murray SS, Frazer KA, Topol EJ. Common vs. rare allele hypotheses for complex diseases. *Curr Opin Genet Dev* 2009; **19**: 212-219 [PMID: 19481926 DOI: 10.1016/j.gde.2009.04.010]

77 **Huyghe JR**, Jackson AU, Fogarty MP, Buchkovich ML, Stančáková A, Stringham HM, Sim X, Yang L, Fuchsberger C, Cederberg H, Chines PS, Teslovich TM, Romm JM, Ling H, McMullen I, Ingersoll R, Pugh EW, Doheny KF, Neale BM, Daly MJ, Kuusisto J, Scott LJ, Kang HM, Collins FS, Abecasis GR, Watanabe RM, Boehnke M, Laakso M, Mohlke KL. Exome array analysis identifies new loci and low-frequency variants influencing insulin processing and secretion. *Nat Genet* 2013; **45**: 197-201 [PMID: 23263489 DOI: 10.1038/ng.2507]

78 **Estrada K**, Aukrust I, Bjørkhaug L, Burtt NP, Mercader JM, García-Ortiz H, Huerta-Chagoya A, Moreno-Macías H, Walford G, Flannick J, Williams AL, Gómez-Vázquez MJ, Fernandez-Lopez JC, Martínez-Hernández A, Jiménez-Morales S, Centeno-Cruz F, Mendoza-Caamal E, Revilla-Monsalve C, Islas-Andrade S, Córdova EJ, Soberón X, González-Villalpando ME, Henderson E, Wilkens LR, Le Marchand L, Arellano-Campos O, Ordóñez-Sánchez ML, Rodríguez-Torres M, Rodríguez-Guillén R, Riba L, Najmi LA, Jacobs SB, Fennell T, Gabriel S, Fontanillas P, Hanis CL, Lehman DM, Jenkinson CP, Abboud HE, Bell GI, Cortes ML, Boehnke M, González-Villalpando C, Orozco L, Haiman CA, Tusié-Luna T, Aguilar-Salinas CA, Altshuler D, Njølstad PR, Florez JC, MacArthur DG,SIGMA Type 2 Diabetes Consortium. Association of a low-frequency variant in HNF1A with type 2 diabetes in a Latino population. *JAMA* 2014; **311**: 2305-2314 [PMID: 24915262 DOI: 10.1001/jama.2014.6511]

79 **Nejentsev S**, Walker N, Riches D, Egholm M, Todd JA. Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. *Science* 2009; **324**: 387-389 [PMID: 19264985 DOI: 10.1126/science.1167728]

80 **Ge Y**, Onengut-Gumuscu S, Quinlan AR, Mackey AJ, Wright JA, Buckner JH, Habib T, Rich SS, Concannon P. Targeted Deep Sequencing in Multiple-Affected Sibships of European Ancestry Identifies Rare Deleterious Variants in PTPN22 That Confer Risk for Type 1 Diabetes. *Diabetes* 2016; **65**: 794-802 [PMID: 26631741 DOI: 10.2337/db15-0322]

81 **Simmons RA**. Developmental origins of beta-cell failure in type 2 diabetes: the role of epigenetic mechanisms. *Pediatr Res* 2007; **61**: 64R-67R [PMID: 17413845 DOI: 10.1203/pdr.0b013e3180457623]

82 **Dabelea D**, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, Roumain J, Bennett PH, Knowler WC. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* 2000; **49**: 2208-2211 [PMID: 11118027 DOI: 10.2337/diabetes.49.12.2208]

83 **Tateishi K**, Okada Y, Kallin EM, Zhang Y. Role of Jhdm2a in regulating metabolic gene expression and obesity resistance. *Nature* 2009; **458**: 757-761 [PMID: 19194461 DOI: 10.1038/nature07777]

84 **Milagro FI**, Campión J, García-Díaz DF, Goyenechea E, Paternain L, Martínez JA. High fat diet-induced obesity modifies the methylation pattern of leptin promoter in rats. *J Physiol Biochem* 2009; **65**: 1-9 [PMID: 19588726 DOI: 10.1007/BF03165964]

85 **Park JH**, Stoffers DA, Nicholls RD, Simmons RA. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. *J Clin Invest* 2008; **118**: 2316-2324 [PMID: 18464933 DOI: 10.1172/JCI33655]

86 **Eyileten C**, Wicik Z, De Rosa S, Mirowska-Guzel D, Soplinska A, Indolfi C, Jastrzebska-Kurkowska I, Czlonkowska A, Postula M. MicroRNAs as Diagnostic and Prognostic Biomarkers in Ischemic Stroke-A Comprehensive Review and Bioinformatic Analysis. *Cells* 2018; **7** [PMID: 30563269 DOI: 10.3390/cells7120249]

87 **Zampetaki A**, Kiechl S, Drozdov I, Willeit P, Mayr U, Prokopi M, Mayr A, Weger S, Oberhollenzer F, Bonora E, Shah A, Willeit J, Mayr M. Plasma microRNA profiling reveals loss of endothelial miR-126 and other microRNAs in type 2 diabetes. *Circ Res* 2010; **107**: 810-817 [PMID: 20651284 DOI: 10.1161/CIRCRESAHA.110.226357]

88 **Kong L**, Zhu J, Han W, Jiang X, Xu M, Zhao Y, Dong Q, Pang Z, Guan Q, Gao L, Zhao J, Zhao L. Significance of serum microRNAs in pre-diabetes and newly diagnosed type 2 diabetes: a clinical study. *Acta Diabetol* 2011; **48**: 61-69 [PMID: 20857148 DOI: 10.1007/s00592-010-0226-0]

89 **Balasubramanyam M**, Aravind S, Gokulakrishnan K, Prabu P, Sathishkumar C, Ranjani H, Mohan V. Impaired miR-146a expression links subclinical inflammation and insulin resistance in Type 2 diabetes. *Mol Cell Biochem* 2011; **351**: 197-205 [PMID: 21249428 DOI: 10.1007/s11010-011-0727-3]

90 **Karolina DS**, Tavintharan S, Armugam A, Sepramaniam S, Pek SL, Wong MT, Lim SC, Sum CF, Jeyaseelan K. Circulating miRNA profiles in patients with metabolic syndrome. *J Clin Endocrinol Metab* 2012; **97**: E2271-E2276 [PMID: 23032062 DOI: 10.1210/jc.2012-1996]

91 **Zhang T**, Lv C, Li L, Chen S, Liu S, Wang C, Su B. Plasma miR-126 is a potential biomarker for early prediction of type 2 diabetes mellitus in susceptible individuals. *Biomed Res Int* 2013; **2013**: 761617 [PMID: 24455723 DOI: 10.1155/2013/761617]

92 **Liu Y**, Gao G, Yang C, Zhou K, Shen B, Liang H, Jiang X. The role of circulating microRNA-126 (miR-126): a novel biomarker for screening prediabetes and newly diagnosed type 2 diabetes mellitus. *Int J Mol Sci* 2014; **15**: 10567-10577 [PMID: 24927146 DOI: 10.3390/ijms150610567]

93 **Zhang T**, Li L, Shang Q, Lv C, Wang C, Su B. Circulating miR-126 is a potential biomarker to predict the onset of type 2 diabetes mellitus in susceptible individuals. *Biochem Biophys Res Commun* 2015; **463**: 60-63 [PMID: 25986735 DOI: 10.1016/j.bbrc.2015.05.017]

94 **Luo M**, Li R, Deng X, Ren M, Chen N, Zeng M, Yan K, Xia J, Liu F, Ma W, Yang Y, Wan Q, Wu J. Platelet-derived miR-103b as a novel biomarker for the early diagnosis of type 2 diabetes. *Acta Diabetol* 2015; **52**: 943-949 [PMID: 25820527 DOI: 10.1007/s00592-015-0733-0]

95 **Olivieri F**, Spazzafumo L, Bonafè M, Recchioni R, Prattichizzo F, Marcheselli F, Micolucci L, Mensà E, Giuliani A, Santini G, Gobbi M, Lazzarini R, Boemi M, Testa R, Antonicelli R, Procopio AD, Bonfigli AR. MiR-21-5p and miR-126a-3p levels in plasma and circulating angiogenic cells: relationship with type 2 diabetes complications. *Oncotarget* 2015; **6**: 35372-35382 [PMID: 26498351 DOI: 10.18632/oncotarget.6164]

96 **Witkowski M**, Weithauser A, Tabaraie T, Steffens D, Kränkel N, Witkowski M, Stratmann B, Tschoepe D, Landmesser U, Rauch-Kroehnert U. Micro-RNA-126 Reduces the Blood Thrombogenicity in Diabetes Mellitus via Targeting of Tissue Factor. *Arterioscler Thromb Vasc Biol* 2016; **36**: 1263-1271 [PMID: 27127202 DOI: 10.1161/ATVBAHA.115.306094]

97 **Jansen F**, Wang H, Przybilla D, Franklin BS, Dolf A, Pfeifer P, Schmitz T, Flender A, Endl E, Nickenig G, Werner N. Vascular endothelial microparticles-incorporated microRNAs are altered in patients with diabetes mellitus. *Cardiovasc Diabetol* 2016; **15**: 49 [PMID: 27005938 DOI: 10.1186/s12933-016-0367-8]

98 **Ghorbani S**, Mahdavi R, Alipoor B, Panahi G, Nasli Esfahani E, Razi F, Taghikhani M, Meshkani R. Decreased serum microRNA-21 level is associated with obesity in healthy and type 2 diabetic subjects. *Arch Physiol Biochem* 2018; **124**: 300-305 [PMID: 29113498 DOI: 10.1080/13813455.2017.1396349]

99 **Giannella A**, Radu CM, Franco L, Campello E, Simioni P, Avogaro A, de Kreutzenberg SV, Ceolotto G. Circulating levels and characterization of microparticles in patients with different degrees of glucose tolerance. *Cardiovasc Diabetol* 2017; **16**: 118 [PMID: 28927403 DOI: 10.1186/s12933-017-0600-0]

100 **Deng X**, Liu Y, Luo M, Wu J, Ma R, Wan Q, Wu J. Circulating miRNA-24 and its target YKL-40 as potential biomarkers in patients with coronary heart disease and type 2 diabetes mellitus. *Oncotarget* 2017; **8**: 63038-63046 [PMID: 28968969 DOI: 10.18632/oncotarget.18593]

101 **Fejes Z**, Póliska S, Czimmerer Z, Káplár M, Penyige A, Gál Szabó G, Beke Debreceni I, Kunapuli SP, Kappelmayer J, Nagy B Jr. Hyperglycaemia suppresses microRNA expression in platelets to increase P2RY12 and SELP levels in type 2 diabetes mellitus. *Thromb Haemost* 2017; **117**: 529-542 [PMID: 27975100 DOI: 10.1160/TH16-04-0322]

102 **Al-Muhtaresh HA**, Al-Kafaji G. Evaluation of Two-Diabetes Related microRNAs Suitability as Earlier Blood Biomarkers for Detecting Prediabetes and type 2 Diabetes Mellitus. *J Clin Med* 2018; **7** [PMID: 29373500 DOI: 10.3390/jcm7020012]

103 **Jiménez-Lucena R**, Rangel-Zúñiga OA, Alcalá-Díaz JF, López-Moreno J, Roncero-Ramos I, Molina-Abril H, Yubero-Serrano EM, Caballero-Villarraso J, Delgado-Lista J, Castaño JP, Ordovás JM, Pérez-Martinez P, Camargo A, López-Miranda J. Circulating miRNAs as Predictive Biomarkers of Type 2 Diabetes Mellitus Development in Coronary Heart Disease Patients from the CORDIOPREV Study. *Mol Ther Nucleic Acids* 2018; **12**: 146-157 [PMID: 30195754 DOI: 10.1016/j.omtn.2018.05.002]

104 **Amr KS**, Abdelmawgoud H, Ali ZY, Shehata S, Raslan HM. Potential value of circulating microRNA-126 and microRNA-210 as biomarkers for type 2 diabetes with coronary artery disease. *Br J Biomed Sci* 2018; **75**: 82-87 [PMID: 29452547 DOI: 10.1080/09674845.2017.1402404]

105 **Stępień EŁ**, Durak-Kozica M, Kamińska A, Targosz-Korecka M, Libera M, Tylko G, Opalińska A, Kapusta M, Solnica B, Georgescu A, Costa MC, Czyżewska-Buczyńska A, Witkiewicz W, Małecki MT, Enguita FJ. Circulating ectosomes: Determination of angiogenic microRNAs in type 2 diabetes. *Theranostics* 2018; **8**: 3874-3890 [PMID: 30083267 DOI: 10.7150/thno.23334]

106 **Ruan Q**, Wang T, Kameswaran V, Wei Q, Johnson DS, Matschinsky F, Shi W, Chen YH. The microRNA-21-PDCD4 axis prevents type 1 diabetes by blocking pancreatic beta cell death. *Proc Natl Acad Sci U S A* 2011; **108**: 12030-12035 [PMID: 21730150 DOI: 10.1073/pnas.1101450108]

107 **Sims EK**, Lakhter AJ, Anderson-Baucum E, Kono T, Tong X, Evans-Molina C. MicroRNA 21 targets BCL2 mRNA to increase apoptosis in rat and human beta cells. *Diabetologia* 2017; **60**: 1057-1065 [PMID: 28280903 DOI: 10.1007/s00125-017-4237-z]

108 **Grieco FA**, Sebastiani G, Juan-Mateu J, Villate O, Marroqui L, Ladrière L, Tugay K, Regazzi R, Bugliani M, Marchetti P, Dotta F, Eizirik DL. MicroRNAs miR-23a-3p, miR-23b-3p, and miR-149-5p Regulate the Expression of Proapoptotic BH3-Only Proteins DP5 and PUMA in Human Pancreatic β-Cells. *Diabetes* 2017; **66**: 100-112 [PMID: 27737950 DOI: 10.2337/db16-0592]

109 **Zheng Y**, Wang Z, Tu Y, Shen H, Dai Z, Lin J, Zhou Z. miR-101a and miR-30b contribute to inflammatory cytokine-mediated β-cell dysfunction. *Lab Invest* 2015; **95**: 1387-1397 [PMID: 26367486 DOI: 10.1038/labinvest.2015.112]

110 **Tsukita S**, Yamada T, Takahashi K, Munakata Y, Hosaka S, Takahashi H, Gao J, Shirai Y, Kodama S, Asai Y, Sugisawa T, Chiba Y, Kaneko K, Uno K, Sawada S, Imai J, Katagiri H. MicroRNAs 106b and 222 Improve Hyperglycemia in a Mouse Model of Insulin-Deficient Diabetes via Pancreatic β-Cell Proliferation. *EBioMedicine* 2017; **15**: 163-172 [PMID: 27974246 DOI: 10.1016/j.ebiom.2016.12.002]

111 **Nabih ES**, Andrawes NG. The Association Between Circulating Levels of miRNA-181a and Pancreatic Beta Cells Dysfunction via SMAD7 in Type 1 Diabetic Children and Adolescents. *J Clin Lab Anal* 2016; **30**: 727-731 [PMID: 26892629 DOI: 10.1002/jcla.21928]

112 **Zhang Y**, Feng ZP, Naselli G, Bell F, Wettenhall J, Auyeung P, Ellis JA, Ponsonby AL, Speed TP, Chong MM, Harrison LC. MicroRNAs in CD4(+) T cell subsets are markers of disease risk and T cell dysfunction in individuals at risk for type 1 diabetes. *J Autoimmun* 2016; **68**: 52-61 [PMID: 26786119 DOI: 10.1016/j.jaut.2015.12.006]

113 **de Jong VM**, van der Slik AR, Laban S, van 't Slot R, Koeleman BP, Zaldumbide A, Roep BO. Survival of autoreactive T lymphocytes by microRNA-mediated regulation of apoptosis through TRAIL and Fas in type 1 diabetes. *Genes Immun* 2016; **17**: 342-348 [PMID: 27467285 DOI: 10.1038/gene.2016.29]

114 **Berry GJ**, Budgeon LR, Cooper TK, Christensen ND, Waldner H. The type 1 diabetes resistance locus B10 Idd9.3 mediates impaired B-cell lymphopoiesis and implicates microRNA-34a in diabetes protection. *Eur J Immunol* 2014; **44**: 1716-1727 [PMID: 24752729 DOI: 10.1002/eji.201344116]

115 **Bhatt S**, Gupta MK, Khamaisi M, Martinez R, Gritsenko MA, Wagner BK, Guye P, Busskamp V, Shirakawa J, Wu G, Liew CW, Clauss TR, Valdez I, El Ouaamari A, Dirice E, Takatani T, Keenan HA, Smith RD, Church G, Weiss R, Wagers AJ, Qian WJ, King GL, Kulkarni RN. Preserved DNA Damage Checkpoint Pathway Protects against Complications in Long-Standing Type 1 Diabetes. *Cell Metab* 2015; **22**: 239-252 [PMID: 26244933 DOI: 10.1016/j.cmet.2015.07.015]

116 **Yu M**, Liu Y, Zhang B, Shi Y, Cui L, Zhao X. Inhibiting microRNA-144 abates oxidative stress and reduces apoptosis in hearts of streptozotocin-induced diabetic mice. *Cardiovasc Pathol* 2015; **24**: 375-381 [PMID: 26164195 DOI: 10.1016/j.carpath.2015.06.003]

117 **Yang M**, Ye L, Wang B, Gao J, Liu R, Hong J, Wang W, Gu W, Ning G. Decreased miR-146 expression in peripheral blood mononuclear cells is correlated with ongoing islet autoimmunity in type 1 diabetes patients 1miR-146. *J Diabetes* 2015; **7**: 158-165 [PMID: 24796653 DOI: 10.1111/1753-0407.12163]

118 **Bonner C**, Nyhan KC, Bacon S, Kyithar MP, Schmid J, Concannon CG, Bray IM, Stallings RL, Prehn JH, Byrne MM. Identification of circulating microRNAs in HNF1A-MODY carriers. *Diabetologia* 2013; **56**: 1743-1751 [PMID: 23674172 DOI: 10.1007/s00125-013-2939-4]

119 **Shi Z**, Zhao C, Guo X, Ding H, Cui Y, Shen R, Liu J. Differential expression of microRNAs in omental adipose tissue from gestational diabetes mellitus subjects reveals miR-222 as a regulator of ERα expression in estrogen-induced insulin resistance. *Endocrinology* 2014; **155**: 1982-1990 [PMID: 24601884 DOI: 10.1210/en.2013-2046]

120 **Cao JL**, Zhang L, Li J, Tian S, Lv XD, Wang XQ, Su X, Li Y, Hu Y, Ma X, Xia HF. Up-regulation of miR-98 and unraveling regulatory mechanisms in gestational diabetes mellitus. *Sci Rep* 2016; **6**: 32268 [PMID: 27573367 DOI: 10.1038/srep32268]

121 **Zhao C**, Zhang T, Shi Z, Ding H, Ling X. MicroRNA-518d regulates PPARα protein expression in the placentas of females with gestational diabetes mellitus. *Mol Med Rep* 2014; **9**: 2085-2090 [PMID: 24639097 DOI: 10.3892/mmr.2014.2058]

122 **Stirm L**, Huypens P, Sass S, Batra R, Fritsche L, Brucker S, Abele H, Hennige AM, Theis F, Beckers J, Hrabě de Angelis M, Fritsche A, Häring HU, Staiger H. Maternal whole blood cell miRNA-340 is elevated in gestational diabetes and inversely regulated by glucose and insulin. *Sci Rep* 2018; **8**: 1366 [PMID: 29358694 DOI: 10.1038/s41598-018-19200-9]

123 **Tryggestad JB**, Vishwanath A, Jiang S, Mallappa A, Teague AM, Takahashi Y, Thompson DM, Chernausek SD. Influence of gestational diabetes mellitus on human umbilical vein endothelial cell miRNA. *Clin Sci (Lond)* 2016; **130**: 1955-1967 [PMID: 27562513 DOI: 10.1042/CS20160305]

124 **Feng Y**, Qu X, Chen Y, Feng Q, Zhang Y, Hu J, Li X. MicroRNA-33a-5p sponges to inhibit pancreatic β-cell function in gestational diabetes mellitus LncRNA DANCR. *Reprod Biol Endocrinol* 2020; **18**: 61 [PMID: 32505219 DOI: 10.1186/s12958-020-00618-8]

125 **Sebastiani G**, Guarino E, Grieco GE, Formichi C, Delli Poggi C, Ceccarelli E, Dotta F. Circulating microRNA (miRNA) Expression Profiling in Plasma of Patients with Gestational Diabetes Mellitus Reveals Upregulation of miRNA miR-330-3p. *Front Endocrinol (Lausanne)* 2017; **8**: 345 [PMID: 29312141 DOI: 10.3389/fendo.2017.00345]

126 **He Y**, Bai J, Liu P, Dong J, Tang Y, Zhou J, Han P, Xing J, Chen Y, Yu X. miR-494 protects pancreatic β-cell function by targeting PTEN in gestational diabetes mellitus. *EXCLI J* 2017; **16**: 1297-1307 [PMID: 29333131 DOI: 10.17179/excli2017-491]

127 **Li L**, Wang S, Li H, Wan J, Zhou Q, Zhou Y, Zhang C. microRNA-96 protects pancreatic β-cell function by targeting PAK1 in gestational diabetes mellitus. *Biofactors* 2018; **44**: 539-547 [PMID: 30536654 DOI: 10.1002/biof.1461]

128 **Zhao H**, Tao S. MiRNA-221 protects islet β cell function in gestational diabetes mellitus by targeting PAK1. *Biochem Biophys Res Commun* 2019; **520**: 218-224 [PMID: 31587871 DOI: 10.1016/j.bbrc.2019.09.139]

129 **Mujwara D**, Henno G, Vernon ST, Peng S, Di Domenico P, Schroeder B, Busby GB, Figtree GA, Bottà G. Integrating a Polygenic Risk Score for Coronary Artery Disease as a Risk-Enhancing Factor in the Pooled Cohort Equation: A Cost-Effectiveness Analysis Study. *J Am Heart Assoc* 2022; **11**: e025236 [PMID: 35699184 DOI: 10.1161/JAHA.121.025236]

130 **Natarajan P**, Young R, Stitziel NO, Padmanabhan S, Baber U, Mehran R, Sartori S, Fuster V, Reilly DF, Butterworth A, Rader DJ, Ford I, Sattar N, Kathiresan S. Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting. *Circulation* 2017; **135**: 2091-2101 [PMID: 28223407 DOI: 10.1161/CIRCULATIONAHA.116.024436]

131 **Howe LJ**, Dudbridge F, Schmidt AF, Finan C, Denaxas S, Asselbergs FW, Hingorani AD, Patel RS. Polygenic risk scores for coronary artery disease and subsequent event risk amongst established cases. *Hum Mol Genet* 2020; **29**: 1388-1395 [PMID: 32219344 DOI: 10.1093/hmg/ddaa052]

132 **Elliott J**, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive Accuracy of a Polygenic Risk Score-Enhanced Prediction Model vs a Clinical Risk Score for Coronary Artery Disease. *JAMA* 2020; **323**: 636-645 [PMID: 32068818 DOI: 10.1001/jama.2019.22241]

133 **Padilla-Martínez F**, Collin F, Kwasniewski M, Kretowski A. Systematic Review of Polygenic Risk Scores for Type 1 and Type 2 Diabetes. *Int J Mol Sci* 2020; **21** [PMID: 32131491 DOI: 10.3390/ijms21051703]

134 **Lyssenko V**, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, Berglund G, Altshuler D, Nilsson P, Groop L. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* 2008; **359**: 2220-2232 [PMID: 19020324 DOI: 10.1056/NEJMoa0801869]

135 **Meigs JB**, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 2008; **359**: 2208-2219 [PMID: 19020323 DOI: 10.1056/NEJMoa0804742]

136 **Lango H**; UK Type 2 Diabetes Genetics Consortium, Palmer CN, Morris AD, Zeggini E, Hattersley AT, McCarthy MI, Frayling TM, Weedon MN. Assessing the combined impact of 18 common genetic variants of modest effect sizes on type 2 diabetes risk. *Diabetes* 2008; **57**: 3129-3135 [PMID: 18591388 DOI: 10.2337/db08-0504]

137 **Mahajan A**, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N, Cook JP, Schmidt EM, Wuttke M, Sarnowski C, Mägi R, Nano J, Gieger C, Trompet S, Lecoeur C, Preuss MH, Prins BP, Guo X, Bielak LF, Below JE, Bowden DW, Chambers JC, Kim YJ, Ng MCY, Petty LE, Sim X, Zhang W, Bennett AJ, Bork-Jensen J, Brummett CM, Canouil M, Ec Kardt KU, Fischer K, Kardia SLR, Kronenberg F, Läll K, Liu CT, Locke AE, Luan J, Ntalla I, Nylander V, Schönherr S, Schurmann C, Yengo L, Bottinger EP, Brandslund I, Christensen C, Dedoussis G, Florez JC, Ford I, Franco OH, Frayling TM, Giedraitis V, Hackinger S, Hattersley AT, Herder C, Ikram MA, Ingelsson M, Jørgensen ME, Jørgensen T, Kriebel J, Kuusisto J, Ligthart S, Lindgren CM, Linneberg A, Lyssenko V, Mamakou V, Meitinger T, Mohlke KL, Morris AD, Nadkarni G, Pankow JS, Peters A, Sattar N, Stančáková A, Strauch K, Taylor KD, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tuomilehto J, Witte DR, Dupuis J, Peyser PA, Zeggini E, Loos RJF, Froguel P, Ingelsson E, Lind L, Groop L, Laakso M, Collins FS, Jukema JW, Palmer CNA, Grallert H, Metspalu A, Dehghan A, Köttgen A, Abecasis GR, Meigs JB, Rotter JI, Marchini J, Pedersen O, Hansen T, Langenberg C, Wareham NJ, Stefansson K, Gloyn AL, Morris AP, Boehnke M, McCarthy MI. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 2018; **50**: 1505-1513 [PMID: 30297969 DOI: 10.1038/s41588-018-0241-6]

138 **Vujkovic M**, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, Huffman JE, Assimes TL, Lorenz K, Zhu X, Hilliard AT, Judy RL, Huang J, Lee KM, Klarin D, Pyarajan S, Danesh J, Melander O, Rasheed A, Mallick NH, Hameed S, Qureshi IH, Afzal MN, Malik U, Jalal A, Abbas S, Sheng X, Gao L, Kaestner KH, Susztak K, Sun YV, DuVall SL, Cho K, Lee JS, Gaziano JM, Phillips LS, Meigs JB, Reaven PD, Wilson PW, Edwards TL, Rader DJ, Damrauer SM, O'Donnell CJ, Tsao PS; HPAP Consortium; Regeneron Genetics Center; VA Million Veteran Program, Chang KM, Voight BF, Saleheen D. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat Genet* 2020; **52**: 680-691 [PMID: 32541925 DOI: 10.1038/s41588-020-0637-y]

139 **Polfus LM**, Darst BF, Highland H, Sheng X, Ng MCY, Below JE, Petty L, Bien S, Sim X, Wang W, Fontanillas P, Patel Y; 23andMe Research Team; DIAMANTE Hispanic/Latino Consortium; MEta-analysis of type 2 DIabetes in African Americans Consortium, Preuss M, Schurmann C, Du Z, Lu Y, Rhie SK, Mercader JM, Tusie-Luna T, González-Villalpando C, Orozco L, Spracklen CN, Cade BE, Jensen RA, Sun M, Joo YY, An P, Yanek LR, Bielak LF, Tajuddin S, Nicolas A, Chen G, Raffield L, Guo X, Chen WM, Nadkarni GN, Graff M, Tao R, Pankow JS, Daviglus M, Qi Q, Boerwinkle EA, Liu S, Phillips LS, Peters U, Carlson C, Wikens LR, Marchand LL, North KE, Buyske S, Kooperberg C, Loos RJF, Stram DO, Haiman CA. Genetic discovery and risk characterization in type 2 diabetes across diverse populations. *HGG Adv* 2021; **2** [PMID: 34604815 DOI: 10.1016/j.xhgg.2021.100029]

140 **Winkler C**, Krumsiek J, Buettner F, Angermüller C, Giannopoulou EZ, Theis FJ, Ziegler AG, Bonifacio E. Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes. *Diabetologia* 2014; **57**: 2521-2529 [PMID: 25186292 DOI: 10.1007/s00125-014-3362-1]

141 **Oram RA**, Patel K, Hill A, Shields B, McDonald TJ, Jones A, Hattersley AT, Weedon MN. A Type 1 Diabetes Genetic Risk Score Can Aid Discrimination Between Type 1 and Type 2 Diabetes in Young Adults. *Diabetes Care* 2016; **39**: 337-344 [PMID: 26577414 DOI: 10.2337/dc15-1111]

142 **Perry DJ**, Wasserfall CH, Oram RA, Williams MD, Posgai A, Muir AB, Haller MJ, Schatz DA, Wallet MA, Mathews CE, Atkinson MA, Brusko TM. Application of a Genetic Risk Score to Racially Diverse Type 1 Diabetes Populations Demonstrates the Need for Diversity in Risk-Modeling. *Sci Rep* 2018; **8**: 4529 [PMID: 29540798 DOI: 10.1038/s41598-018-22574-5]

143 **Sharp SA**, Rich SS, Wood AR, Jones SE, Beaumont RN, Harrison JW, Schneider DA, Locke JM, Tyrrell J, Weedon MN, Hagopian WA, Oram RA. Development and Standardization of an Improved Type 1 Diabetes Genetic Risk Score for Use in Newborn Screening and Incident Diagnosis. *Diabetes Care* 2019; **42**: 200-207 [PMID: 30655379 DOI: 10.2337/dc18-1785]

144 **Weedon MN**, McCarthy MI, Hitman G, Walker M, Groves CJ, Zeggini E, Rayner NW, Shields B, Owen KR, Hattersley AT, Frayling TM. Combining information from common type 2 diabetes risk polymorphisms improves disease prediction. *PLoS Med* 2006; **3**: e374 [PMID: 17020404 DOI: 10.1371/journal.pmed.0030374]

145 **Chatterjee N**, Wheeler B, Sampson J, Hartge P, Chanock SJ, Park JH. Projecting the performance of risk prediction based on polygenic analyses of genome-wide association studies. *Nat Genet* 2013; **45**: 400-405, 405e1-405e3 [PMID: 23455638 DOI: 10.1038/ng.2579]

146 **Vassy JL**, Hivert MF, Porneala B, Dauriz M, Florez JC, Dupuis J, Siscovick DS, Fornage M, Rasmussen-Torvik LJ, Bouchard C, Meigs JB. Polygenic type 2 diabetes prediction at the limit of common variant detection. *Diabetes* 2014; **63**: 2172-2182 [PMID: 24520119 DOI: 10.2337/db13-1663]

147 **Läll K**, Mägi R, Morris A, Metspalu A, Fischer K. Personalized risk prediction for type 2 diabetes: the potential of genetic risk scores. *Genet Med* 2017; **19**: 322-329 [PMID: 27513194 DOI: 10.1038/gim.2016.103]

148 **Chikowore T**, van Zyl T, Feskens EJ, Conradie KR. Predictive utility of a genetic risk score of common variants associated with type 2 diabetes in a black South African population. *Diabetes Res Clin Pract* 2016; **122**: 1-8 [PMID: 27744072 DOI: 10.1016/j.diabres.2016.09.019]

149 **Khera AV**, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018; **50**: 1219-1224 [PMID: 30104762 DOI: 10.1038/s41588-018-0183-z]

150 **Kawai VK**, Levinson RT, Adefurin A, Kurnik D, Collier SP, Conway D, Stein CM. A genetic risk score that includes common type 2 diabetes risk variants is associated with gestational diabetes. *Clin Endocrinol (Oxf)* 2017; **87**: 149-155 [PMID: 28429832 DOI: 10.1111/cen.13356]

151 **Lauenborg J**, Grarup N, Damm P, Borch-Johnsen K, Jørgensen T, Pedersen O, Hansen T. Common type 2 diabetes risk gene variants associate with gestational diabetes. *J Clin Endocrinol Metab* 2009; **94**: 145-150 [PMID: 18984664 DOI: 10.1210/jc.2008-1336]

152 **Powe CE**, Nodzenski M, Talbot O, Allard C, Briggs C, Leya MV, Perron P, Bouchard L, Florez JC, Scholtens DM, Lowe WL Jr, Hivert MF. Genetic Determinants of Glycemic Traits and the Risk of Gestational Diabetes Mellitus. *Diabetes* 2018; **67**: 2703-2709 [PMID: 30257980 DOI: 10.2337/db18-0203]

153 **Perišić MM**, Vladimir K, Karpov S, Štorga M, Mostashari A, Khanin R. Polygenic Risk Score and Risk Factors for Gestational Diabetes. *J Pers Med* 2022; **12** [PMID: 36143166 DOI: 10.3390/jpm12091381]

154 Standards of Medical Care in Diabetes-2016: Summary of Revisions. *Diabetes Care* 2016; **39** Suppl 1: S4-S5 [PMID: 26696680 DOI: 10.2337/dc16-S003]

155 **Klonoff DC**, Kerr D. Smart Pens Will Improve Insulin Therapy. *J Diabetes Sci Technol* 2018; **12**: 551-553 [PMID: 29411641 DOI: 10.1177/1932296818759845]

156 **Sangave NA**, Aungst TD, Patel DK. Smart Connected Insulin Pens, Caps, and Attachments: A Review of the Future of Diabetes Technology. *Diabetes Spectr* 2019; **32**: 378-384 [PMID: 31798296 DOI: 10.2337/ds18-0069]

157 **Colberg SR**, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care* 2016; **39**: 2065-2079 [PMID: 27926890 DOI: 10.2337/dc16-1728]

158 **Ebrahimi M**, Guilan-Nejad TN, Pordanjani AF. Effect of yoga and aerobics exercise on sleep quality in women with Type 2 diabetes: a randomized controlled trial. *Sleep Sci* 2017; **10**: 68-72 [PMID: 28966742 DOI: 10.5935/1984-0063.20170012]

159 **Boström P**, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Boström EA, Choi JH, Long JZ, Kajimura S, Zingaretti MC, Vind BF, Tu H, Cinti S, Højlund K, Gygi SP, Spiegelman BM. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012; **481**: 463-468 [PMID: 22237023 DOI: 10.1038/nature10777]

160 **Lee NK**, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G. Endocrine regulation of energy metabolism by the skeleton. *Cell* 2007; **130**: 456-469 [PMID: 17693256 DOI: 10.1016/j.cell.2007.05.047]

161 **Wang ZV**, Scherer PE. Adiponectin, the past two decades. *J Mol Cell Biol* 2016; **8**: 93-100 [PMID: 26993047 DOI: 10.1093/jmcb/mjw011]

162 **Barnard RJ**, Jung T, Inkeles SB. Diet and exercise in the treatment of NIDDM. The need for early emphasis. *Diabetes Care* 1994; **17**: 1469-1472 [PMID: 7882819 DOI: 10.2337/diacare.17.12.1469]

163 **Nicholson AS**, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S. Toward improved management of NIDDM: A randomized, controlled, pilot intervention using a lowfat, vegetarian diet. *Prev Med* 1999; **29**: 87-91 [PMID: 10446033 DOI: 10.1006/pmed.1999.0529]

164 **Moreno-Valdespino CA**, Luna-Vital D, Camacho-Ruiz RM, Mojica L. Bioactive proteins and phytochemicals from legumes: Mechanisms of action preventing obesity and type-2 diabetes. *Food Res Int* 2020; **130**: 108905 [PMID: 32156360 DOI: 10.1016/j.foodres.2019.108905]

165 **Hackett RA**, Steptoe A. Type 2 diabetes mellitus and psychological stress - a modifiable risk factor. *Nat Rev Endocrinol* 2017; **13**: 547-560 [PMID: 28664919 DOI: 10.1038/nrendo.2017.64]

166 **Faulenbach M**, Uthoff H, Schwegler K, Spinas GA, Schmid C, Wiesli P. Effect of psychological stress on glucose control in patients with Type 2 diabetes. *Diabet Med* 2012; **29**: 128-131 [PMID: 21883440 DOI: 10.1111/j.1464-5491.2011.03431.x]

167 **Arora T**, Taheri S. Sleep Optimization and Diabetes Control: A Review of the Literature. *Diabetes Ther* 2015; **6**: 425-468 [PMID: 26537705 DOI: 10.1007/s13300-015-0141-z]

168 **Vgontzas AN**, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: A population-based study. *Diabetes Care* 2009; **32**: 1980-1985 [PMID: 19641160 DOI: 10.2337/dc09-0284]

169 **Reutrakul S**, Thakkinstian A, Anothaisintawee T, Chontong S, Borel AL, Perfect MM, Janovsky CC, Kessler R, Schultes B, Harsch IA, van Dijk M, Bouhassira D, Matejko B, Lipton RB, Suwannalai P, Chirakalwasan N, Schober AK, Knutson KL. Sleep characteristics in type 1 diabetes and associations with glycemic control: systematic review and meta-analysis. *Sleep Med* 2016; **23**: 26-45 [PMID: 27692274 DOI: 10.1016/j.sleep.2016.03.019]

170 Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI,International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; **33**: 676-682 [PMID: 20190296 DOI: 10.2337/dc09-1848]

171 **American Diabetes Association**. Standards of medical care in diabetes--2012. *Diabetes Care* 2012; **35** Suppl 1: S11-S63 [PMID: 22187469 DOI: 10.2337/dc12-s011]

172 Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. *Diabetes Res Clin Pract* 2014; **103**: 341-363 [PMID: 24847517 DOI: 10.1016/j.diabres.2013.10.012]

173 Practice Bulletin No. 137: Gestational diabetes mellitus. *Obstet Gynecol* 2013; **122**: 406-416 [PMID: 23969827 DOI: 10.1097/01.AOG.0000433006.09219.f1]

174 **Gloyn AL**, Drucker DJ. Precision medicine in the management of type 2 diabetes. *Lancet Diabetes Endocrinol* 2018; **6**: 891-900 [PMID: 29699867 DOI: 10.1016/S2213-8587(18)30052-4]

175 **Fodor A**, Cozma A, Suharoschi R, Sitar-Taut A, Roman G. Clinical and genetic predictors of diabetes drug's response. *Drug Metab Rev* 2019; **51**: 408-427 [PMID: 31456442 DOI: 10.1080/03602532.2019.1656226]

176 **Kahn SE**, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355**: 2427-2443 [PMID: 17145742 DOI: 10.1056/NEJMoa066224]

177 **American Diabetes Association**. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020; **43**: S98-S110 [PMID: 31862752 DOI: 10.2337/dc20-S009]

178 **Martin T,** Campbell RK. Vitamin D and diabetes *Diabetes spectrum*, 2011; **24**: pp 113-118 [DOI: 10.2337/diaspect.24.2.113]

179 **Cojic M**, Kocic R, Klisic A, Kocic G. The Effects of Vitamin D Supplementation on Metabolic and Oxidative Stress Markers in Patients With Type 2 Diabetes: A 6-Month Follow Up Randomized Controlled Study. *Front Endocrinol (Lausanne)* 2021; **12**: 610893 [PMID: 34489860 DOI: 10.3389/fendo.2021.610893]

180 **Zhang DW**, Fu M, Gao SH, Liu JL. Curcumin and diabetes: a systematic review. *Evid Based Complement Alternat Med* 2013; **2013**: 636053 [PMID: 24348712 DOI: 10.1155/2013/636053]

181 **Ghorbani A**. Mechanisms of antidiabetic effects of flavonoid rutin. *Biomed Pharmacother* 2017; **96**: 305-312 [PMID: 29017142 DOI: 10.1016/j.biopha.2017.10.001]

182 **Li R**, Zhang Y, Rasool S, Geetha T, Babu JR. Effects and Underlying Mechanisms of Bioactive Compounds on Type 2 Diabetes Mellitus and Alzheimer's Disease. *Oxid Med Cell Longev* 2019; **2019**: 8165707 [PMID: 30800211 DOI: 10.1155/2019/8165707]

183 **Youl E**, Bardy G, Magous R, Cros G, Sejalon F, Virsolvy A, Richard S, Quignard JF, Gross R, Petit P, Bataille D, Oiry C. Quercetin potentiates insulin secretion and protects INS-1 pancreatic β-cells against oxidative damage via the ERK1/2 pathway. *Br J Pharmacol* 2010; **161**: 799-814 [PMID: 20860660 DOI: 10.1111/j.1476-5381.2010.00910.x]

184 **Ae Park S**, Choi MS, Cho SY, Seo JS, Jung UJ, Kim MJ, Sung MK, Park YB, Lee MK. Genistein and daidzein modulate hepatic glucose and lipid regulating enzyme activities in C57BL/KsJ-db/db mice. *Life Sci* 2006; **79**: 1207-1213 [PMID: 16647724 DOI: 10.1016/j.lfs.2006.03.022]

185 **Mahmoud AM**, Ashour MB, Abdel-Moneim A, Ahmed OM. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced type 2 diabetic rats. *J Diabetes Complications* 2012; **26**: 483-490 [PMID: 22809898 DOI: 10.1016/j.jdiacomp.2012.06.001]

186 **Singh AK**, Raj V, Keshari AK, Rai A, Kumar P, Rawat A, Maity B, Kumar D, Prakash A, De A, Samanta A, Bhattacharya B, Saha S. Isolated mangiferin and naringenin exert antidiabetic effect via PPAR(γ)/GLUT4 dual agonistic action with strong metabolic regulation. *Chem Biol Interact* 2018; **280**: 33-44 [PMID: 29223569 DOI: 10.1016/j.cbi.2017.12.007]

187 **Prasath GS**, Pillai SI, Subramanian SP. Fisetin improves glucose homeostasis through the inhibition of gluconeogenic enzymes in hepatic tissues of streptozotocin induced diabetic rats. *Eur J Pharmacol* 2014; **740**: 248-254 [PMID: 25064342 DOI: 10.1016/j.ejphar.2014.06.065]

188 **Loureiro G,** Martel F. The effect of dietary polyphenols on intestinal absorption of glucose and fructose: Relation with obesity and type 2 diabetes. *Food Rev. Int* 2019; **35**: 390-406 [DOI: 10.1080/87559129.2019.1573432]

189 **Liu CL**, Yan L, Cai KR, Sun K, Qi Y, Han YL, Zhang XD, Sun XD. Effects of soybean isoflavones on Wnt/β-catenin and the TGF-β1 signaling pathway in renal tissue of type 2 diabetic rats. *J Biol Regul Homeost Agents* 2018; **32**: 455-464 [PMID: 29921370]

190 **Li F**, Gao C, Yan P, Zhang M, Wang Y, Hu Y, Wu X, Wang X, Sheng J. EGCG Reduces Obesity and White Adipose Tissue Gain Partly Through AMPK Activation in Mice. *Front Pharmacol* 2018; **9**: 1366 [PMID: 30524290 DOI: 10.3389/fphar.2018.01366]

191 **Pei K**, Ou J, Huang J, Ou S. p-Coumaric acid and its conjugates: dietary sources, pharmacokinetic properties and biological activities. *J Sci Food Agric* 2016; **96**: 2952-2962 [PMID: 26692250 DOI: 10.1002/jsfa.7578]

192 **Reis CEG**, Dórea JG, da Costa THM. Effects of coffee consumption on glucose metabolism: A systematic review of clinical trials. *J Tradit Complement Med* 2019; **9**: 184-191 [PMID: 31193893 DOI: 10.1016/j.jtcme.2018.01.001]

193 **Shi M,** Loftus H, McAinch AJ, Su XQ. Blueberry as a source of bioactive compounds for the treatment of obesity, type 2 diabetes and chronic inflammation. *J Funct Foods* 2017; **30**: pp 16-29 [DOI: 10.1016/j.jff.2016.12.036]

194 **Bahmanzadeh M**, Goodarzi MT, Rezaei Farimani A, Fathi N, Alizadeh Z. Resveratrol supplementation improves DNA integrity and sperm parameters in streptozotocin-nicotinamide-induced type 2 diabetic rats. *Andrologia* 2019; **51**: e13313 [PMID: 31179568 DOI: 10.1111/and.13313]

**Footnotes**

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

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** December 26, 2022

**First decision:** February 28, 2023

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** India

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cai L, United States; Nagamine T, Japan; Vorobjova T, Estonia; Zeng Y, China **S-Editor:** Li L **L-Editor:** A **P-Editor:**

**Figure Legends**

****

**Figure 1 Types of diabetes and their symptoms.** Hyperglycemia and potential metabolic pathways in the pathogenesis of diabetic complications (microvascular and macrovascular) are also indicated. AGE: Advanced glycation end-products; RAGE: Receptor for advanced glycation end-products; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GDM: Gestational diabetes mellitus; MODY: Maturity-onset diabetes of young.



**Figure 2 Predicted percentage increase in the global prevalence of diabetes mellitus from 2021 to 2045[24].**



****

**Figure 3 Pathogenesis of gestational diabetes mellitus, type 2 diabetes mellitus-ominous octet, and type 1 diabetes mellitus.** Pharmacological glycemic management targets have also been shown here. DPP-4: Dipeptidyl peptide-4 inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; SGLT2: Sodium-Glucose co-transporter 2 inhibitor; IL-2: Interleukin-2; IFN-γ: Interferon gamma.

**Table 1 List of various circulating microRNAs reported in diabetes mellitus individuals**

|  |  |  |
| --- | --- | --- |
| **Mechanism/pathway (diabetes type)** | **Expression of miRNAs** | **Ref.** |
| 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 |
|  | ↓ 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] |
|  | ↑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] |

miRNAs: MicroRNAs; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; GDM: Gestational diabetes mellitus; MODY: Maturity-onset diabetes of young.

**Table 2 Studies on polygenic risk score for type 1 diabetes mellitus and type 2 diabetes mellitus**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Diabetes type** | **SNPs** | **AUC for PRS** | **Ethnicity** | **Ref.** |
| 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 United States 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; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

**Table 3 Polygenic risk scores studies for gestational diabetes mellitus**

|  |  |  |  |
| --- | --- | --- | --- |
| **Diabetes type** | **SNPs** | **OR 95%CI** | **Ref.** |
| 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] |

SNP: Single nucleotide polymorphisms; OR: Odds ratio; T2DM: Type 2 diabetes mellitus; GDM: Gestational diabetes mellitus.

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Phytochemical** | **Source** | **Outcomes** | **Ref.** |
| 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] |
| 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] |

HbA1c: Glycated hemoglobin.