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REVIEW

Genetics of macrovascular complications in type 2 diabetes

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Abstract

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that currently affects more than 400 million worldwide and is projected to cause 552 million cases by the year 2030. Long-term vascular complications, such as coronary artery disease, myocardial infarction, stroke, are the leading causes of morbidity and mortality among diabetic patients. The recent advances in genome-wide technologies have given a powerful impetus to the study of risk markers for multifactorial diseases. To date, the role of genetic and epigenetic factors in modulating susceptibility to T2DM and its vascular complications is being successfully studied that provides the accumulation of genomic knowledge. In the future, this will provide an opportunity to reveal the pathogenetic pathways in the development of the disease and allow to predict the macrovascular complications in T2DM patients. This review is focused on the evidence of the role of genetic variants and epigenetic changes in the development of macrovascular pathology in diabetic patients.

Key Words: Type 2 diabetes; Epigenetics; Genetics; Macrovascular complications

Core Tip: Type 2 diabetes mellitus (T2DM) is often associated with life-threatening macrovascular complications which may lead to an eye injury, kidney failure, and reduction in life expectancy in patients with diabetes. This review is focused on genetic and epigenetic risk factors for macrovascular complications development in patients with T2DM.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that currently affects more than 400 million worldwide and is projected to cause 552 million cases by the year 2030[1]. Long-term vascular complications, such as coronary artery disease (CAD), myocardial infarction (MI), stroke, are the leading causes of morbidity and mortality among diabetic patients[2]. T2DM is strongly associated with both microvascular and macrovascular complications which may lead to an eye injury, kidney failure, and reduction in life expectancy in patients with diabetes. Diabetic microvascular (involving small vessels such as capillaries) and macrovascular (involving large vessels such as arteries and veins) complications have similar etiologic characteristics [3]. Chronic hyperglycemia plays a major role in the development of microvascular and macrovascular pathology in diabetic patients through several molecular mechanisms, including overproduction of reactive oxygen species (ROS), advanced glycation end-products formation (AGE), activation of protein kinase C as well as polyol and hexosamine pathways[2] (Figure 1). The key pathological mechanism of macrovascular complications is assumed to be an injury to the vascular endothelium. The altered glucose metabolism inhibits the enzyme responsible for NO production and increases production of ROS[3]. In combination with endothelial cell insulin resistance, it causes endothelial dysfunction manifesting itself in increased expression of adhesion molecules and further changes[4]. Another factor involved in the development and progression of diabetic macrovascular complications is impaired platelet function which may lead to increased risks for thrombus formation and atherosclerosis progression[5]. A number of studies, including family- and twin-based studies, demonstrated the role of a genetic component in both T2DM and macrovascular pathology[6]. The development of high-throughput and affordable genotyping technologies, statistical tools, and computational software allowed remarkable progress over the past decade in the search for genetic associations of complex disorders such as T2DM, CAD, MI, stroke[7,8]. However, the pathogenetic mechanisms leading to macrovascular complications in individuals with diabetes are not yet fully understood. Moreover, the question of how genetic susceptibility interacts with environmental factors and epigenetic factors remains unsolved. In this review, we summarize the evidence for genetic variants and epigenetic factors involved in the development of macrovascular pathology in T2DM and discuss the pathogenetic mechanisms underlying their development in T2DM.

GENETIC VARIANTS ASSOCIATED WITH DEVELOPMENT OF MACROVASCULAR COMPLICATIONS IN T2DM PATIENTS

Cardiovascular diseases

CAD represents the manifestation of atherosclerosis in the coronary arteries which supply the myocardium with oxygen and other nutrients and is the leading cause of morbidity and mortality worldwide due to serious complications like MI[9]. Diabetes mellitus is associated with increased risk factor of CAD, independent of other risk factors such as hypertension, hyperlipidemia, and tobacco smoking. Patients with T2DM have a 2-3 times higher rate of cardiovascular disease as compared to people without T2DM[10]. To date, genomic research led to the identification of more than 150 common genetic risk loci of CAD and MI[8]. And some of these variants were demonstrated to be significantly associated with cardiovascular diseases (CVD) in individuals with diabetes[11,12]. Several studies that analyzed T2DM or CAD using the mendelian randomization (MR) approach, commonly used for testing causal associations between a risk factor and outcome of interest, were published. The results of these studies provided genetic evidence that higher BMI and hyperglycemia had a positive causal association with CAD[13]. Early studies in the genetics of T2DM and CAD identified several shared loci associated with both diseases[14]. Some studies were performed to evaluate whether CAD-susceptibility loci identified by genome-

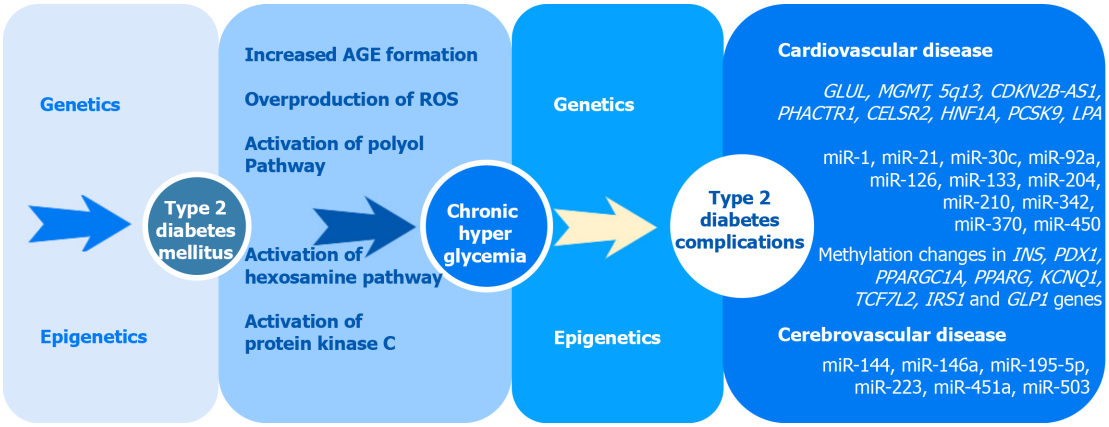

Figure 1 Genetic and epigenetic factors involved in development of diabetic complications. AGE: Advanced glycation end-products formation; ROS: Reactive oxygen species.

wide association (GWA) studies of the general population also contributed to CAD in type 2 diabetes. The association between 9p21 Locus (the variants rs2383206 and rs10757278) and CAD in individuals with type 2 diabetes was shown in a case-control study performed by Doria *et al*[11] in 2008. Previous GWA studies reported the independent association of this locus with CAD[15,16]. The association of rs10757274 with MI risk was later replicated in a Chinese study[17]. In 2011, Qi *et al*[12] genotyped 15 genetic markers in three cohorts of diabetic patients: the prospective Nurses' Health Study (309 CAD cases and 544 controls) and Health Professional Follow-up Study (345 CAD cases and 451 controls), and the cross-sectional Joslin Heart Study (422 CAD cases and 435 controls). Five single-nucleotide polymorphisms, rs4977574 (*CDKN2A/2B*), rs12526453 (*PHACTR1*), rs646776 (*CELSR2-PSRC1-SORT1*), rs2259816 (*HNF1A*), and rs11206510 (*PCSK9*) showed directionally consistent association with CAD in the 3 studies[12].

A total of 1517 CAD cases and 2671 CAD-negative controls, all with type 2 diabetes, were included in the 3-stage genome-wide analysis performed by Qi *et al*[12]. A previously unknown genetic variant rs10911021 in the region of the *GLUL* gene on chromosome 1q25 was found to be associated with CAD. The *GLUL* encodes glutamate-ammonia ligase (also known as glutamine synthase) which catalyzes the conversion of glutamic acid and ammonia into glutamine. Evidence from experimental and human studies points to glutamine/glutamic acid metabolism contribute to the regulation of insulin secretion and glucose metabolism. According to the results of this GWAS, the minor allele had a protective effect. The authors also observed that the risk homozygous genotype of rs10911021 was associated with a 32% lower expression level of the nearest downstream gene *GLUL* compared to the protective allele homozygous genotype in endothelial cells. The identified variant was not associated with the risk of type 2 diabetes in the DIAGRAM database. No association between the risk variant and serum fasting insulin, HOMA-IR, or 2 h-glucose was found in the MAGIC database. This suggests that the pathways underlying the association of the variant with CAD are distinct from those involved in the etiology of type 2 diabetes and insulin-resistance mechanisms[18]. The association of the variant rs10911021 with CVD in T2DM was confirmed in several follow-up studies[19,20]. In 2016 Shah *et al* conducted a GWA study of cardiovascular mortality in the ACCORD intensive arm and found two loci at 10q26 and 5q13 specifically associated with cardiovascular mortality. The lead variant (rs9299870) was shown to be associated with a 3.6-fold increased risk of cardiovascular death. The variant rs9299870 is located in intron 1 of the *MGMT* gene. The *MGMT* encodes for O-6-methylguanine-DNA methyltransferase that is involved in cellular defense against mutagenesis and toxicity from alkylating agents, and in gene methylation[21,22]. The other locus is located on chromosome 5, upstream and proximal to three long intergenic noncoding (LINC) RNAs (LINC1335, LINC1333, and LINC1331) and associated with *NSA2* expression. The lead variant (rs57922) was associated with a 2.7-fold increased risk of cardiovascular death[23]. A GWAS of CAD was conducted in the UK Biobank in the cohort that included 15666 unrelated individuals (3968 CAD cases and 11698 controls) of white British ancestry with diabetes. Significant evidence for association of the previously well-established *LPA* locus (rs74617384) and locus at 9p21 (rs10811652) with CAD was reported. Moreover, some other variants previously associated with CAD showed similar effects

in patients with and without diabetes[24]. In a recent GWAS, a systematic assessment of genetic overlap between CAD and T2DM was performed on a large cohort (66643 subjects). The results of the study demonstrated that none of the previously characterized CAD loci had a specific effect on CAD in T2DM individuals[25]. The results of this study, indicated that the increased risk of CAD in diabetic patients could be explained not only by known genetic variants with a large effect but by the other risk factors, including epigenetic changes, that may contribute to the pathogenesis of T2DM, should be considered. Genes associated with macrovascular complications of T2DM are summarized in Table 1.

Cerebrovascular diseases

Cerebrovascular diseases (CeVD) include a variety of medical conditions that affect the blood vessels of the brain and cerebral circulation. About 20%-40% of patients with type 2 diabetes suffer from cerebral blood vessel diseases. The mechanisms of the CeVD development in type 2 diabetes are complex and not fully understood, but the underlying process is associated with atherosclerotic changes in the cerebral arteries [26,27]. Individuals with diabetes develop dyslipidemia characterized by small dense low-density lipoproteins (LDLs), reduced high-density lipoproteins, and increased triacylglycerol levels[28]. Epidemiologic studies showed that type 2 diabetes was associated with a 2- to 5-fold increased risk of ischemic CeVD[29,30]. To date, information on the role of genetic variants associated with CeVD in individuals with T2DM is extremely limited. To explore the effects of genetic predisposition to T2DM, hyperglycemia, insulin resistance, and β-cell dysfunction on the risk of stroke subtypes and related cerebrovascular phenotypes, the MR analysis was recently performed by Georgakis *et al*[31]. Results of the study provided genetic evidence for a causal effect of T2DM and elevated HbA1c levels in the pre-diabetic range on the risk of an ischemic stroke, large artery stroke, carotid plaque, and small vessel stroke. Genetic predisposition to insulin resistance was found to be associated with large artery and small vessel stroke, whereas predisposition to β-cell dysfunction was associated with small vessel stroke[31]. Further studies are needed to clarify etiological mechanisms of the CeVD-T2DM association and genetic variants involved in it.

EPIGENETIC MECHANISMS INVOLVED IN MACROVASCULAR DISEASE IN DIABETIC PATIENTS

Investigation of the epigenetic pathways will allow us to get closer to a complete understanding of the causes and mechanisms of T2DM complications development. Based on the results of previous studies, the main epigenetic changes, contributing to the occurrence and progress of T2DM and its complications, include alteration of microRNA (miRNA) expression, DNA methylation, and histone acetylation.

MiRNA

Increasing evidence demonstrated an impact of epigenetics on the development of T2DM macrovascular complications. Several theories were proposed, focusing on miRNAs, histone modifications, and DNA methylation.miRNAs are small noncoding RNAs involved in the post-transcriptional regulation of gene expression. Previous researches showed changes in the miRNA expression profile in T2DM patients[32]. A series of recent studies indicated that miRNA expression profiling might contribute to the identification of miRNAs with prognostic value for the early detection of macrovascular complications of diabetes (Table 2).

For example, based on the results of the recent research by Al-Kafaji *et al*[33], miR-126 was differentially expressed in T2DM patients with CAD, T2DM patients without macrovascular complications, and healthy control subjects. An inverse correlation with LDL was also demonstrated in the first group of patients[33]. These findings were successfully replicated in more recent work[34]. MiR-126 also was found to have lower expression levels in diabetic patients with CAD compared to T2DM patients without MVC in this study. The authors additionally showed that a significantly higher expression level of miR-210 was a risk factor for developing MVC and might potentially serve as a biomarker for CAD. MiR-126 is endothelial cell-specific and is known to directly inhibit negative regulators of the VEGF (vascular endothelial growth factor) and to affect vascular integrity and angiogenesis[35,36], which indicates the possible involvement of miR-126 in the pathogenesis of CAD. As was previously reported in the literature, the decreased expression level of miR-126 is significantly

Table 1 Genetic variants associated with macrovascular complications of type 2 diabetes mellitus

	Gene symbol	Region	dbSNP ID	Risk allele	Condition	Ref.
1	*GLUL*	1q25	rs10911021	*C*	CAD	Qi *et al*[18], Beaney *et al*[19], and Look AHEAD Research Group[20]
2	*MGMT*	10q26.3	rs9299870	*A*	Cardiovascular mortality	Shah *et al*[23]
3	Intergenic	5q13	rs57922	*T*	Cardiovascular mortality	Shah *et al*[23]
4	*CDKN2B-AS1*	9p21	rs10757274	*G*	MI	Doria *et al*[11], and Zhang *et al*[17]
5	*CDKN2B-AS1*	9p21	rs2383206	*G*	MI	Doria *et al*[11], and Zhang *et al*[17]
6	*CDKN2B-AS1*	9p21	rs4977574	*G*	CAD	Qi *et al*[12]
7	*PHACTR1*	6p24	rs12526453	*C*	CAD	Qi *et al*[12]
8	*CELSR2*	1p21	rs646776	*T*	CAD	Qi *et al*[12]
9	*HNF1A*	12q24	rs2259816	*T*	CAD	Qi *et al*[12]
10	*PCSK9*	1p32	rs11206510	*T*	CAD	Qi *et al*[12]
11	*LPA*	6q25	rs74617384	*T*	CAD	Fall *et al*[24]
12	*CDKN2B-AS1*	9p21	rs10811652	*C*	CAD	Fall *et al*[24]

CAD: Coronary artery disease; MI: Myocardial infarction.

Table 2 MicroRNAs associated with macrovascular complications of type 2 diabetes mellitus

miRNA	miRNA detection method	Condition	Source	Country	Ref.
miR-92a	qRT-PCR	Acute coronary syndrome	Serum	China	Wang *et al*[69]
miR-30c	qRT-PCR	CAD	Plasma	China	Luo *et al*[70]
miR-126	qRT-PCR	CAD	Whole blood	Bahrain	Al-Kafaji *et al*[33]
miR-126, miR-210	qRT-PCR	CAD	Plasma	Egypt	Amr *et al*[34]
miR-370	qRT-PCR	CAD	Serum	Egypt	Motawae *et al*[80]
miR-21	qRT-PCR	In-stent restenosis CAD	Plasma	China	Guan *et al*[59]
miR-342, miR-450	qRT-PCR	CAD	Serum	Egypt	Seleem *et al*[81]
miR-1, miR-133	qRT-PCR	CAD	Whole blood	Bahrain	Al-Muhtaresh *et al*[87]
miR-204	qRT-PCR	Coronary artery calcification	Plasma	China	Ding *et al*[94]
miR-21	qRT-PCR	Acute heart failure	Serum	Turkey	Al-Hayali *et al*[54]
miR-144, miR-223	qRT-PCR	Ischemic stroke	Platelet, plasma	China	Yang *et al*[88]
miR-223, miR-146a	qRT-PCR	Ischemic stroke	Platelet	China	Duan *et al*[97]
miR-195-5p, miR-451a	qRT-PCR	Transient ischemic attack	Serum	Italy	Giordano *et al*[106]
miR-503	qRT-PCR	Ischemic stroke	Plasma	Iran	Sheikhbahaei *et al*[118]
miR-223	qRT-PCR	Ischemic stroke	PBMC	China	Long *et al*[99]

miRNA: MicroRNA; qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction; CAD: Coronary artery disease; PBMC: Peripheral blood mononuclear cells.

associated with CAD risk[37] and elevated levels of LDL cholesterol in CAD patients [38]. Furthermore, many studies provided evidence for the implication of miR-126 in T2DM pathogenesis. A number of authors identified low circulating miR-126 in T2DM individuals with CAD[33,34,39] and without MVC[40].

MiR-210 expression is induced during hypoxia in normal and transformed cells. Aberrant expression of miR-210 was detected in many pathological conditions such as tumor progression, MI, cutaneous ischemic wounds[41]. This can be explained by a wide range of miR-210 targets involved in the processes of angiogenesis, DNA repair, mitochondrial metabolism, and cell survival[42]. There is some evidence that the

expression of miR-210 is significantly elevated in stable atherosclerotic plaques[43]. This can be explained by the protective effect of miR-210 that provides fibrous cap stability and prevents plaque rupture[44]. MiR-210 may also play a role in atherosclerosis progression through inhibiting endothelial apoptosis and regulating cell proliferation and differentiation during hypoxia, thus protecting a heart from damage [45,46]. Increased miR-210 expression is required for endothelial cell survival and migration during oxygen deficiency[47]. According to Hu *et al*[48], angiogenesis stimulation and apoptosis inhibition by miR-210 allowed to improve cardiac function and to reduce negative consequences of MI in mice. Another study demonstrated that miR-210 overexpression protected limbs from muscular and vascular ischemic damage in transgenic mouse strain[49,50]. Several studies suggest that miR-210 may be considered as a potential therapeutic target for ischemic conditions, in particular for ischemic heart disease[44,48], and also serve as biomarkers for peripheral artery disease[51]. Results concerning aberrant miR-210 expression in T2DM patients also showed tissue-dependent expression changes. The miR-210 level was reduced in adipose tissue of diabetic individuals according to Pek *et al*[52]. However, its circulating level was higher compared to normal control in peripheral blood of newly diagnosed T2DM patients based on the results of another research[53]. Since miR-210 is involved in multiple hypoxia-regulated metabolic pathways, its differential expression was detected in many diseases. This leaves us with an open question of the potential use of miR-210 as a single biomarker. A possible way out is to determine co-expressed miRNAs for a more accurate prediction of a particular disease or complication.

An association between miR-21 expression profile and T2DM MVC was confirmed in 2 independent studies. It was found out that miR-21 was overexpressed in diabetic patients with CAD or with heart failure or without any MVC compared to the control group[54]. However, a still unsolved question is whether miR-21 may be used as a potential biomarker for MVC. Numerous studies were conducted to investigate miR-21 expression levels in T2DM patients. Most of them demonstrated significantly elevated amounts of circulating miR-21 in plasma and serum in subjects with T2DM [55-58]. At this stage, authors suggest that combined analysis of miR-21 expression, galectin-3, and N-terminal pro-brain natriuretic peptide can help to overcome the limitations and to improve the predictive value of miR-21[54]. Nevertheless, despite the low specificity of miR-21 as an independent prognostic marker of MVC, there is some evidence to suggest miR-21 expression profiling may be used for predicting the occurrence of in-stent restenosis for CAD patients after percutaneous coronary intervention[59]. MiR-21 also was found to be upregulated in patients with acute coronary syndrome and could be a possible candidate of a biomarker for CAD prediction[60].

Previous studies in mice showed that downregulation of miR-92a expression had a positive effect on the state of the vascular wall, attenuated inflammation of endothelium, prevented the development of atherosclerosis, promoted the stability of atherosclerotic plaques and the re-endothelization process[61,62]. These findings were confirmed by subsequent studies in CAD and pre-atherosclerotic patients in which miR-92a expression was increased in comparison to healthy controls[63-65]. Also, an increased level of miR-92a expression was found in coronary atherosclerotic plaques while comparing expression profiles with intact internal mammary arteries[66]. Interestingly, patients with acute MI were shown to have upregulated expression level of miR-92a compared to patients with a stable form of CAD[67]. The still open question is whether miR-92a can be used as a biomarker for T2DM MVC. In the study of Karolina *et al*[68], miR-92a expression was downregulated in T2DM patients. According to recent reports, an elevated circulating miR-92a level was associated with acute coronary syndrome in diabetic subjects[69].

The association of circulating miR-30c with the risk of MVC of T2DM was demonstrated in the study performed by Luo *et al*[70]. The expression levels of circulating miR-30c were significantly downregulated in patients with T2DM complicated by CAD. Authors also found out that decreased circulating miR-30c was associated with severe coronary artery lesions[70]. These data confirmed the previous findings, according to which downregulation of miR-30c-5p in macrophage-derived microparticles might result in the development of early atherosclerosis[71]. A decrease in expression of miR-30c also contributes to the pathogenesis of diabetic cardiomyopathy[72]. Moreover, miR-30c was shown to be associated with an increased risk of recurrent ischemic events in intracranial atherosclerotic disease[73]. Stimulation of miR-30c expression was proposed as a therapy for the prevention of atherosclerosis [71] and diabetic cardiomyopathy[72].

One of the first reports demonstrating the participation of miR-370 in the pathogenesis of atherosclerosis showed that patients suffering from a stable form of CAD had a high miR-370 level in peripheral blood mononuclear cells (PBMC). Based on the results, the authors suggested miR-370 could be used to determine individuals at risk for acute coronary syndromes[74]. The results were replicated in another study, according to which the expression levels of miR-370 in PBMC were upregulated compared to controls. This study also revealed that miR-370 was involved in atherosclerosis development through targeting *FOXO1* gene[75]. Genetic variations and epigenetic modifications of *FOXO1* are known to be associated with atherosclerotic plaque formation[76,77]. Upregulation of circulating miR-370 expression in plasma of CAD patients was found by several authors[78,79]. At the same time, decreased expression was shown in the peripheral blood in pre-atherosclerotic subjects[63]. Concerning diabetic patients, expression of miRNA 370 was higher in the T2DM+CAD group while compared to T2DM patients without MVC[80].

The recent research performed by Seleem *et al*[81] confirmed the importance of miR-450 and miR-342 in developing T2DM MVC by demonstrating an aberrant expression in patients suffering from T2DM complicated by CAD with clots. Downregulation of miR-450 in a mouse model with diabetic cardiomyopathy was previously reported in the literature[82]. The stimulating effect of miR-342-3p on the fibroblast growth factor 11 gene (*FGF11*) is known to promote the proliferation and migration of endothelial cells. Hyperinsulinemia results in the instability of interaction of miR-342 and *FGF11*, leading to vascular dysfunction in diabetic subjects[83]. Moreover, the upregulation of miR-342-5p in early atherosclerotic lesions in mice was discovered by Wei *et al*[84]. The authors proposed a possible use of miR-342-5p as a target for the therapy of atherosclerotic lesions.

MiR-1 and miR-133 also deserve attention as possible biomarkers for MVC development in T2DM patients. MiR-1 is known to be selectively expressed in heart muscle and to regulate cardiomyocyte growth responses[85]. MiR-133 also was shown to be expressed in cardiac muscle and to regulate cardiomyocyte proliferation through targeting *CCND2* gene[86]. MiR-1 and miR-133 both were significantly associated with CAD risk in T2DM patients according to Al-Muhtaresh *et al*[87]. Although the association was stronger for miR-1 after adjustment for some anthropometric and clinical characteristics, authors proposed the use of a combined assessment of the expression levels of miR-1 and miR-133 to improve the diagnostic power for MVC prediction[87]. An elevated miR-1 expression level in individuals with CAD compared to healthy subjects was also shown in the previous research[88]. At the same time, the results were not replicated in another study, where miR-1 expression level did not show a significant difference between CAD patients and controls[89]. MiR-133b, in turn, was downregulated in CAD individuals according to Kumar *et al*[60].

MiR-204 is known to regulate cardiomyocyte proliferation through targeting the Jarid2 pathway[90,91]. Recently, there were several studies of miR-204 association with CAD that demonstrated significant downregulation of miR-204 expression in atherosclerotic plaques[92,93]. Interestingly, the decreased level of miR-204 expression in T2DM patients was associated with coronary artery calcification[94]. The contribution of miR-204 downregulation to vascular smooth muscle cell calcification also was previously shown by another group of authors in mice[95].

MiR-223 as well may be a substantial factor in the development of T2DM. As known, it is important for the regulation of *GLUT4* expression and glucose uptake in the heart[96]. The correlation between miR-223 expression level and susceptibility to MVC of T2DM was described several times by now but remains controversial. For instance, in the study performed by Duan *et al*[97], platelet and plasma expression of miR-223 was significantly altered in diabetic patients with and without ischemic stroke compared to healthy controls, but there was no difference between T2DM and T2DM + ischemic stroke groups. Also, no differences were found between patients with ischemic stroke and controls[97]. According to another study, expression of miR-223 was decreased in diabetic subjects, but these changes were more noticeable in T2DM patients with ischemic stroke[98]. The lack of association between expression of miR-223-3p in PBMC and risk of ischemic stroke was confirmed afterward by Long *et al*[99], although expression level in PBMC of T2DM patients was also significantly decreased. An interesting finding regarding miR-223-3p was described recently. MiR-223-3p was found to be upregulated in atherosclerotic plaques in individuals with unstable CAD[100]. This fact allows suggesting the potential use of miR-223-3p as a biomarker for acute coronary events in diabetic subjects.

MiR-144 plays an important role in the T2DM pathogenesis, since one of its target genes, *IRS1*, encodes insulin receptor substrate 1[101]. IRS1/PI3K/AKT signaling pathway is involved in the translocation of glucose transporter type 4 into the plasma

membrane[102]. MiR-144 may thus regulate glucose uptake by skeletal muscle, cardiac muscle, and adipose tissue. At the same time, there is a proven association between miR-144 and predisposition to CAD. A study by Chen *et al*[103] concluded that increased plasma level of miR-144 might serve as a promising biomarker for CAD and its severity. This association can be partially explained by the recent research that demonstrated the involvement of miR-144 in cholesterol and oxysterol metabolism in male CAD mice[104]. Moreover, altered expression of miR-144 was shown to be a risk factor for ischemic stroke in T2DM patients[98]. Upregulated miR-144 expression was detected in samples from individuals with large-vessel stroke in the study by Tan *et al*[105].

According to the results of recent research, miR-451a and miR-195-5p were found to be upregulated in diabetic patients after a transient ischemic attack in comparison to control patients and non-diabetic patients after a transient ischemic attack[106]. The earlier study also demonstrated an increased expression level of miR-451a in the serum of subjects with ischemic stroke[107]. It is worth noting that aberrant expression of miR-451a was also found in T2DM[108] and CAD patients[109]. MiR-195, in turn, was downregulated in diabetic subjects[110].

One of the most promising miRNAs for consideration as a biomarker for stroke in diabetic patients is miR-146a. Previous research showed a significant reduction in miR-146a expression level in whole blood and serum of patients with acute ischemic stroke[111,112]. The data contradict the results of the previous study that showed no difference in the expression of miR-146a when comparing stroke patients with controls, although expression in plasma and platelet was downregulated in diabetic individuals with stroke[97]. This inconsistency can be explained by the different material in which expression was analyzed. There are several theories about the mechanism of miR-146a involvement in stroke pathogenesis. Li *et al*[111] suggest upregulation of the miR-146a target, Fbxl10, protects neurons from ischemic damage. Also, researchers demonstrated a different mechanism for miR-146a involvement in stroke recovery. MiR-146a was shown to repress its other targets TRAF6 and IRAK1 which are components of TRAF6/NF-κB signaling pathway responsible for cellular responses to stress. This makes the expression of miR-146a important for the proliferation, migration, and angiogenesis ability of endothelial progenitor cells[113]. Upregulation of miR-146a also had an anti-inflammatory effect and prevented oxidative stress in mice after hemorrhagic stroke[114]. At the same time, alongside the protective potential in stroke, miR-146a was shown to participate in the process of atherogenesis[115]. For instance, miR-146a was upregulated in human atherosclerotic plaques in the Tampere Vascular Study[43]. Cheng *et al*[116] demonstrated knockout of miR-146a in the vasculature might contribute to atherogenesis by endothelial activation. Nguyen and co-authors described atherosclerosis progression resulting from a miR-146a-mediated decrease in cell migration and macrophage entrapment in vascular intima[117].

The data obtained by Sheikhbahaei *et al*[118] allows raising the question of the potential use of miR-503 as a biomarker for ischemic stroke in T2DM patients. The study also provides evidence that miR-503 may serve as an indicator of short-term outcomes of ischemic stroke in diabetic individuals. Another group of authors earlier demonstrated upregulated miR-503 in ischemic limbs of diabetic mice. Circulating miR-503 was also elevated in T2DM patients[119]. The mechanism of influence on the vascular wall was explained by the inhibiting of vascular smooth muscle cells migration and proliferation through targeting the *INSR* gene[120]. The same effect was demonstrated afterward in HUVECs in high glucose conditions[121].

DNA methylation and histone acetylation

With the expansion of knowledge of epigenetic mechanisms, the question of the importance of DNA methylation and histone acetylation in the pathogenesis of MVC of T2DM arises. The main mechanism in the development of MVC of T2DM is atherosclerotic lesions of major arteries. There is wide evidence of a key role of epigenetics in atherosclerotic plaque formation. The association of DNA methylation and histone acetylation with atherosclerosis was discussed in detail in a recent review by Lee. In particular, the authors described a cascade that begins with endothelial dysfunction through *Dnmt1* overexpression mediated by DNA methylation changes in mice with disturbed blood flow and after leads to infiltration into the intima and subintima by macrophages[122,123]. A significant DNA hypomethylation was detected in human atherosclerotic lesions and ApoE knock-out mice[124]. The same processes are affected by histone acetylation, as illustrated by numerous studies[123]. Histone acetylation is connected with the expression of matrix metalloproteinases which play an important role in extracellular matrix destruction that leads to plaque rupture[125,126]. Histone

modifications were also reported to contribute to oxLDL mediated expression of inflammatory IL-8 and monocyte-chemoattractant protein-1 in endothelial cells[127], increasing the endothelium permeability and subsequent infiltration by macrophages. Another process in atherogenesis is related to increased H3K9 and H3K27 acetylation, which is associated with smooth muscle cell proliferation, migration, and stabilization of plaque[128].

The influence of DNA methylation changes on T2DM pathogenesis was extensively studied. A recent literature review[129] provides information on hypermethylated genes responsible for beta cell function in diabetic patients. These genes include promoters of *INS*, encoding insulin[130], *PDX1*, responsible for beta cell development and regeneration[131,132], *PPARGC1A*, significantly associated with type 2 diabetes during increased physical activity[133,134], and *GLP1R*, encoding receptor of glucagon-like peptide 1[135].

The inflammatory process also plays an important role in the development of diabetes[136]. Macrophage activation is mediated by epigenetic changes and contributes to chronic inflammation and the pathogenesis of diabetes complications. The main mechanisms of epigenetic modification of macrophage activity were described in detail in a review article by Ahmed *et al*[137]. The authors described a hyperlipidemia-induces pathway of macrophage activation through DNA methylation and suppression of anti-inflammatory genes in macrophages of diabetic rats with hindlimb ischemia[138] and obese mice[139]. Another reported activation pathway was through increased histone methylation of the promoter of RelA (or p65) subunit of NF-κB (nuclear factor-κappa beta), a regulator of innate immune cell responses[140-142]. The research also concluded hypoxia stimulated macrophage activation through histone acetylation.

Overweight and obesity are associated with insulin resistance and metabolic syndrome. It is a well-known risk factor for T2DM and its complications. Several recent studies indicated the altered level of DNA methylation in the adipose tissue of diabetic patients. Genes with aberrant methylation status were mainly related to carbohydrate and lipid metabolism, insulin resistance, inflammation, and cell cycle regulation[143]. For instance, methylation of *PPARG*, *KCNQ1*, *TCF7L2*, and *IRS1* was different in adipose tissue of individuals with T2DM and subjects from the control group[144]. DNA methylation level was also increased in B cells from obese and T2DM patients and natural killer cells from diabetic patients, and associated with insulin resistance[145,146].

Epigenetic changes may also mediate the impact of environmental factors on the development of T2DM, in addition to controlling the regulation of gene expression. For example, transient spikes of hyperglycemia result in epigenetic changes in the promoter of RelA subunit of the nuclear factor κB in aortic endothelial cells in mice, leading to upregulated RelA expression, associated with endothelial cell inflammation [147,148].

MANAGEMENT OF MVC IN T2DM PATIENTS

Prophylactic measures play an important role in preventing the development of MVC in T2DM patients and include correction of hyperglycemia, dyslipidemia, antihypertensive therapy, and lifestyle modification with diet, physical activity, and smoking cessation[149]. Main standards for hypoglycemic therapy were described by the American Diabetes Association and European Association for the Study of Diabetes[150,151]. The effectiveness of antiglycemic therapy largely depends on genetic factors, which was repeatedly shown by many pharmacogenetic candidate gene studies and GWAS. The data on the main polymorphisms affecting the effectiveness of both metformin and new oral hypoglycemic drugs were summarized in a recent review by Mannino[152]. Interindividual variability in response to different classes of antihypertensive drugs and adverse reactions may also be partially explained by genetic polymorphisms[153]. Pharmacogenetics is of particular importance in the correction of dyslipidemia in T2DM due to muscle toxicity of statins, observed in about 10% of patients[154]. However, the results of many pharmacogenetic studies conducted in small cohorts were not replicated in larger populations. Also, the inconsistency may be associated with the ethnicity of the population analyzed, which must be taken into account when prescribing personalized therapy [155].

IMPACT OF GENETIC FACTORS IN VASCULAR COMPLICATIONS IN DIABETIC PATIENTS WITH CORONAVIRUS DISEASE 2019

Coronavirus disease 2019 (COVID-19) pandemic made it clear that the presence of metabolic syndrome and its components (T2DM, hypertension, and obesity) significantly aggravated the severity of infectious diseases[156,157]. The most common comorbidity in COVID-19 patients is hypertension, followed by T2DM, which are observed in 30% and 19% of patients respectively[158]. Diabetic patients with COVID-19 are more likely to suffer from CVD and associated vascular complications which lead to a poor prognosis and an increased risk of in-hospital death[159]. The high incidence of MVC in COVID-19 patients with T2DM and hypertension can be explained by the virus targeting the endothelium[160]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to bind to angiotensin-converting enzyme 2, encoded by *ACE2* gene, for entering cells[161]. Previous researches showed that variants in the *ACE2* and its expression level might influence the severity of the disease[162,163]. Also, the question of the possible influence of *ACE2* expression on the clinical outcome during therapy with ACE inhibitors and angiotensin II receptor blocker remains open. A recent study by Sardu *et al*[164] showed that anti-hypertensive drugs did not affect the clinical outcomes in COVID-19 patients. Moreover, a combination of those drugs with anti-inflammatory and immune therapies might even improve the prognosis. *ACE2* is expressed in lungs, kidneys, heart, and, importantly, in pancreatic islets, namely, in β-cells producing insulin[165,166]. Besides, there is evidence of the participation of *ACE2* in glucose metabolism. Ace2-knockout mice had β-cells defects in research performed by Bernardi *et al*[167], although the defect was compensated by energy shift to glucose utilization. *ACE2* deletion also led to cardiovascular dysfunction, which was demonstrated in studies in mice[162,168,169]. At the same time, *ACE2* overexpression resulted in improvement of β-cell function[170]. The association between *ACE2* polymorphisms and SARS-CoV-2 susceptibility or severity of outcomes was investigated in numerous previous studies. For instance, *ACE2* variants were shown to be protective against COVID-19 in African and Eastern Mediterranean populations, but no association was found in American and European cohorts[171]. Three rare variants in *ACE2* were found to have a possible impact on the disease severity in patients of Russian ancestry[172]. A recent analysis of a large genomic dataset allowed to identify 17 potentially protective polymorphisms in *ACE2* gene and 9 variants increasing susceptibility[173]. Interestingly, the *ACE2* gene promoter region contains a binding site for hepatocyte nuclear factor 1 alpha that induces *ACE2* expression in pancreatic islet cells[174]. Polymorphisms within the promoter region of *ACE2* may thus also contribute to the severity of disease, especially in diabetic patients, and should be considered as possible variants predisposing to susceptibility to SARS-CoV-2 and severe course of COVID-19 disease[175].

CONCLUSION

Type 2 diabetes is associated with vascular complications of both small and large vessels, which seriously impair the overall quality of life and can result in lower life expectancy. The discovery of genetic determinants of T2DM complications would advance the development of personalized treatment of diabetic patients and significantly reduce adverse outcomes. Despite the recent progress in the discovery of new genetic and epigenetic determinants of T2DM and its complications, the pathogenetic mechanisms of their participation remain largely unknown. An additional challenge for genetic studies of complex diseases is to establish the causal relationship of the genes involved in pathogenesis and their interactions in the development of the underlying disease and comorbid pathologies. Further research in the large independent cohorts, deep phenotyping of participants, and functional studies are needed to reveal pathogenetic pathways underlying the disorders. It is especially important to pay attention to genetic and epigenetic factors during pregnancy or in cases when a diabetic individual has a comorbid disease. As for pregnancy, the frequency of MI was shown to be 3-4 times higher during the peripartum period[176]. As was discussed above, the presence of an acute infectious pathology can significantly increase the risks of diabetes complications. The study of the development of macrovascular complications in diabetic patients with SARS-CoV-2 infection may be of particular interest.

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