Diabetology & Metabolic Syndrome

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New insights on genetic background of major diabetic vascular complications

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Abstract

Background By 2045, it is expected that 693 million individuals worldwide will have diabetes and with greater risk of morbidity, mortality, loss of vision, renal failure, and a decreased quality of life due to the devastating effects of macro- and microvascular complications. As such, clinical variables and glycemic control alone cannot predict the onset of vascular problems. An increasing body of research points to the importance of genetic predisposition in the onset of both diabetes and diabetic vascular complications.

Objectives Purpose of this article is to review these approaches and narrow down genetic findings for Diabetic Mellitus and its consequences, highlighting the gaps in the literature necessary to further genomic discovery.

Material and methods In the past, studies looking for genetic risk factors for diabetes complications relied on methods such as candidate gene studies, which were rife with false positives, and underpowered genome-wide association studies, which were constrained by small sample sizes.

Results The number of genetic findings for diabetes and diabetic complications has over doubled due to the discovery of novel genomics data, including bioinformatics and the aggregation of global cohort studies. Using genetic analysis to determine whether diabetes individuals are at the most risk for developing diabetic vascular complications (DVC) might lead to the development of more accurate early diagnostic biomarkers and the customization of care plans.

Conclusions A newer method that uses extensive evaluation of single nucleotide polymorphisms (SNP) in big datasets is Genome-Wide Association Studies (GWAS).

Keywords Type 2 diabetes mellitus, Vascular complications, Genetic risk factors, Genome-wide association studies, Single nucleotide polymorphisms

Introduction

Current clinical biomarkers and treatment

In the clinical setting, a typical case would usually present with a long duration of Diabetes Mellitus (DM), uncontrolled blood glucose levels, hypertension, dyslipidemia, and obesity predisposing the individuals to diabetic vascular complications (DVC). It is worth noting that hypertension is a vital risk factor for DVC as it is characterized by vascular dysfunction and injury [1]. Additionally, chronic hyperglycemia and insulin resistance play an important role in the initiation of vascular complications of DM and involve a number of mechanisms (Fig. 1). However, these clinical characteristics cannot be used solely to predict the risk of DVC. Emerging evidence suggests MicroRNAs (miRNAs) may play a role in the vasculopathy of DM [2].

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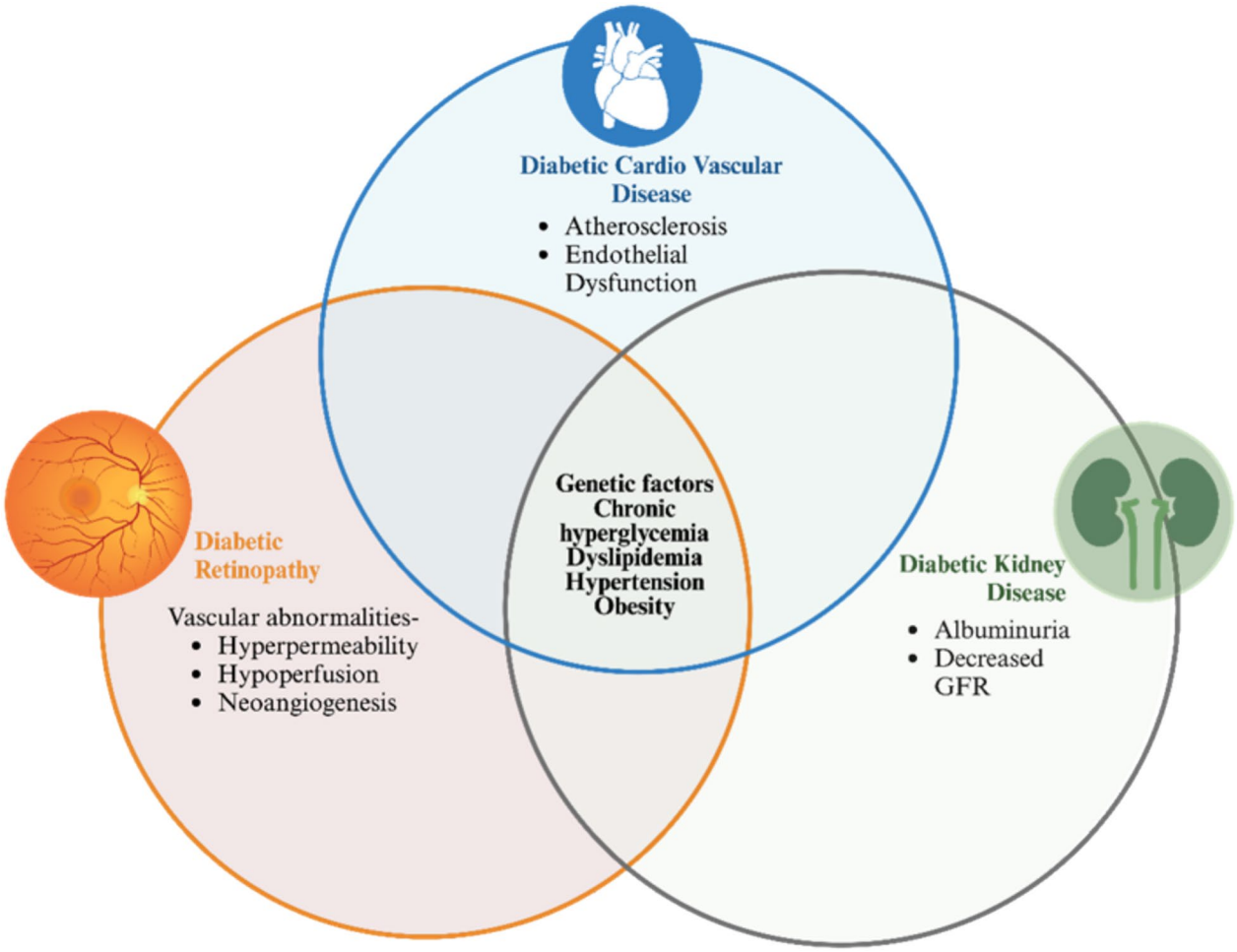

Fig. 1 Illustrating the interlinked relationship and overlap of Major Diabetic Vascular Complications (Diabetic Cardiovascular Disease; DCVD, Diabetic Kidney Disease; DKD, Diabetic Retinopathy; DR). Alongside common shared risk factors, shared genetic may contribute to long term diabetic patient's susceptibility to Micro and Macro vascular complications GFR; glomerular filtration rate

The current treatments for DVC complications do not work to reverse the disease process; instead, they focus almost entirely on preventing or managing problems that have already developed. Studies have shown an apparent decline in both the onset and progression of DVC through intensive glucose-lowering treatments and further reduce the risk of complications by controlling blood pressure with antihypertensive medications (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) [3]. These medications inhibit the renin–angiotensin–aldosterone system (RAAS) and reduce the risk of complications [3]. Recently, a new class of anti-hyperglycemic drugs, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have demonstrated significant renal and cardiovascular benefits in patients with T2DM [4]. This is supposedly due to both glucose-dependent and glucose-independent mechanisms [4]. It is worth noting that mutations in the Solute Carrier Family 5 Member 2 (SLC5A2) gene that encodes SGLT2, the major glucose co-transporter in the kidney's proximal tubule, known to cause familial renal glycosuria [5]. This condition is characterized by decreased renal glucose reabsorption and increased glucose excretion. This paradigm demonstrates that investigating the genetics of disorders associated with glucose dysregulation and the relationship between genetics and therapy may give insight into the clinical effectiveness of innovative treatments. Interestingly, over the last few decades, research in the field of genetic factors in DM has gained much interest and has clearly shown their contribution to the development and its progression.

Genetic exploration

There have been various methods by which the genetic risk for this complex disease has been studied. So far, multiple studies using Genetic Linkage Analysis (GLA) and Alpha Glucosidase (GAA) have shown to cause variants or genes, showing evidence for genetic susceptibility. While GAA is based on the common variant hypothesis [6], GLA was performed using the rare variant hypothesis to identify susceptible genes [7]. However, GLA had its limitations and drawbacks. And more recently, Genetic wide association studies (GWAS) and epigenetics have been used to identify the susceptible variants or genes.

In this literature review, the focus is on the latest advances in genetic (GWAS) and epigenetic (miRNA) studies in T2DM. Moreover, it summarizes data from prior genetic research methodologies on susceptibility genetic variants and epigenetic modifications that influence dorsal vagal complex (DVC). Finally, Understanding the etiological mechanisms underlying DVC can greatly help identify genetic variants, structural variants, and epigenetic changes that either contribute to the development of or protect against DVC, which in turn has important implications for the development of personalized medicine for DVC and potential biomarkers.

Genetic background of T2DM complications

Several important organ systems, such as the eyes, kidneys, and cardiovascular system, are affected by either DVC, which are typically categorized as microvascular complications, such as diabetic nephropathy (DN) and diabetic retinopathy (DR), or macrovascular complications, such as diabetic cardiovascular complications (DCC) [8–11]. There is currently evidence that genetic factors have a role in DVC, namely DN, DR, and DCC [12]. This complicated diseases' genetic risk has been investigated using a variety of approaches.

Genetic linkage analysis (GLA) identifies the chromosomal location of disease genes because genes that are physically nearby on a chromosome remain connected during meiosis [13].

For candidate gene analysis, based on their physiological roles, candidate genes with a known sequence and location that may be implicated in the pathogenesis of the disease are identified. In contrast, Genome-wide screens are a more effective method that may be used to screen the completely human genome for gene linkage or association with a disease without assuming anything about disease pathophysiology. This type of approach has been used successfully to identify susceptibility genetic loci for DVC. Genetic linkage study typically includes the following steps: discovering linked loci, verifying linked loci, precise mapping of verified loci, and assessing genes in the linked area through functional tests [14].

GWAS are more sensitive than genetic linkage studies and can identify minor susceptibility genes [15]. Single nucleotide polymorphisms (SNPs) are the most significant genetic variation for genetic association study due to the high density of SNPs throughout the whole human genome [15]. This study showed that a newer method that uses extensive evaluation of SNP in big datasets is GWAS. Type 2 DM (T2DM) is a complex metabolic disease that occurs as a result of insulin resistance and low insulin production. T2DM involves many organ systems that include macro-vascular and micro-vascular complications [16]. Several GWAS and candidate gene studies have suggested a large number of SNPs on several genes such as Hematopoietically expressed homeobox protein (HHEX) that were associated with T2DM susceptibility [16].

Gowing number of studies have demonstrated the association between gut microbiome and T2DM microvascular complications, however the causal relationship remains unclear [17]. Recently, using Mendelian Randomization (MR) methods, it was demonstrated the causal relationship between gut microbiome and microvascular complications in T2DM, providing a new strategy for the prevention and treatment of T2DM [17].

Candidate gene association analysis uses candidate genes of a known sequence and location that are involved in the disease pathology. However, approaches based on prior hypotheses have limited power to detect novel genetic variants. Instead, a non-prior hypothesis is a more powerful approach for identifying gene association with a disease by screening the whole human genome.

Epigenetics is the study of changes in gene expression that are not caused by changes in the DNA sequence. Things like DNA methylation, histone modification, and microRNAs can cause these changes. Epigenetics help explain how cells with the same DNA can change into different cell types with different phenotypes [18]. miRNAs are noncoding RNAs with 22 nucleotides. When they bind to the 3′-untranslated region of target mRNAs, they can either stop the mRNA from being made or break it down [19]. Importantly, miRNAs play important roles in how tissues respond to environmental signals without changing the DNA sequence. They do this by regulating genes quickly and in a way that can be modified. miRNAs may also be controlled by epigenetics, as histone modifications and changes in chromatin structure can affect miRNA transcription and expression [19]. Recent research indicates that microRNAs have a crucial role in a variety of disorders. miRNA expression is changed in diabetic cardiac and skeletal muscle, liver, kidney, and endothelium, all of which are tissues negatively impacted

by DM. It has been demonstrated that microRNAs can affect genes in numerous biological processes, such as the secretion of insulin, lipid production, fat metabolism, and adipogenesis, which are essential pathways in the etiology of DM [18].

Microvascular: diabetic kidney disease

Diabetic Kidney Disease (DKD), more commonly known as DN, is a progressive renal disease associated with long-term DM, which can progress to end-stage renal disease, requiring dialysis or kidney transplantation [20]. Patients typically present in association with long-standing DM, DR, albuminuria, and a progressive decline of estimated Glomerular Filtration Rate (eGFR) [23]. In addition, the presence of chronic hyperglycemia is a risk factor for both micro and macrovascular complications, including DKD, Diabetic Cardiovascular Disease (DCVD), DR, and Diabetic Foot Ulcers (DFU), increasing the mortality rate of T2DM patients [23].

At present, Urinary Albumin Creatinine Ratio (UACR) and eGFR are the only key markers used to identify and assess DKD [24]. The Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines have staged Chronic Kidney Disease (CKD) based on these two critical markers which help in predicting the prognosis of the disease (Fig. 2) [25].

The pathophysiology of DKD a significant microvascular consequence of T2DM is complicated and heterogeneous in nature [26]. Hemodynamic alterations, such as increased intra glomerular pressure and hyper filtration, have already been recognized as effective mechanisms in the initiation and development of DKD [26]. However, the detailed pathogenesis of the disease remains to be understood. Evidence suggests that inherited factors and acquired elements accumulation of Advanced Glycation End products (AGEs) known as "metabolic memory" have been crucial in developing T2DM-induced DKD in recent years [27].In addition, many non-modifiable risk factors for DKD, including ethnicity and genetics, have been documented [27]. Hyperglycemia, hyperlipidemia, and hypertension are some risk factors contributing to the pathologic changes in DKD. Therefore, the current management strategy for DKD includes a multidisciplinary approach including glucose, lipid, and BP management with the help of anti-hyperglycemic, statins, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs), respectively. In 2019, SGLT2 inhibitors were added as a new drug of choice for treating DKD [28]. The Canagliflozin and Renal Events in DM with Established Nephropathy Clinical Evaluation (CREDENCE) study showed that SGLT2 inhibitors stopped DKD from progressing [28]. However, despite these measures, many people with DKD still progress to end-stage renal disease [27]. Therefore, novel molecular pathways causing DKD should be studied to identify potential biomarkers for the

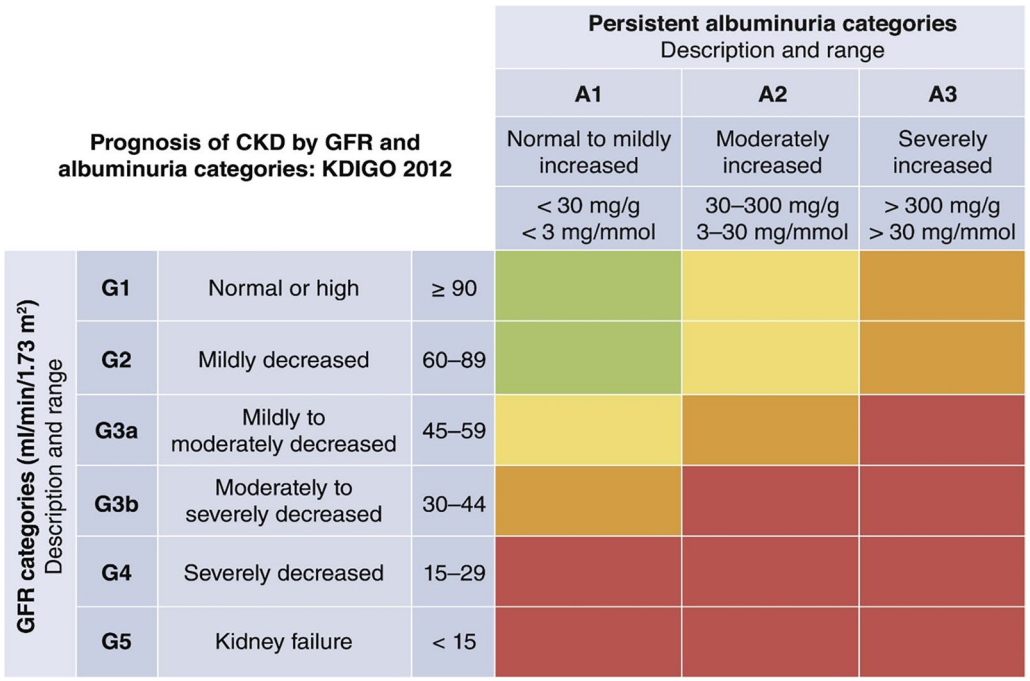

Fig. 2 eGFR categories based on the clinical guidelines of KDIGO. Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR; glomerular filtration rate

progression of the disease. The importance of epigenetic processes, particularly miRNAs, has been investigated in this review with the development of technology.

Heritance

Multiple heritability studies conducted earlier have proved a vital link in the family-based studies in DKD. Interestingly, those with DKD-affected siblings had roughly 2–4 times the probability of getting DKD compared to those with DM-affected siblings but without DKD. In T2DM, people estimate single nucleotide polymorphisms (SNPs) heritability to be 8%, perhaps because of the significant phenotypic heterogeneity of kidney disease in T2DM.

Linkage studies

Functional polymorphisms affecting the activity of candidate pathways, such as the nitric oxide, renin-angiotensin, and bradykinin systems, have been investigated in candidate gene linkage studies for DKD. In addition, other pathways associated with glucose homeostasis, lipid synthesis, and insulin resistance were investigated since they may be involved in multiple disease processes through shared mechanisms. Despite this, there has been no consistent and reproducible discovery of genetic loci or candidate genes for DKD risk or protection; however, this may be due to several factors, such as a small sample size or considerable genetic and phenotypic heterogeneity.

In 1998, the first linkage studies for DKD were performed on Pima Indians, showing a strong association to chromosome 3q24 [29]. Later, in the early 2000s, further studies were conducted in Turkish populations showing a strong association of chromosome 18q to DKD in T2DM with an odds score of 6.1[30]. Furthermore, a genome-wide search for DKD in African American families showed evidence for nephropathy loci on for susceptibility loci on chromosomes 3q, 7p, and 18q [31]. A brief list of detected chromosome regions for DKD is illustrated in (Table 1).

Candidate gene association studies

The gene to be examined is chosen based on an understanding of its contribution towards DKD pathophysiology, such as those involving blood pressure management, proteinuria severity, insulin resistance, lipid metabolism, or other pathways implicated in the progression of DKD. In addition, the current review highlights the most recent data on genetic variations (related to RAS, glucose and lipid metabolism, and some cytoskeleton proteins) that confirm the importance of genetic factors in diabetic nephropathy. Over the years, Comprehensive Geriatric Assessment (CGA) studies have identified more than150 important genes that have shown their association with DKD, for example, angiotensin I converting enzyme (ACE), carnosine dipeptidase 1 (CNDP1), fatty acid binding protein (FABP2), Ectonucleotide Pyrophosphatase/Phosphodiesterase(ENPP1) and Glucose Transporter 1 (GLUT1).

ACE helps convert Angiotensin I to Angiotensin II by the potent vasoconstrictor effect. It also deactivates the bradykinin vasodilatory effect by causing proteolysis. In Brazilian T2DM patients, a connection between the Insertion/Deletion (I/D) polymorphism in ACE and the development of DKD has been described [33]. The role of the ACE gene on chromosome 17q23 in DKD has been investigated multiple times and shown an association in a meta-analysis conducted on relevant studies conducted between 1994 and 2004, especially in the Asian population [34]. Clearly, polymorphisms in this gene correlate

Table 1 Linkage analysis of DKD

Diabetic Complication	Chromosome Region	Population	References
Diabetic Kidney Disease	3q24	Pima Indians	[41]
	2q14.1 7q21.1,7q21.3 10p15.3 14q23.1 15q26.3	Caucasian and African Americans	[44]
	18q, 18q22.3–23	Turkish African Americans	[42]
Diabetic retinopathy	Chr 3 Chr 9 Chr 1	Pima Indian cohort	[82, 83]
	3q11-q12 12p13.2-p12	Mexican	[84]
Diabetic cardiovascular complications	19p13.2 3p12.1-3q13.31 11p15.4-11p11.3 19p13.2-19q13.42	Caucasians Caucasians Hispanic African Americans	[99, 100]

with circulating ACE levels. Additionally, ACE inhibitors are regularly used as antihypertensive medicines in treating DKD, and the ACE I/D polymorphism is arguably the most well researched candidate gene in DN.

The CNDP1 (carnosine dipeptidase 1) gene is located in chromosome 18q22.3, encoding serum carnosinase (CN-1), found to confer the susceptibility for DKD and end-stage renal disease (ESRD) in T2DM [35]. In a study conducted illustrated that the serum CN-1 concentrations were considerably lower in T2DM patients with poor or moderate renal function (eGFR 60 ml/min/1.73m2) comparing those with adequate renal function (eGFR 60 ml/min/1.73m2), but higher in the latter group compared to healthy individuals [36]. This is consistent with previous observations that a high serum CN-1 concentration increases the likelihood of developing DKD [37]. Serum CN-1 concentrations decline as DKD advances, probably as a result of urine excretion and protein loss [38]. Additionally, the study showed the presence of urinary CN-1 in individuals with low eGFR provides additional evidence for the previously stated notion [36]. Additionally, polymorphisms in protein ezrin, radixin, moesin (FERM) domain containing 3 FRMD3 gene is located in chromosome 9q21.32, are associated with DKD in T2D [37, 38]. Fatty Acid Binding Protein 2 (FABP2) is also a potential gene for DKD susceptibility since it has been associated with albuminuria in patients with T2DM [40, 41].

In addition, ENPP1 polymorphism was associated with integrated reporting (IR) in a meta-analysis conducted in patients with T2DM detected a significant association between the ENPP1K121Q polymorphism and increased susceptibility of DKD in European and Asian populations [42]. In other studies, Glucose transporter type 1 (GLUT1) polymorphisms were investigated as a risk factor for DKD as its association with early kidney changes as it works as a glucose transporter in kidneys, which is pivotal in raising intracellular glucose levels by activating pathogenic pathways. GLUT1 polymorphisms related to DKD were also studied in genomic analysis [43]. A data from GAA in DKD using CGA approach in (Table 2).

Table 2 Data from GAA in DKD using CGA approach

Mechanism	Candidate gene	Population	Refs
RAAS	*ACE1*	Brazilian Asians	[45, 46]
Glucose metabolism	*GLUT-1*	Chinese	[56]
Albuminuria	*FABP2*		[53, 54]
Insulin Resistance	*ENPP1*	European, Asian	[55]
	CNDP1		[48]
	FRMD3		[52]

Genome-wide association studies and single nucleotide polymorphisms

DN is a condition shared by people with both T1DM and T2DM. However, it depicts a diverse collection of disorders that are perpetuated by different processes and could even coexist in various combinations, especially in people with T2DM. It has been shown that the prevalence of DKD is higher in T2DM, with a rapid decline in renal function that could be attributed to concurrent risk factors like hypertension and obesity [44]. In addition, the phenotypic variations in T2DM patients need to be better understood, lending credence to the genetic contribution. Thus, the genetic discoveries in T2DM are challenged by the fact that the prevalence of DKD varies across ethnic populations. It is worth noting that a decline in kidney function is measured by the decline in the eGFR, while glomerular filtration barrier dysfunction, is measured by albuminuria, can occur independently. This indicates that the two fundamental characteristics of DKD are caused by various mechanisms and may contribute to the genetic effects.

Genome-wide association studies and DKD - important discoveries

In 2005, the first GWAS revealed engulfment and motility protein 1 (ELMO1) as a gene conferring susceptibility for DKD in T2DM in Japanese patients [45]. The ELMO1 locus on chromosome p14.1 encodes a member of the engulfment and cell motility protein family that is hardly detectable in podocytes and tubular epithelial cells in healthy kidneys but significantly elevated in diabetic kidneys and CV-1 (simian) in Origin, and carrying the SV40 genetic material (COS) cells exposed to high glucose. Furthermore, ELMO1 enhances the expression of extracellular matrix protein extracellular matrix genes (COL1A1, MMP2 and FN1) in COS cells in a TGF-β-independent manner, which leads to the accumulation of ECM, thickening of renal tubules and glomerular basement membrane, thus increasing the risk of DN [45].

Further discovery of 6 polymorphism sites (rs741301 rs1345365, rs11769038, rs10951509, rs1882080, rs6462776, rs6462777) of ELMO1 gene showed association to DKD in 200 Chinese subjects (123 T2DM with DN case subjects and 77 T2DM without DN control subjects) [46].

In one of the largest combined GWAS data from four studies of European descent. Genetics of Diabetes Audit, Research in Tayside Scotl, (GoDARTS), Scania Diabetes Registry (SDR), Steno Diabetes Centre, and BENEDICT (phases A and B) conducted in subjects with T2DM. Using eight different DKD phenotypes involved 5,717 T2DM subjects, 3,345 with DKD successfully identified a novel locus, GABRR1 (led by rs9942471)

($P < 5 \times 10 - 8$), for a microalbuminuria phenotype in European subjects with T2DM [47–50]. However, only one locus reached genome-wide significance: PLCB4 (encoding 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase β-4) on chromosome 20 on variant rs2206136 was associated with the CKD phenotype ($P = 2.1 \times 10 - 8$).While, two other genes Uromodulin (UMOD) and Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma 2 (PRKAG2), showed association to eGFR, replicate at genome-wide significance [51]. A Genome-wide association studies genetic discoveries in (Table 3).

In another, GWAS comparing African American individuals with T2DM and ESRD with non-diabetic and non-DKD controls identified six independent genome-wide significant associations with ESRD (rs58627064 at chr3q26, independent SNPs rs142563193 and rs142671759 near Ectonucleotide Pyrophosphatase/Phosphodiesterase family member 7 (ENPP7), rs4807299 in Guanine nucleotide-binding protein (GNG7), rs72858591 at chr2q23, and rs9622363 in Apolipoprotein L1 (APOL1) [52].

In 2018, the FTO gene locus showed an association with DKD (SNP rs56094641) ($P = 7.7 \times 10 - 10$) in GWAS of Japanese individuals with T2DM. Furthermore, in 2019, GWAS of UACR was conducted that identified four genome-wide significant signals in the DM subset, namely Kazrin, Periplakin Interacting Protein (KAZN), MIR4432HG- B-Cell CLL/Lymphoma 11A (BCL11A), Forkhead box protein P2 (FOXP2) and Cadherin-2 (CDH2) [52]. The MYH9 (myosin, heavy chain 9)/APOL1 (apolipoprotein L1) locus was associated with T2DM in African Americans, according to results from another high-density GWAS, and these results were replicated in a study of candidate gene and in a familial linkage analysis [55].The MYH9/APOL1 function in DKD is fast growing and remains a hotly debated issue.

The impact of these small risk variants is uncertain on the development and progression of DKD, as it could be induced by the cumulative or synergistic impact of many variations with small risks. However, further studies with bigger patient cohorts are required to find rare but significant variants of DKD. In addition, genetics research utilizing more precisely defined patient populations, such as patients with progressive DKD, will aid in identifying genes related to a more precisely defined disease phenotype. We can only uncover novel rare sequence variations linked with DKD when we can gather sufficiently large sample numbers and use advanced gene aggregation studies.

Epigenetics (non-coding RNA dysregulation)

In addition to the qualitative and quantitative control of gene activity provided by genetic variations, epigenetic control of gene regulation adds an extra layer of regulation to genes implicated in the pathogenesis of DKD. Latest developments in large genome-wide screenings and sequencing tools have made it possible to scan epigenetic alteration of the whole genome, known as "epigenome-wide association studies (EWAS)," a significant

Table 3 GWAS genetic discoveries

Gene	Chromosome	SNP	P-value	Population	Phenotype	Ref
ELMO1	p14.1	rs741301 rs1345365, rs11769038, rs10951509, rs1882080, rs6462776, rs6462777	P = 0.004	Chinese	T2D-DKD	[59]
GABRR1	Chr 6: 89,948,232	rs9942471	$P = 2.1 \times 10 - 7$	European	T2DMmicroalbuminuria	
PLCB4	Chr 20: 9,351,150	rs2206136	$P = 2.1 \times 10 - 8$	European	T2DMCKD	
UMOD	Chr 16: 20,400,839	rs11864909	$P = 2.7 \times 10 - 5$	European	T2DMeGFR	
PRKAG2					T2DMeGFR	
ENPP7		rs142563193 rs142671759	P < 5 × 10–8	African Americans	T2DMESRD	
GNG7		rs4807299	P < 5 × 10–8	African Americans	T2DMESRD	
APOL1		rs9622363	P < 5 × 10–8	African Americans	T2DMESRD	
FTO		rs56094641)	$P = 7.7 \times 10 - 10$	Japanese individuals		
MYH9	Chr 22	rs5750250,	P = 3.00 × 10–7	African Americans	T2D-ESRD	
MIR4432HG-BCL11A, FOXP2, and CDH2			$P < 9.7 \times 10 - 5$	European ancestry, African Americans, East Asian ancestry, South Asian ancestry, Hispanics	UACR	

complementary to GWAS. In the context of DKD, different miRNAs are engaged in pathogenesis-related pathways (apoptosis, fibrosis, and extracellular matrix accumulation). Hyperglycemia causes the release of cytokines, growth factors, and miRNA dysregulation. miRNAs have a role in DKD development by affecting genes involved in different pathways.

miR21

The miR-21 located on chromosome 17, has an important role in the development of DN, and enhanced expression has been detected not just in DN tissues but also in DN patients' plasma and urine [56]. MiR-21 involves in the process of DN, promotes urinary protein excretion, and aggravates renal function damage [57]. Both DN patients and DN mice had higher MiR-21-5p expression in their serum or kidneys. This increased expression in DN correlates with tubulointerstitial fibrosis, renal damage, and decreased eGFR. Furthermore, miR-21-5p influences cardiovascular events associated with Chronic Kidney Disease (CKD) [56].

A prospective case–control study was conducted highlighted the clinical significance of five potential miR's (miR-21, miR-29a, miR-29b, miR-29c and miR192) in T2DM patients who have existing DR with differential ACR and eGFR was performed using quantitative RT-PCR analysis. It was shown that the miR-21 level was significantly upregulated in the low-eGFR group compared with high-eGFR patients implying the clinical potential of DKD associated miR-21 in monitoring and preventing disease advancement [58].

The first study to identify a specific miRNA involved in DKD discovered that miRNA192 was upregulated in vitro in mesangial cells (MCs) and in vivo in glomeruli from type 1 streptozotocin-induced and type 2 db/db DKD animal models show that MiRNA192 repression may increase collagen deposition in response to TGF-β [59]. In a systemic review conducted, six miRNAs repeatedly showed to be dysregulated in DKD patients compared to controls in a systemic review: miR-21-5p, miR-29a-3p, miR-126-3p, miR-192-5p, miR-214-3p, and miR-342-3p [59]. Bioinformatics investigation revealed that these six miRNAs are involved in DKD pathogenesis pathways such as apoptosis, fibrosis, and extracellular matrix buildup [59].

A study described the link between microRNA-126, T2DM, and DKD expression, comprised of 52 patients with T2DM and normal albuminuria, 50 patients with T2DM with increased albuminuria (29 with moderate to severe and 21 with severe albuminuria), and 50 non-diabetic healthy people [61]. When compared to controls, microRNA-126 expression was considerably lower in T2DM and even lower in people with DKD [59]. A meta-analysis conducted on 2,747 patients showed that the downregulation of miR-126 was significant (OR: 0.57; 95% CI: 0.44–0.74; p-value < 0.0001) in blood from patients with DKD, while its urinary level was significantly upregulated (OR: 2931.12; 95% CI: 9.96–862,623.21; p-value = 0.0059), suggesting microRNA-126 may have important diagnostic and pathogenetic implications for DN [62].

Transforming growth factor-β

The most notable pathological hallmark of ESRD is kidney fibrosis, characterized by increasing tissue scarring that leads to glomerular and tubulointerstitial fibrosis. TGF-β is the primary regulator of this process, acting as the principal driver of matrix production, matrix degradation inhibition, and myofibroblast activation. In addition, TGF-β1, the most abundant isoform of TGF-β, which is released by all types of renal cells and infiltrating inflammatory cells, is a key participant in the pathogenesis of DKD, owing to its intense profibrotic properties. As a result, this cytokine works on various cells in the kidney, including podocytes and tubular epithelial cells and inflammatory cells such as macrophages and T cells.

According to a recent theory, TGF1 may have an essential role in the early stages of DKD development, and several miRNAs and long non-coding RNAs (lncRNAs) control the critical molecules in the TGF1 pathway. These ncRNAs might be used as biomarkers to determine possible targets for DKD prevention and therapy. Specific miRNAs, such as miR-192, miR-216a, miR-217, and miR-377, have been linked to TGF signaling and the pathophysiology of DKD [63].

The predominant pathogenic hallmark of ESRD is kidney fibrosis, which is characterized by increasing tissue scarring that leads to glomerular and tubulointerstitial fibrosis (TIF). The fibrotic role of TGF-β1 is mainly due to the Smad-dependent pathway after the phosphorylated SMAD2 and SMAD3 bind to SMAD4 to form a complex. This complex is known to upregulate the miR-21 and develop renal fibrosis. On the other hand, SMAD 2 may exert a protective role in renal fibrosis by inhibiting smad 3 to TGF-β1 and SMAD3 nuclear translocations. The Smad-dependent pathway has been shown to regulate the expression of many miRNAs, such as miR-21, miR-29, miR-192, and miR-214. This evidence suggests that miRNA can be utilized as prognostic biomarkers of DKD and add more knowledge about the mechanisms leading to diabetic renal complications [64]. However, the same group of Smad proteins affects diverse gene expression patterns; therefore, the result of TGF-β stimulation results is cell- and context-dependent.

Phosphatase and tensin homolog

By now we know that DKD is a multifactorial illness marked by inflammation, oxidative stress, and TIF. Because of its diverse actions in the pathogenesis of DKD, the role of PTEN is gaining importance as we learn more about its molecular mechanism. Phosphatase and tensin homolog (PTEN) are potent tumor suppressor genes that inhibit the proto-oncogenic PI3K/Akt signaling pathway and regulate basic cellular metabolic activities [65]. According to research, they lower PTEN expression by acting as significant autophagy regulators and TIF via stimulation of the Akt/mammalian target of the rapamycin (mTOR) signaling pathway [66].

Mirna 21 induces renal cell hypertrophy, and matrix expansion as its overexpression lowers PTEN levels and increases Akt phosphorylation, all of which can contribute to the pathologic characteristics of DKD. Thus, miR-21 is the reciprocal regulation of PTEN levels and Akt/TORC1 activity that mediate critical pathologic features of DKD [67]. A (Table 4) illustrate epigenetics in DKD.

Diabetic retinopathy

Diabetic Retinopathy (DR) is thought to be a complex polygenic disease of the eyes and the most prevalent DM complication, with a 27.0% overall prevalence for the period 2015 to 2019, with highest prevalence in Africa at 33.8%, Middle East and North Africa 33.8%, and the Western Pacific region at 36.2% [72].

Chronic hyperglycemia can cause gradual damage to the blood vessels in the retina, resulting in hemorrhage, retinal detachment, and/or blindness. DR is divided into two main types: The early, more common non-Proliferative Diabetic Retinopathy form is characterized by compromised blood vessels. The more severe, late-stage Proliferative Diabetic Retinopathy (PDR) form is characterized by the proliferation of new fragile and leaky blood vessels in the retina or the vitreous chamber. A subtype of DR known as clinically severe macular edema involves direct damage to the macula. While metabolic control has shown to play an essential role in the variability of DR, researchers have investigated the possible connection to genetic factors.

Heritage

Previous family clustering studies in the Diabetes Control and Complications Trial (DCCT) cohort have shown that those individuals with a strong family history of severe DR had an OR of 3.1 [73]. In regard to this, the role of genetic factors in influencing DR ranges from 25 to 50% [74].

Alpha-galactosidase A

For monogenic diseases with Mendelian inheritance, linkage analysis has been best suited [75]. However, this technique has not been successful in a multifactorial disease such as DR. In the Pima Indian cohort, there was limited evidence of linkage to DR susceptibility on chromosomes 3 and 9, with limit of detection (LOD) values of 1.36 and 1.46, respectively 40. A subsequent investigation in this population discovered a locus on chromosome 1 (LOD score of 3.1) similar study revealed locations on chromosomes 3 and 12 (LOD scores 2.41 and 2.47, respectively) in the Mexican American cohort in Starr County [76, 77].

Candidate gene association studies

RAGE

A large candidate gene study conducted in a Caucasian population identified polymorphisms in the RAGE gene associated with DR. It suggested that the effect is linked to HBA1C levels, and the results have been consistently reproduced in other studies performed in Asian Indians [78]. Recently, it has been reported in a Malaysian population that the 2245A allele is associated with the development of DR [79].

Vascular endothelial growth factor (VEGF)

Another candidate gene, VEGF, is linked to the neovascularization process in proliferative retinopathy is located on chr 6 [80]. Multiple SNPs in the promoter region of VEGF have shown their association with DR, mainly the + 405 genotype, which has been shown in a number of diseases, in particular those with an angiogenic basis, like DR [81].

Table 4 Epigenetics in DKD

miRNA	Source	Method	Population	Refs
miR21	Urinary exomes	RT-PCR	T2DM (n = 87)	[81]
miR192	Urinary ECV	RT—PCR	T2DM (n = 80)	[82]
miR29c	Urinary exomes	RT-PCR	CKD (n = 32)	[83]
miR133b	Urinary exomes	RT-PCR & Bioinformatics	T2DM (156)	[84]
miR126	Urine	Metanalysis	Metanalysis (n = 2747)	[75]

Aldose reductase gene

The gene encoding ALR2, located on chromosome 7q35, is the first rate-limiting enzyme of the major metabolic polyol pathway and linked to DM-specific tissue complications [82]. Hyperglycemia increases the intracellular sorbitol, eventually resulting in osmotic stress, playing a key role in the development of DR.

Endothelial nitric oxide synthase (eNOS)

eNOS is a protein that catalyzes the synthesis of nitric oxide (NO) from L-arginine and has been linked to the development of DVC. The eNOS gene (NOS) is found on chromosome 7q35-26, and variations in it have been linked to an increased risk of developing DR. Recently, a meta-analysis was performed to investigate the connection between the previously identified polymorphisms, showing 4b/a polymorphism's intron 4a allele was discovered to be associated with a lower risk of DR [83].

Angiotensin-I converting enzyme (ACE)

The ACE gene, which is found on chromosome 17q23, is one of the most researched candidate genes. The insertion/deletion (I/D) polymorphism has been associated with DR. A recent meta-analysis of over 2000 Chinese patients found that the I/D polymorphism was related with PDR but not with non-proliferative DR [84]. Increased ACE expression has been demonstrated to have a negative effect on retinal blood flow and vascular structure, along with encouraging the development of new retinal blood vessels. Apart from this, newer candidate genes associated with DR have also been reported like Insulin Receptor (INSR), Growth Factor Receptor Bound Protein 2 (GRB2), C-reactive protein (CRP) and Selectin P (SELP).

Genome-wide association studies (SNPs)

SNP rs9896052 on growth factor receptor bound protein 2 (GRB2)

Growth factor receptor bound protein 2 (GRB2) is involved in VEGF signaling and DR is associated with a genetic mutation near GRB2 on chromosome 17q25.1. Several genes in this region are potential candidates, with GRB2 being notably increased during retinal stress and neovascularization. Only polymorphism of rs9896052 [p = 6.55 10(−5)] was shown to be related with sight-threatening diabetic retinopathy in both the type 2 (p = 0.035) and type 1 (p = 0.041) replication cohorts, as well as the Indian cohort (p = 0.016) in recent research [85].

A SNP in rs3913535, NOX4

A SNP in rs3913535, was identified in NOX4 in the Genetics of Go DARTS [86]. This variant was associated with severe DR or PDR; however, the authors were unable to replicate these findings across multiple cohorts.

Epigenetics (miRNA)

Intracellular miRNA

Most miRNAs are intracellular, and their dysregulation has been discovered as an early biomarker in many disorders. Overexpression of miR-21 has been shown to play a key role in the pathogenesis of DR by contributing to DM induced endothelial dysfunction as well as low-grade inflammation [87]. The overexpression of miR-216a protects against human retinal microvascular endothelial cell (HRMEC) injury in DR by downregulating the Nitric oxide synthase/Janus kinase/signal transducer and activator of transcription (NOS2/JAK/STAT) axis [88]. Dysregulation of miR-210 is involved in the development of diabetic retinopathy and serves a regulatory role in retinal vascular endothelial cell proliferation [89]. The miRNA-29b-3p promotes HRMEC apoptosis via blocking Sirtuin 1 (SIRT1) in DR [90]. The upregulation of miR-203a-3p might inhibit retinal neovascularization in oxygen-induced retinopathy (OIR) rat models via targeting VEGFA and Hypoxia-inducible factor 1-alpha (HIF-1α) [91].

Circulatory miRNA

Many circulating miRNAs revealed differential expression across DM patients when analyzed from serum or plasma samples with and without DR (Table 5).

The miR-210 serum expression was higher in DR patients compared to DM patients without retinopathy and healthy controls [89]. The differential overexpression implies that elevated serum miR-210 might be utilized to distinguish PDR patients from NPDR patients. Interestingly, chronic exposure to hyperglycemic environment has shown decreased expression of microRNA 320 (miR-320) but increased the expression of endothelin 1 (ET-1), vascular endothelial growth factor (VEGF), and fibronectin (FN) in human umbilical vein endothelial cells (HUVECs). A study conducted showed that miR-320 negatively regulates expression of ET-1, VEGF, and FN through Extracellular Signal-Regulated Kinase (ERK) ½. The discovery of such a unique glucose-induced mechanisms controlling expression of genes might provide a new therapeutic approach for DR [92]

Macro vascular complication: diabetic cardiovascular disease

Studies have shown that patients with DM are 2 to 4 times more likely to develop Coronary Artery Disease (CAD) and Myocardial Infarction (MI). CVD in T2DM is the highest cause of mortality among individuals above 65 years old. Interestingly, CVD and T2DM share similar pathophysiology. Particularly the presence of insulin

Table 5 Comparison between serum and plasma MiRNA samples in Diabetic Retinopathy

Sample	miRNA	Target	Function	Phenotype	Refs.
Intracellular miRNA	miR-21	EC dysfunction	Pathogenic → inflammation	DR	[98]
	miR-216a	Suppression of NOS2/JAK/STAT	Protective effect → HRMECs	DR	[104]
	miR-29b-3p	Blocking SIRT1	Pathogenic effect → HRMEC apoptosis	DR	[105]
	miR-203a-3p	VEGFA, HIF-1α	Inhibits angiogenesis	PDR	[102]
	miR-200b	VEGF	Inhibits VEGF	DR	[106]
Circulatory miRNA	miR210	EC proliferation	Upregulation Biomarker for PDR vs. NPDR	DR	[100]
	miR320a		Protective effect → increased expression of endothelin 1 (ET-1), vascular endothelial growth factor (VEGF), and fibronectin (FN) in human umbilical vein endothelial cells (HUVECs)	DR	[103]

resistance and high blood glucose in relation to inflammation and chronically elevated oxidative stress, finally resulting in endothelial dysfunction and further associated complications [94].

This complex etiology of CVD in T2DM has been attributed to multiple factors, such as hypertension, dyslipidemia and obesity. Existing data suggest the relationship between T2DM and CVD influences the mechanisms that contribute to vascular damage causing. Moreover, lifestyle modifications, e.g. regular exercise and weight loss, reduce risk of CVD in pre-diabetic people [94].

While the hunt for these SNPs is still underway, several common single-nucleotide polymorphisms (SNPs) have previously been related with an elevated risk of CVD and T2DM. In addition, studies focusing on epigenetics have also shown new connections between these diseases. In this review, we will attempt to address the present state of knowledge concerning the genetic linkages between T2DM and CVD, as well as to show their possible pathophysiological function in the setting of both illnesses.

Linkage analysis

Various chromosome regions (such as 19q, 3p and 11p) were analyzed for the susceptibility to DCVD in two linkage studies resulting showing its linkage to the disease [95, 96].

In a study conducted in Caucasians detected chr 19q13.2 with the strongest linkage evidence109, while Chromosomes 3p, 11p and 19p-q showed association in Caucasian, Hispanic and African American populations, respectively [96].

Candidate gene association analysis

Genes associated with CVD and/or DM mellitus have been the subject of several candidate association studies, with certain connections being repeatedly documented [97]. Polymorphisms in genes involved in lipid metabolism or fibrinolysis, such as apolipoprotein E (APOE), Apolipoprotein B (APOB), Apolipoprotein C (APOC), paraoxonase (PON), Cepher endopeptidase (CETP) and Plasminogen Activator Inhibitor 1(PAI1), have been linked to an increased risk of ischemic vascular disease in diabetic individuals. As known oxidized lipids have shown their role in the progression of metabolic syndrome in DCVD [98, 99].

Paraoxonase

PON is a potential gene for DCVD because it encodes for paraoxons, an enzyme found in HDL [100].

Cepher endopeptidase CETP

CETP polymorphism is a substantial and independent risk factor for atherosclerotic vascular disease, and it plays a vital role in the metabolism of HDL, which controls absorption of cholesterol by hepatocytes. Notably, CETP polymorphism in rs1800774 has been linked to macrovascular disease in T2DM male individuals, regardless of lipid levels [101].

Despite these findings, the question remained unanswered. However recent advances in genetic studies have increased our understanding in the pathophysiology of DR.

Genome-wide association studies (SNPs)

Genetic factors are important in CVD risk; current genome-wide association studies (GWASs) strongly support the notion that genetic predisposition to CVD is often caused by genetic mutations or variance. Loci around such single nucleotide polymorphisms (SNPs) were discovered to have high genome-wide association with increased BMI, hypertension, dyslipidemia, DM, coronary artery disease (CAD), and stroke. However, in recent years, the majority of GWAS examining CVDs or

their sequelae of events have been conducted in European white lineage groups, with minimal evidence in Asian populations. Since the discovery of the chromosome 9p21 susceptibility region by four independent research teams in 2007, GWAS for CVD have yielded a variety of hopeful results [102–105]. By 2009, in separate genome-wide association studies had found a total of twelve additional genetic susceptibility variations [106–108].

Furthermore, large GWAS consortia such as the CAD Genome-wide Replication and Meta-analysis (CARDIoGRAM) Consortium [109], the MIGen Consortium [106], the CAD Genetics Consortium [110], and, most recently, the UK Biobank (UKBB) were formed and merged, eventually analyzing hundreds of thousands of individuals [111]. In 2011 and 2013, the CARDIoGRAM (plus C4D) consortia reported 25 and 46 loci associated with CAD, respectively, both confirming previously published variants, and identifying new associations [112, 113].

Overall, 64 novel CAD risk loci were found by analyzing the UKBB data set (34,541 CAD patients and 261,984 controls) and using CARDIoGRAMplusC4D 1000G data for replication. To present date, > 150 CVD-related loci have been found across the entire genome, with just a few suggesting an increased risk in people with DM [111].

Antisense non coding RNA in the INK4 locus

For instance, a non-coding area on chromosome 9p21, next to the CDKN2A and CDKN2B genes, in the context of a known non-coding RNA locus (ANRIL), was found as one of the most linked spots for MI and CAD by GWA techniques in cohorts of diverse ethnicities [114].

Glutamate-ammonia ligase

Another GWAS discovered SNP rs10911021 in the glutamate-ammonia ligase (GLUL) gene to be associated with CHD in people with T2DM but no evidence of a connection in those without DM [115]. It is an enzyme implicated in ammonia and glutamate detoxification, acid–base homeostasis, cell signaling, and cell proliferation.

Methylguanine methyltransferase (MGMT)

The ACCORD study discovered two significant genome-wide locations, SNP rs9299870 in the MGMT gene and SNP rs57922 at 5q13 [116]. Surprisingly, neither SNP was associated with non-cardiovascular or cardiovascular mortality in people on conventional glycemic control therapy [116]. Furthermore, these SNPs interacted significantly with therapeutic intervention on cardiovascular mortality, suggesting that these genetic variables are regulated via glycemic management.

Glucagon-like peptide-1 (GLP1)

Finally, recently, a significant relationship was discovered with a change in GLP1 levels in the group that received intensive therapy, highlighting GLP1's cardioprotective impact with good glycemic management. As a result, establishing that diabetics have a particular hereditary relationship to CVD [116].

Transcription factor 7 like 2 (TCF7L2)

The transcription factor 7-like 2 gene 2, a member of the Wt signaling pathway, also known as TCF7L2, was discovered to be one of the most important risk factors for T2DM when genome-wide association studies (GWAS) were conducted. Variations in TCF7L2 have been linked to CVD in certain but not all studies. Later investigations looked at the link between three TCF7L2 variations (rs7903146, rs12255372, and rs11196205) and coronary artery disease (CAD) in patients who had had coronary angiography [117]. They discovered that these variations were significantly more strongly associated with CAD in diabetic patients than in non-diabetic ones.

Epigenetics (miRNA) of CVD

Recent scientific research has looked on the relationship between epigenetic changes in T2DM and CVD several studies have demonstrated the involvement of different miRNAs in the pathogenic processes leading to atherosclerosis summarized in (Fig. 1).

The overexpression of miR-185 decreased the expression of the glutathione peroxidase-1 (GPx-1) gene, which codes an enzyme necessary for preventing oxidative stress [118].miR-126 has pro—angiogenic and anti-inflammatory effects on the endothelium. Functionally, it increases the activities of VEGF and fibroblast growth factor, hence contributing to vascular stability and angiogenesis [119, 120]. It inhibits inflammation by blocking TNF-, ROS, and NADPH oxidase via High Mobility Group Box 1 (HMGB1) and attracts progenitor cells through the chemokine CXC Motif Chemokine Ligand 12 (CXCL12) [121, 122]. miR-126 levels are substantially decreased in both cardiomyocytes and plasma in T2DM individuals with no established CVD health history [122, 123]. Patients with CAD [122], indicating that it might serve as a potential diagnostic marker for DM and CVD. Other investigations on endothelial colony-forming cells and progenitor endothelial cells (EPCs) subjected to hyperglycemic environment revealed that miR-134 and miR-130a influenced cell motility and death, respectively [128, 129].

In DM, Vascular Smooth Muscle Cells (VSMCs) lose their muscle contraction and gain proliferative and migratory features, hence promoting the initiation of pathogenic processes associated with CVD [126].

miR-145 has been shown to decrease in concentration in the presence of excessive glucose, to inhibit myocardia gene function via Krüppel-like factor 4(Klf4), and to promote VSMC proliferation [127, 128]. In this regard, it has also been observed that miR-504 and miR-24 promote VSMC proliferation and migration [129, 130].

The relationship between lipid metabolism and microRNAs in DCVD is a crucial issue. Several essential genes involved in lipid production or metabolism. Such as Forkhead box (FoxA2), Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, 3-hydroxy-3-methylglutaryl-CoA synthase-2, and Abhydrolase Domain Containing 5, Lysophosphatidic Acid Acyltransferase, are downregulated by miR-29 in diabetic fat rats [131]. Whereas HNF-4 alpha was discovered to be elevated in diabetic rats and insulin-resistant HepG2 cells due to higher levels of miR-122 [132]. Both miR-122 and HNF-4 alpha could upregulate the expression of the Sterol regulatory-element binding proteins (SREBP-1) and FAAS genes, resulting in aberrant lipid homeostasis and elevated levels of fatty acids and triglyceride production [132].

Platelets have a crucial role in CVD, and their contribution to the onset of cardiovascular problems is enhanced in DM [133]. Patients with diabetes have lower plasma levels of miR-223 and miR-126 [123, 134]. This causes an increase in the P2Y12 receptor and P-selectin, which contributes to platelet dysfunction [134]. Because of this relationship, platelet activation is enhanced in T2DM.

Additionally, macrophages play a crucial function in atherosclerotic plaques. Endothelial cells reduced miR-181b expression in the presence of hyperglycemia or in insulin-resistance, whereas the synthesis of this miR, through the suppression of Phospho-Akt (Ser473) phosphorylation, was related with an M2 macrophages anti-inflammatory response, and not with antiangiogenic effects [135].

Furthermore, study indicates that early glucose management in people with DM is vital in preventing long-term DVC. These findings support the hypothesis that hyperglycemia might have a lasting effect on patient outcomes, a phenomenon known as "metabolic memory". As work in the domain of miRNA connecting T2DM with CVD has progressed, overexpression or under expression from certain miRNAs has demonstrated vulnerability to atherosclerosis via numerous pathogenic pathways. MiRNAs are involved in several processes, involving endothelial function, vascular smooth muscle cells, cardiac myocytes, platelets, and inflammatory processes.

Shared genetic features of vascular complications

Overall, there is evidence indicating the co-occurrence of microvascular and macrovascular problems in patients with diabetes; however, the molecular links underlying how and why they co-occur are less obvious. It is difficult to determine if shared connections represent a common molecular pathway for various microvascular problems or merely the co-occurrence of these complications in the same individual, in whom the linked allele is causal for only one of the issues. Large sample sizes, in-depth phenotyping, more robust findings, and functional studies will be required to conduct the demanding sensitivity, mediation, and mechanistic analyses needed to clarify which loci represent overlapping vs complication-specific biology.

Because DVC is involved in many vital human organ systems, including the kidney, eyes, and cardiovascular system, both in a normal and diabetic setting, we can speculate that common genes impact the development of both these systems and DM mellitus. Thus, using data from DVC genome wide scans, we can perform multivariate genome wide association analyses for these systems as well as DM mellitus.

A whole genome sequencing research utilizing next-generation sequencing technology is an effective way for sequencing the human genome in order to identify new genes associated with uncommon and common diseases. Soon, whole genome sequencing will be the standard, enabling us to get a greater understanding of genetic heterogeneity within populations. Due to the enormous price and time required to sequence substantial parts of the genome, this technology is currently impracticable. This method has the potential to provide more locations for DVC genomic study. In addition, new genetic analytic methods based on next-generation sequencing technology, in conjunction with gene-environment interaction and pathway-based approach studies, provide a powerful tool for examining the genetic pathways implicated in the development of DVC.

Diabetic retinopathy

The genes that cause DR have been the subject of extensive study. Many possible genetic variations that contribute to illness vulnerability have been suggested through linkage studies and candidate gene techniques. However, reproducing these findings has been sporadic at best. Overlap in the DR phenotype and a lack of consistent retinopathy documentation may both contribute to the phenomenon. However, genetic association analyses have shown a few persistent relationships including variants in the ALR2, VEGF, and RAGE genes.

Diabetic cardiovascular disease

In terms of cardiovascular problems, in earlier studies 9p21 has been linked to CAD and DM, implying a potential common candidate gene for both disorders.

Interestingly, chromosome 3 has been found to link the three complications.The early detection of the condition, which results in changes in lifestyle and dietary habits, is critical for disease prevention and control. Characterization of the genetic factors involved in the development of DM and its consequences is expected to lead to a better understanding of molecular etiology and the development of new treatment methods.

Current challenges and future perspective

A better knowledge of the disease's epigenetic background could aid future studies on tailored treatment for DM and its consequences. Emerging research highlights the pivotal role of miRNAs in insulin regulation. DM and chronic hyperglycemia disrupt MiRNA expression in various tissues, impacting disease onset and progression. Furthermore, advancements in the research of how to target miRNAs in vivo may provide significant clues for the future treatment of DM and its consequences.

While we have made progress in understanding the epigenetic mechanisms linked to hyperglycemia in DM, we must acknowledge the challenges in studying epigenetics. To unravel the precise role of epigenetic events that influence gene interactions in DM, advanced sequencing technologies and sophisticated methodologies are imperative. This method can identify miRNAs as valuable indicators of DM susceptibility and prognosis, potentially transforming personalized medicine.

By combining miRNA profiling with genetic information, we can identify at-risk individuals and prescribe tailored treatments, enhancing preventive measures. Centralizing this data, alongside clinical information, is crucial for combating DM effectively. Furthermore, exploring MiRNA alterations in the brain, a key player in glucose regulation, can provide a comprehensive understanding of DM's systemic impact in response to hyperglycemia and hyperlipidemia.

Conclusion

Our understanding of the genetics of monogenic and polygenic types of DM has made significant progress in recent decades. Consequently, the precision medicine strategy of adapting treatment to the features of each patient has been effectively applied to monogenic DM subtypes, Maturity-onset diabetes of the young, and neonatal DM. In contrary, in polygenic diabetic subgroups, and notably in T2DM, subgroup recognition is difficult, and indications for patient therapy are generally absent. However, new data predict the likelihood of T2DM, and when paired with appropriate phenotypes, these are expected to shed light on the pathogenesis of T2DM subgroups in the near future making it an important part as both diagnostic and therapeutic tools.

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