

World Journal of *Diabetes*

World J Diabetes 2021 August 15; 12(8): 1141-1362



EDITORIAL

- 1141 Clinical effects of antidiabetic drugs on psoriasis: The perspective of evidence-based medicine
Zhang MX, Zheng BY, Chen HX, Chien CW

REVIEW

- 1146 Gut microbiota as a target for prevention and treatment of type 2 diabetes: Mechanisms and dietary natural products
Xia F, Wen LP, Ge BC, Li YX, Li FP, Zhou BJ
- 1164 Current progress in metabolomics of gestational diabetes mellitus
Wang QY, You LH, Xiang LL, Zhu YT, Zeng Y
- 1187 Progress in treatment of type 2 diabetes by bariatric surgery
Jin ZL, Liu W
- 1200 Genetics of macrovascular complications in type 2 diabetes
Tonyan ZN, Nasykhova YA, Danilova MM, Glotov AS

MINIREVIEWS

- 1220 Place of intravitreal dexamethasone implant in the treatment armamentarium of diabetic macular edema
Karti O, Saatci AO
- 1233 Cardiac changes in infants of diabetic mothers
Al-Biltagi M, El razaky O, El Amrousy D
- 1248 Effect of inflammatory bowel disease treatments on patients with diabetes mellitus
Bower JAJ, O'Flynn L, Kakad R, Aldulaimi D
- 1255 Perioperative challenges in management of diabetic patients undergoing non-cardiac surgery
Galway U, Chahar P, Schmidt MT, Araujo-Duran JA, Shivakumar J, Turan A, Ruetzler K

ORIGINAL ARTICLE**Basic Study**

- 1267 Decabromodiphenyl ether causes insulin resistance and glucose and lipid metabolism disorders in mice
Alimu A, Abudureman H, Wang YZ, Li MY, Wang JS, Liu ZL

Case Control Study

- 1282 Clinical significance of serum miR-129-5p in patients with diabetes mellitus presenting macrovascular complications
He XY, Ou CL

Retrospective Study

- 1292 Association of β -cell function and insulin resistance with pediatric type 2 diabetes among Chinese children
Xu ZR, Du HW, Cui LW, Zheng RX, Li GM, Wei HY, Lu FY, Chen LL, Wu CS, Zhang SX, Zhang SL, Liu F, Zhang MY, Pei Z, Sun CJ, Wu J, Luo FH

Observational Study

- 1304 Polymorphisms in HIF-1 α gene are not associated with diabetic retinopathy in China
Liu YH, Guo C, Sun YQ, Li Q

SYSTEMATIC REVIEWS

- 1312 Which predictors could effect on remission of type 2 diabetes mellitus after the metabolic surgery: A general perspective of current studies?
Akkus G, Tetiker T
- 1325 What can we learn from β -cell failure biomarker application in diabetes in childhood? A systematic review
Calderón-Hernández MF, Altamirano-Bustamante NF, Revilla-Monsalve C, Mosquera-Andrade MB, Altamirano-Bustamante MM

ABOUT COVER

Editorial Board Member, Vaia D Raikou, PhD, Chief Doctor, Department of Nephrology, Doctors' Hospital, Athens 11257, Greece. vraikou@med.uoa.gr

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes (WJD, World J Diabetes)* is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJD* as 3.763; IF without journal self cites: 3.684; 5-year IF: 7.348; Journal Citation Indicator: 0.64 □ Ranking: 80 among 145 journals in endocrinology and metabolism; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Lin-YuTong Wang*; Production Department Director: *Yu-Jie Ma*, Editorial Office Director: *Jia-Ping Yan*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Timothy Koch

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

August 15, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Genetics of macrovascular complications in type 2 diabetes

Ziravard N Tonyan, Yulia A Nasykhova, Maria M Danilova, Andrey S Glotov

ORCID number: Ziravard N Tonyan 0000-0001-9050-5886; Yulia A Nasykhova 0000-0002-3543-4963; Maria M Danilova 0000-0002-3656-230X; Andrey S Glotov 0000-0002-7465-4504.

Author contributions: All authors contributed equally to the work.

Supported by Ministry of Science and Higher Education of the Russian Federation within the Applied Science Research Program, No. AAAA-A20-120041390028-0; and Estonia-Russia Cross Border Cooperation Programme 2014-2020, No. ER24.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

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

Manuscript source: Invited

Ziravard N Tonyan, Yulia A Nasykhova, Maria M Danilova, Andrey S Glotov, Department of Genomic Medicine, D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology, Saint-Petersburg 199034, Russia

Yulia A Nasykhova, Andrey S Glotov, Laboratory of Biobanking and Genomic Medicine of Institute of Translation Biomedicine, St. Petersburg State University, Saint-Petersburg 199034, Russia

Corresponding author: Andrey S Glotov, DSc, PhD, Senior Scientist, Department of Genomic Medicine, D.O. Ott Research Institute of Obstetrics, Gynecology and Reproductology, Mendeleevskaya Line 3, Saint-Petersburg 199034, Russia. anglotov@mail.ru

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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

manuscript

Specialty type: Endocrinology and metabolism**Country/Territory of origin:** Russia**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

Received: March 1, 2021**Peer-review started:** March 1, 2021**First decision:** April 20, 2021**Revised:** May 4, 2021**Accepted:** July 9, 2021**Article in press:** July 9, 2021**Published online:** August 15, 2021**P-Reviewer:** Verma AK**S-Editor:** Gao CC**L-Editor:** Filipodia**P-Editor:** Wang LL**Citation:** Tonyan ZN, Nasykhova YA, Danilova MM, Glotov AS. Genetics of macrovascular complications in type 2 diabetes. *World J Diabetes* 2021; 12(8): 1200-1219**URL:** <https://www.wjgnet.com/1948-9358/full/v12/i8/1200.htm>**DOI:** <https://dx.doi.org/10.4239/wjd.v12.i8.1200>

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-

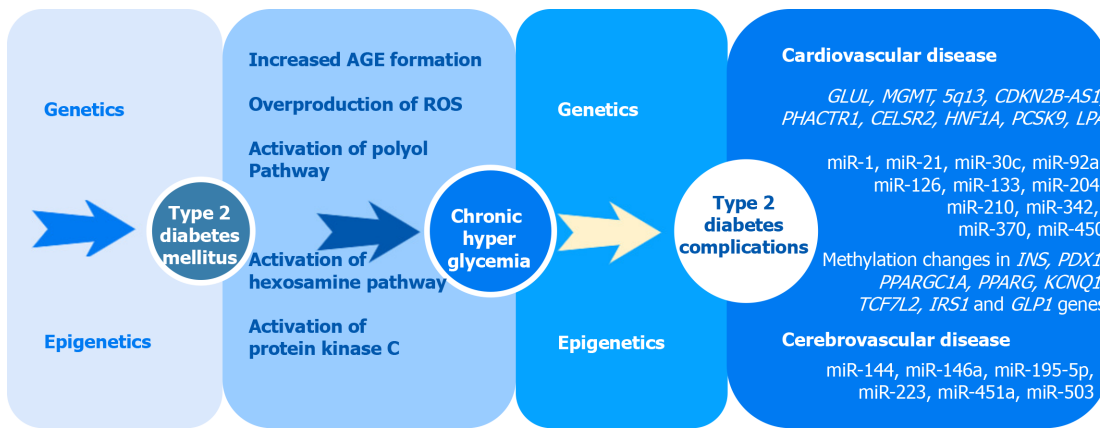


Figure 1 Genetic and epigenetic factors involved in development of diabetic complications. AGE: Advanced glycation end-products formation; ROS: Reactive oxygen species.

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 <i>et al</i> [18], Beaney <i>et al</i> [19], and Look AHEAD Research Group[20]
2	MGMT	10q26.3	rs9299870	A	Cardiovascular mortality	Shah <i>et al</i> [23]
3	Intergenic	5q13	rs57922	T	Cardiovascular mortality	Shah <i>et al</i> [23]
4	CDKN2B-AS1	9p21	rs10757274	G	MI	Doria <i>et al</i> [11], and Zhang <i>et al</i> [17]
5	CDKN2B-AS1	9p21	rs2383206	G	MI	Doria <i>et al</i> [11], and Zhang <i>et al</i> [17]
6	CDKN2B-AS1	9p21	rs4977574	G	CAD	Qi <i>et al</i> [12]
7	PHACTR1	6p24	rs12526453	C	CAD	Qi <i>et al</i> [12]
8	CELSR2	1p21	rs646776	T	CAD	Qi <i>et al</i> [12]
9	HNF1A	12q24	rs2259816	T	CAD	Qi <i>et al</i> [12]
10	PCSK9	1p32	rs11206510	T	CAD	Qi <i>et al</i> [12]
11	LPA	6q25	rs74617384	T	CAD	Fall <i>et al</i> [24]
12	CDKN2B-AS1	9p21	rs10811652	C	CAD	Fall <i>et al</i> [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 <i>et al</i> [69]
miR-30c	qRT-PCR	CAD	Plasma	China	Luo <i>et al</i> [70]
miR-126	qRT-PCR	CAD	Whole blood	Bahrain	Al-Kafaji <i>et al</i> [33]
miR-126, miR-210	qRT-PCR	CAD	Plasma	Egypt	Amr <i>et al</i> [34]
miR-370	qRT-PCR	CAD	Serum	Egypt	Motawae <i>et al</i> [80]
miR-21	qRT-PCR	In-stent restenosis CAD	Plasma	China	Guan <i>et al</i> [59]
miR-342, miR-450	qRT-PCR	CAD	Serum	Egypt	Seleem <i>et al</i> [81]
miR-1, miR-133	qRT-PCR	CAD	Whole blood	Bahrain	Al-Muhtaresh <i>et al</i> [87]
miR-204	qRT-PCR	Coronary artery calcification	Plasma	China	Ding <i>et al</i> [94]
miR-21	qRT-PCR	Acute heart failure	Serum	Turkey	Al-Hayali <i>et al</i> [54]
miR-144, miR-223	qRT-PCR	Ischemic stroke	Platelet, plasma	China	Yang <i>et al</i> [88]
miR-223, miR-146a	qRT-PCR	Ischemic stroke	Platelet	China	Duan <i>et al</i> [97]
miR-195-5p, miR-451a	qRT-PCR	Transient ischemic attack	Serum	Italy	Giordano <i>et al</i> [106]
miR-503	qRT-PCR	Ischemic stroke	Plasma	Iran	Sheikhbahaei <i>et al</i> [118]
miR-223	qRT-PCR	Ischemic stroke	PBMC	China	Long <i>et al</i> [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-Muhtareh *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- κ B 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 Sheikhabaehi *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- κ B (nuclear factor-kappa 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 κ B 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, anti-hypertensive 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.

REFERENCES

- 1 **Whiting DR**, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; **94**: 311-321 [PMID: 22079683 DOI: 10.1016/j.diabres.2011.10.029]
- 2 **Cole JB**, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol* 2020; **16**: 377-390 [PMID: 32398868 DOI: 10.1038/s41581-020-0278-5]
- 3 **Cade WT**. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther* 2008; **88**: 1322-1335 [PMID: 18801863 DOI: 10.2522/ptj.20080008]
- 4 **Rask-Madsen C**, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. *Cell Metab* 2013; **17**: 20-33 [PMID: 23312281 DOI: 10.1016/j.cmet.2012.11.012]
- 5 **Grant PJ**. Diabetes mellitus as a prothrombotic condition. *J Intern Med* 2007; **262**: 157-172 [PMID: 17645584 DOI: 10.1111/j.1365-2796.2007.01824.x]
- 6 **Rich SS**. Mapping genes in diabetes. Genetic epidemiological perspective. *Diabetes* 1990; **39**: 1315-1319 [PMID: 2227105 DOI: 10.2337/diab.39.11.1315]
- 7 **Malik R**, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, Anderson CD, Chong M, Adams HHH, Ago T, Almgren P, Amouyel P, Ay H, Bartz TM, Benavente OR, Bevan S, Boncoraglio GB, Brown RD Jr, Butterworth AS, Carrera C, Carty CL, Chasman DI, Chen WM, Cole JW, Correa A, Cotlarciuc I, Cruchaga C, Danesh J, de Bakker PIW, DeStefano AL, den Hoed M, Duan Q, Engelter ST, Falcone GJ, Gottesman RF, Grewal RP, Gudnason V, Gustafsson S, Haessler J, Harris TB, Hassan A, Havulinna AS, Heckbert SR, Holliday EG, Howard G, Hsu FC, Hyacinth HI, Ikram MA, Ingelsson E, Irvin MR, Jian X, Jiménez-Conde J, Johnson JA, Jukema JW, Kanai M, Keene KL, Kissela BM, Kleindorfer DO, Kooperberg C, Kubo M, Lange LA, Langefeld CD, Langenberg C, Launer LJ, Lee JM, Lemmens R, Leys D, Lewis CM, Lin WY, Lindgren AG, Lorentzen E, Magnusson PK, Maguire J, Manichaikul A, McArdle PF, Meschia JF, Mitchell BD, Mosley TH, Nalls MA, Ninomiya T, O'Donnell MJ, Psaty BM, Pulit SL, Rannikmäe K, Reiner AP, Rexrode KM, Rice K, Rich SS, Ridker PM, Rost NS, Rothwell PM, Rotter JI, Rundek T, Sacco RL, Sakaue S, Sale MM, Salomaa V, Sapkota BR, Schmidt R, Schmidt CO, Schminke U, Sharma P, Slowik A, Sudlow CLM, Tanislav C, Tatlisumak T, Taylor KD, Thijs VNS, Thorleifsson G, Thorsteinsdottir U, Tiedt S, Trompet S, Tzourio C, van Duijn CM, Walters M, Wareham NJ, Wassertheil-Smoller S, Wilson JG, Wiggins KL, Yang Q, Yusuf S; AFGen Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium; International Genomics of Blood Pressure (iGEN-BP) Consortium; INVENT Consortium; STARNET, Bis JC, Pastinen T, Ruusalepp A, Schadt EE, Koplev S, Björkegren JLM, Codoni V, Civelek M, Smith NL, Trégouët DA, Christophersen IE, Roselli C, Lubitz SA, Ellinor PT, Tai ES, Kooper JS, Kato N, He J, van der Harst P, Elliott P, Chambers JC, Takeuchi F, Johnson AD; BioBank Japan Cooperative Hospital Group; COMPASS Consortium; EPIC-CVD Consortium; EPIC-InterAct Consortium; International Stroke Genetics Consortium (ISGC); METASTROKE Consortium; Neurology Working Group of the CHARGE Consortium; NINDS Stroke Genetics Network (SiGN); UK Young Lacunar DNA Study; MEGASTROKE Consortium, Sanghera DK, Melander O, Jern C, Strbian D, Fernandez-Cadenas I, Longstreth WT Jr, Rolfs A, Hata J, Woo D, Rosand J, Pare G, Hopewell JC, Saleheen D, Stefansson K, Worrall BB, Kittner SJ, Seshadri S, Fornage M, Markus HS, Howson JMM, Kamatani Y, Debette S, Dichgans M. Multiethnic genome-wide association study of 520,000 subjects identifies 32 Loci associated with stroke and stroke subtypes. *Nat Genet* 2018; **50**: 524-537 [PMID: 29531354 DOI: 10.1038/s41588-018-0058-3]
- 8 **Erdmann J**, Kessler T, Munoz Venegas L, Schunkert H. A decade of genome-wide association studies for coronary artery disease: the challenges ahead. *Cardiovasc Res* 2018; **114**: 1241-1257 [PMID: 29617720 DOI: 10.1093/cvr/cvy084]
- 9 **GBD 2013 Mortality and Causes of Death Collaborators**. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**: 117-171 [PMID: 25530442 DOI: 10.1016/S0140-6736(14)61682-2]
- 10 **World Health Organization**. Global report on diabetes. [cited 1 March 2021]. In: World Health Organization [Internet]. 2016: 1-83. Available from: <https://www.who.int/publications/i/item/9789241565257>
- 11 **Doria A**, Wojcik J, Xu R, Gervino EV, Hauser TH, Johnstone MT, Nolan D, Hu FB, Warram JH. Interaction between poor glycemic control and 9p21 Locus on risk of coronary artery disease in type 2 diabetes. *JAMA* 2008; **300**: 2389-2397 [PMID: 19033589 DOI: 10.1001/jama.2008.649]
- 12 **Qi L**, Parast L, Cai T, Powers C, Gervino EV, Hauser TH, Hu FB, Doria A. Genetic susceptibility to coronary heart disease in type 2 diabetes: 3 independent studies. *J Am Coll Cardiol* 2011; **58**: 2675-2682 [PMID: 22152955 DOI: 10.1016/j.jacc.2011.08.054]
- 13 **Frayling TM**, Stoneman CE. Mendelian randomisation in type 2 diabetes and coronary artery disease. *Curr Opin Genet Dev* 2018; **50**: 111-120 [PMID: 29935421 DOI: 10.1016/j.gde.2018.05.010]
- 14 **Goodarzi MO**, Rotter JI. Genetics Insights in the Relationship Between Type 2 Diabetes and Coronary Heart Disease. *Circ Res* 2020; **126**: 1526-1548 [PMID: 32437307 DOI: 10.1161/CIRCRESAHA.119.316065]
- 15 **Helgadottir A**, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Sigurdsson

- A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsson H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science* 2007; **316**: 1491-1493 [PMID: 17478679 DOI: 10.1126/science.1142842]
- 16 **McPherson R**, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, Hinds DA, Pennacchio LA, Tybjaerg-Hansen A, Folsom AR, Boerwinkle E, Hobbs HH, Cohen JC. A common allele on chromosome 9 associated with coronary heart disease. *Science* 2007; **316**: 1488-1491 [PMID: 17478681 DOI: 10.1126/science.1142447]
- 17 **Zhang LW**, Li JP, Duan FF, Liu ZK, Zhan SY, Hu YH, Jiang J, Zhang Y, Huo Y, Chen DF. Interaction of type 2 diabetes mellitus with chromosome 9p21 rs10757274 polymorphism on the risk of myocardial infarction: a case-control study in Chinese population. *BMC Cardiovasc Disord* 2014; **14**: 170 [PMID: 25430018 DOI: 10.1186/1471-2261-14-170]
- 18 **Qi L**, Qi Q, Prudente S, Mendonca C, Andreozzi F, di Pietro N, Sturma M, Novelli V, Mannino GC, Formoso G, Gervino EV, Hauser TH, Muehlschlegel JD, Niewczas MA, Krolewski AS, Biolo G, Pandolfi A, Rimm E, Sesti G, Trischitta V, Hu F, Doria A. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. *JAMA* 2013; **310**: 821-828 [PMID: 23982368 DOI: 10.1001/jama.2013.276305]
- 19 **Beaney KE**, Cooper JA, McLachlan S, Wannamethee SG, Jeffers BJ, Whincup P, Ben-Shlomo Y, Price JF, Kumari M, Wong A, Ong K, Hardy R, Kuh D, Kivimaki M, Kangas AJ, Soininen P, Ala-Korpela M, Drenos F, Humphries SE; UCLEB consortium. Variant rs10911021 that associates with coronary heart disease in type 2 diabetes, is associated with lower concentrations of circulating HDL cholesterol and large HDL particles but not with amino acids. *Cardiovasc Diabetol* 2016; **15**: 115 [PMID: 27549350 DOI: 10.1186/s12933-016-0435-0]
- 20 **Look AHEAD Research Group**. Prospective Association of GLUL rs10911021 With Cardiovascular Morbidity and Mortality Among Individuals With Type 2 Diabetes: The Look AHEAD Study. *Diabetes* 2016; **65**: 297-302 [PMID: 26395743 DOI: 10.2337/db15-0890]
- 21 **Fagerberg L**, Hallström BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, Habuka M, Tahmasebpoor S, Danielsson A, Edlund K, Asplund A, Sjöstedt E, Lundberg E, Szegedy CA, Skogs M, Takanen JO, Berling H, Tegel H, Mulder J, Nilsson P, Schwenk JM, Lindskog C, Danielsson F, Mardinoglu A, Sivertsson A, von Feilitzen K, Forsberg M, Zwahlen M, Olsson I, Navani S, Huss M, Nielsen J, Ponten F, Uhlén M. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol Cell Proteomics* 2014; **13**: 397-406 [PMID: 24309898 DOI: 10.1074/mcp.M113.035600]
- 22 **Lin D**, Xiao Y, Huang B, Wu X, Chen C, Liang Y, Zeng. O-6-methylguanine DNA methyltransferase is a favorable biomarker with proliferation suppressive potential in Breast Cancer. *J Cancer* 2020; **11**: 6326-6336 [PMID: 33033516 DOI: 10.7150/jca.46466]
- 23 **Shah HS**, Gao H, Morieri ML, Skupien J, Marvel S, Paré G, Mannino GC, Buranasupkajorn P, Mendonca C, Hastings T, Marcovina SM, Sigal RJ, Gerstein HC, Wagner MJ, Motsinger-Reif AA, Buse JB, Kraft P, Mychaleckyj JC, Doria A. Genetic Predictors of Cardiovascular Mortality During Intensive Glycemic Control in Type 2 Diabetes: Findings From the ACCORD Clinical Trial. *Diabetes Care* 2016; **39**: 1915-1924 [PMID: 27527847 DOI: 10.2337/dc16-0285]
- 24 **Fall T**, Gustafsson S, Orho-Melander M, Ingelsson E. Genome-wide association study of coronary artery disease among individuals with diabetes: the UK Biobank. *Diabetologia* 2018; **61**: 2174-2179 [PMID: 30003307 DOI: 10.1007/s00125-018-4686-z]
- 25 **van Zuydam NR**, Ladenvall C, Voight BF, Strawbridge RJ, Fernandez-Tajes J, Rayner NW, Robertson NR, Mahajan A, Vlachopoulou E, Goel A, Kleber ME, Nelson CP, Kwee LC, Esko T, Mihailov E, Mägi R, Milani L, Fischer K, Kanoni S, Kumar J, Song C, Hartiala JA, Pedersen NL, Perola M, Gieger C, Peters A, Qu L, Willems SM, Doney ASF, Morris AD, Zheng Y, Sesti G, Hu FB, Qi L, Laakso M, Thorsteinsdottir U, Grallert H, van Duijn C, Reilly MP, Ingelsson E, Deloukas P, Kathiresan S, Metspalu A, Shah SH, Sinisalo J, Salomaa V, Hamsten A, Samani NJ, März W, Hazen SL, Watkins H, Saleheen D, Morris AP, Colhoun HM, Groop L, McCarthy MI, Palmer CNA; SUMMIT Steering Committee; CARDIOGRAMplusC4D Steering Committee*. Genetic Predisposition to Coronary Artery Disease in Type 2 Diabetes Mellitus. *Circ Genom Precis Med* 2020; **13**: e002769 [PMID: 33321069 DOI: 10.1161/CIRCGEN.119.002769]
- 26 **Yang R**, Pedersen NL, Bao C, Xu W, Xu H, Song R, Qi X. Type 2 diabetes in midlife and risk of cerebrovascular disease in late life: a prospective nested case-control study in a nationwide Swedish twin cohort. *Diabetologia* 2019; **62**: 1403-1411 [PMID: 31172222 DOI: 10.1007/s00125-019-4892-3]
- 27 **Air EL**, Kissela BM. Diabetes, the metabolic syndrome, and ischemic stroke: epidemiology and possible mechanisms. *Diabetes Care* 2007; **30**: 3131-3140 [PMID: 17848611 DOI: 10.2337/dc06-1537]
- 28 **Lee M**, Saver JL, Hong KS, Song S, Chang KH, Ovbiagele B. Effect of pre-diabetes on future risk of stroke: meta-analysis. *BMJ* 2012; **344**: e3564 [PMID: 22677795 DOI: 10.1136/bmj.e3564]
- 29 **Kissela B**, Air E. Diabetes: impact on stroke risk and poststroke recovery. *Semin Neurol* 2006; **26**: 100-107 [PMID: 16479448 DOI: 10.1055/s-2006-933313]
- 30 **Larsson SC**, Wallin A, Håkansson N, Stackelberg O, Bäck M, Wolk A. Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases. *Int J Cardiol* 2018; **262**: 66-70 [PMID:

- 29605469 DOI: [10.1016/j.ijcard.2018.03.099](https://doi.org/10.1016/j.ijcard.2018.03.099)]
- 31 **Georgakis MK**, Harshfield EL, Malik R, Franceschini N, Langenberg C, Wareham NJ, Markus HS, Dichgans M. Diabetes Mellitus, Glycemic Traits, and Cerebrovascular Disease: A Mendelian Randomization Study. *Neurology* 2021; **96**: e1732-e1742 [PMID: [33495378](https://pubmed.ncbi.nlm.nih.gov/33495378/) DOI: [10.1212/WNL.0000000000011555](https://doi.org/10.1212/WNL.0000000000011555)]
 - 32 **Kim M**, Zhang X. The Profiling and Role of miRNAs in Diabetes Mellitus. *J Diabetes Clin Res* 2019; **1**: 5-23 [PMID: [32432227](https://pubmed.ncbi.nlm.nih.gov/32432227/) DOI: [10.33696/diabetes.1.003](https://doi.org/10.33696/diabetes.1.003)]
 - 33 **Al-Kafaji G**, Al-Mahroos G, Abdulla Al-Muhtaresh H, Sabry MA, Abdul Razzak R, Salem AH. Circulating endothelium-enriched microRNA-126 as a potential biomarker for coronary artery disease in type 2 diabetes mellitus patients. *Biomarkers* 2017; **22**: 268-278 [PMID: [27321479](https://pubmed.ncbi.nlm.nih.gov/27321479/) DOI: [10.1080/1354750X.2016.1204004](https://doi.org/10.1080/1354750X.2016.1204004)]
 - 34 **Amr KS**, Abdelmawgoud H, Ali ZY, Shehata S, Raslan HM. Potential value of circulating microRNA-126 and microRNA-210 as biomarkers for type 2 diabetes with coronary artery disease. *Br J Biomed Sci* 2018; **75**: 82-87 [PMID: [29452547](https://pubmed.ncbi.nlm.nih.gov/29452547/) DOI: [10.1080/09674845.2017.1402404](https://doi.org/10.1080/09674845.2017.1402404)]
 - 35 **Wang S**, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, Richardson JA, Bassel-Duby R, Olson EN. The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. *Dev Cell* 2008; **15**: 261-271 [PMID: [18694565](https://pubmed.ncbi.nlm.nih.gov/18694565/) DOI: [10.1016/j.devcel.2008.07.002](https://doi.org/10.1016/j.devcel.2008.07.002)]
 - 36 **Fish JE**, Santoro MM, Morton SU, Yu S, Yeh RF, Wythe JD, Ivey KN, Bruneau BG, Stainier DY, Srivastava D. miR-126 regulates angiogenic signaling and vascular integrity. *Dev Cell* 2008; **15**: 272-284 [PMID: [18694566](https://pubmed.ncbi.nlm.nih.gov/18694566/) DOI: [10.1016/j.devcel.2008.07.008](https://doi.org/10.1016/j.devcel.2008.07.008)]
 - 37 **Wang X**, Lian Y, Wen X, Guo J, Wang Z, Jiang S, Hu Y. Expression of miR-126 and its potential function in coronary artery disease. *Afr Health Sci* 2017; **17**: 474-480 [PMID: [29062343](https://pubmed.ncbi.nlm.nih.gov/29062343/) DOI: [10.4314/ahs.v17i2.22](https://doi.org/10.4314/ahs.v17i2.22)]
 - 38 **Sun X**, Zhang M, Sanagawa A, Mori C, Ito S, Iwaki S, Satoh H, Fujii S. Circulating microRNA-126 in patients with coronary artery disease: correlation with LDL cholesterol. *Thromb J* 2012; **10**: 16 [PMID: [22925274](https://pubmed.ncbi.nlm.nih.gov/22925274/) DOI: [10.1186/1477-9560-10-16](https://doi.org/10.1186/1477-9560-10-16)]
 - 39 **Rezk NA**, Sabbah NA, Saad MS. Role of MicroRNA 126 in screening, diagnosis, and prognosis of diabetic patients in Egypt. *IUBMB Life* 2016; **68**: 452-458 [PMID: [27118517](https://pubmed.ncbi.nlm.nih.gov/27118517/) DOI: [10.1002/iub.1502](https://doi.org/10.1002/iub.1502)]
 - 40 **Liu Y**, Gao G, Yang C, Zhou K, Shen B, Liang H, Jiang X. The role of circulating microRNA-126 (miR-126): a novel biomarker for screening prediabetes and newly diagnosed type 2 diabetes mellitus. *Int J Mol Sci* 2014; **15**: 10567-10577 [PMID: [24927146](https://pubmed.ncbi.nlm.nih.gov/24927146/) DOI: [10.3390/ijms150610567](https://doi.org/10.3390/ijms150610567)]
 - 41 **Chan YC**, Banerjee J, Choi SY, Sen CK. miR-210: the master hypoxamir. *Microcirculation* 2012; **19**: 215-223 [PMID: [22171547](https://pubmed.ncbi.nlm.nih.gov/22171547/) DOI: [10.1111/j.1549-8719.2011.00154.x](https://doi.org/10.1111/j.1549-8719.2011.00154.x)]
 - 42 **Devlin C**, Greco S, Martelli F, Ivan M. miR-210: More than a silent player in hypoxia. *IUBMB Life* 2011; **63**: 94-100 [PMID: [21360638](https://pubmed.ncbi.nlm.nih.gov/21360638/) DOI: [10.1002/iub.427](https://doi.org/10.1002/iub.427)]
 - 43 **Raitoharju E**, Lyytikäinen LP, Levula M, Oksala N, Mennander A, Tarkka M, Klopp N, Illig T, Kähönen M, Karhunen PJ, Laaksonen R, Lehtimäki T. miR-21, miR-210, miR-34a, and miR-146a/b are up-regulated in human atherosclerotic plaques in the Tampere Vascular Study. *Atherosclerosis* 2011; **219**: 211-217 [PMID: [21820659](https://pubmed.ncbi.nlm.nih.gov/21820659/) DOI: [10.1016/j.atherosclerosis.2011.07.020](https://doi.org/10.1016/j.atherosclerosis.2011.07.020)]
 - 44 **Eken SM**, Jin H, Chernogubova E, Li Y, Simon N, Sun C, Korzunowicz G, Busch A, Bäcklund A, Österholm C, Razuvaev A, Renné T, Eckstein HH, Pelisek J, Eriksson P, González Díez M, Perisic Matic L, Schellinger IN, Raaz U, Leeper NJ, Hansson GK, Paulsson-Berne G, Hedin U, Maegdefessel L. MicroRNA-210 Enhances Fibrous Cap Stability in Advanced Atherosclerotic Lesions. *Circ Res* 2017; **120**: 633-644 [PMID: [27895035](https://pubmed.ncbi.nlm.nih.gov/27895035/) DOI: [10.1161/CIRCRESAHA.116.309318](https://doi.org/10.1161/CIRCRESAHA.116.309318)]
 - 45 **Li Y**, Yang C, Zhang L, Yang P. MicroRNA-210 induces endothelial cell apoptosis by directly targeting PDK1 in the setting of atherosclerosis. *Cell Mol Biol Lett* 2017; **22**: 3 [PMID: [28536634](https://pubmed.ncbi.nlm.nih.gov/28536634/) DOI: [10.1186/s11658-017-0033-5](https://doi.org/10.1186/s11658-017-0033-5)]
 - 46 **Guan Y**, Song X, Sun W, Wang Y, Liu B. Effect of Hypoxia-Induced MicroRNA-210 Expression on Cardiovascular Disease and the Underlying Mechanism. *Oxid Med Cell Longev* 2019; **2019**: 4727283 [PMID: [31249644](https://pubmed.ncbi.nlm.nih.gov/31249644/) DOI: [10.1155/2019/4727283](https://doi.org/10.1155/2019/4727283)]
 - 47 **Fasanaro P**, D'Alessandra Y, Di Stefano V, Melchionna R, Romani S, Pompilio G, Capogrossi MC, Martelli F. MicroRNA-210 modulates endothelial cell response to hypoxia and inhibits the receptor tyrosine kinase ligand Ephrin-A3. *J Biol Chem* 2008; **283**: 15878-15883 [PMID: [18417479](https://pubmed.ncbi.nlm.nih.gov/18417479/) DOI: [10.1074/jbc.M800731200](https://doi.org/10.1074/jbc.M800731200)]
 - 48 **Hu S**, Huang M, Li Z, Jia F, Ghosh Z, Lijkwan MA, Fasanaro P, Sun N, Wang X, Martelli F, Robbins RC, Wu JC. MicroRNA-210 as a novel therapy for treatment of ischemic heart disease. *Circulation* 2010; **122**: S124-S131 [PMID: [20837903](https://pubmed.ncbi.nlm.nih.gov/20837903/) DOI: [10.1161/CIRCULATIONAHA.109.928424](https://doi.org/10.1161/CIRCULATIONAHA.109.928424)]
 - 49 **Zaccagnini G**, Maimone B, Di Stefano V, Fasanaro P, Greco S, Perfetti A, Capogrossi MC, Gaetano C, Martelli F. Hypoxia-induced miR-210 modulates tissue response to acute peripheral ischemia. *Antioxid Redox Signal* 2014; **21**: 1177-1188 [PMID: [23931770](https://pubmed.ncbi.nlm.nih.gov/23931770/) DOI: [10.1089/ars.2013.5206](https://doi.org/10.1089/ars.2013.5206)]
 - 50 **Zaccagnini G**, Maimone B, Fuschi P, Maselli D, Spinetti G, Gaetano C, Martelli F. Overexpression of miR-210 and its significance in ischemic tissue damage. *Sci Rep* 2017; **7**: 9563 [PMID: [28842599](https://pubmed.ncbi.nlm.nih.gov/28842599/) DOI: [10.1038/s41598-017-09763-4](https://doi.org/10.1038/s41598-017-09763-4)]
 - 51 **Li T**, Cao H, Zhuang J, Wan J, Guan M, Yu B, Li X, Zhang W. Identification of miR-130a, miR-27b and miR-210 as serum biomarkers for atherosclerosis obliterans. *Clin Chim Acta* 2011; **412**: 66-70 [PMID: [20888330](https://pubmed.ncbi.nlm.nih.gov/20888330/) DOI: [10.1016/j.cca.2010.09.029](https://doi.org/10.1016/j.cca.2010.09.029)]

- 52 **Pek SL**, Sum CF, Lin MX, Cheng AK, Wong MT, Lim SC, Tavintharan S. Circulating and visceral adipose miR-100 is down-regulated in patients with obesity and Type 2 diabetes. *Mol Cell Endocrinol* 2016; **427**: 112-123 [PMID: 26973292 DOI: 10.1016/j.mce.2016.03.010]
- 53 **Li X**, Jia Z, Zhao X, Xu M, Chen M. Expression of miR-210 in the peripheral blood of patients with newly diagnosed type 2 diabetes mellitus and its effect on the number and function of endothelial progenitor cells. *Microvasc Res* 2020; **131**: 104032 [PMID: 32533960 DOI: 10.1016/j.mvr.2020.104032]
- 54 **Al-Hayali MA**, Sozer V, Durmus S, Erdenen F, Altunoglu E, Gelisgen R, Atukeren P, Atak PG, Uzun H. Clinical Value of Circulating Microribonucleic Acids miR-1 and miR-21 in Evaluating the Diagnosis of Acute Heart Failure in Asymptomatic Type 2 Diabetic Patients. *Biomolecules* 2019; **9** [PMID: 31109008 DOI: 10.3390/biom9050193]
- 55 **Seyhan AA**, Nunez Lopez YO, Xie H, Yi F, Mathews C, Pasarica M, Pratley RE. Pancreas-enriched miRNAs are altered in the circulation of subjects with diabetes: a pilot cross-sectional study. *Sci Rep* 2016; **6**: 31479 [PMID: 27558530 DOI: 10.1038/srep31479]
- 56 **Nunez Lopez YO**, Garufi G, Seyhan AA. Altered levels of circulating cytokines and microRNAs in lean and obese individuals with prediabetes and type 2 diabetes. *Mol Biosyst* 2016; **13**: 106-121 [PMID: 27869909 DOI: 10.1039/c6mb00596a]
- 57 **Andoorfar S**, Hosseini Tafreshi SA, Rezvani Z. Assessment of the expression level of miRNA molecules using a semi-quantitative RT-PCR approach. *Mol Biol Rep* 2019; **46**: 5057-5062 [PMID: 31286390 DOI: 10.1007/s11033-019-04959-5]
- 58 **La Sala L**, Mrakic-Spota S, Tagliabue E, Praticchizzo F, Micheloni S, Sangalli E, Specchia C, Uccellatore AC, Lupini S, Spinetti G, de Candia P, Ceriello A. Circulating microRNA-21 is an early predictor of ROS-mediated damage in subjects with high risk of developing diabetes and in drug-naïve T2D. *Cardiovasc Diabetol* 2019; **18**: 18 [PMID: 30803440 DOI: 10.1186/s12933-019-0824-2]
- 59 **Guan JJ**, Zhang Y, Liu YJ. [Effects of miRNA-1, miRNA-21 in plasma on in-stent restenosis in patients with coronary heart disease and diabetes mellitus after percutaneous coronary intervention]. *Zhongguo Ying Yong Sheng Li Xue Za Zhi* 2018; **34**: 304-308 384 [PMID: 30788936 DOI: 10.12047/j.cjap.5643.2018.070]
- 60 **Kumar D**, Narang R, Sreenivas V, Rastogi V, Bhatia J, Saluja D, Srivastava K. Circulatory miR-133b and miR-21 as Novel Biomarkers in Early Prediction and Diagnosis of Coronary Artery Disease. *Genes (Basel)* 2020; **11** [PMID: 32033332 DOI: 10.3390/genes11020164]
- 61 **Loyer X**, Potteaux S, Vion AC, Guérin CL, Boulkroun S, Rautou PE, Ramkhalawon B, Esposito B, Dalloz M, Paul JL, Julia P, Maccario J, Boulanger CM, Mallat Z, Tedgui A. Inhibition of microRNA-92a prevents endothelial dysfunction and atherosclerosis in mice. *Circ Res* 2014; **114**: 434-443 [PMID: 24255059 DOI: 10.1161/CIRCRESAHA.114.302213]
- 62 **Dutzmann J**, Daniel JM, Bauersachs J, Sedding D. MiR-92a – a key player in cardiovascular remodeling. *RNA Dis* 2014; **1**: e371 [DOI: 10.14800/rd.371]
- 63 **Jiang Y**, Wang HY, Li Y, Guo SH, Zhang L, Cai JH. Peripheral blood miRNAs as a biomarker for chronic cardiovascular diseases. *Sci Rep* 2014; **4**: 5026 [PMID: 24848278 DOI: 10.1038/srep05026]
- 64 **Niculescu LS**, Simionescu N, Sanda GM, Carmuta MG, Stancu CS, Popescu AC, Popescu MR, Vlad A, Dimulescu DR, Simionescu M, Sima AV. MiR-486 and miR-92a Identified in Circulating HDL Discriminate between Stable and Vulnerable Coronary Artery Disease Patients. *PLoS One* 2015; **10**: e0140958 [PMID: 26485305 DOI: 10.1371/journal.pone.0140958]
- 65 **Wang Z**, Zhang J, Zhang S, Yan S, Wang Z, Wang C, Zhang X. MiR30e and miR92a are related to atherosclerosis by targeting ABCA1. *Mol Med Rep* 2019; **19**: 3298-3304 [PMID: 30816508 DOI: 10.3892/mmr.2019.9983]
- 66 **Parahuleva MS**, Lipps C, Parviz B, Hölschermann H, Schieffer B, Schulz R, Euler G. MicroRNA expression profile of human advanced coronary atherosclerotic plaques. *Sci Rep* 2018; **8**: 7823 [PMID: 29777114 DOI: 10.1038/s41598-018-25690-4]
- 67 **Zhang Y**, Cheng J, Chen F, Wu C, Zhang J, Ren X, Pan Y, Nie B, Li Q, Li Y. Circulating endothelial microparticles and miR-92a in acute myocardial infarction. *Biosci Rep* 2017; **37** [PMID: 28213360 DOI: 10.1042/BSR20170047]
- 68 **Karolina DS**, Tavintharan S, Armugam A, Sepramaniam S, Pek SL, Wong MT, Lim SC, Sum CF, Jeyaseelan K. Circulating miRNA profiles in patients with metabolic syndrome. *J Clin Endocrinol Metab* 2012; **97**: E2271-E2276 [PMID: 23032062 DOI: 10.1210/jc.2012-1996]
- 69 **Wang W**, Li Z, Zheng Y, Yan M, Cui Y, Jiang J. Circulating microRNA-92a level predicts acute coronary syndrome in diabetic patients with coronary heart disease. *Lipids Health Dis* 2019; **18**: 22 [PMID: 30670045 DOI: 10.1186/s12944-019-0964-0]
- 70 **Luo M**, Wang G, Xu C, Zeng M, Lin F, Wu J, Wan Q. Circulating miR-30c as a predictive biomarker of type 2 diabetes mellitus with coronary heart disease by regulating PAI-1/VN interactions. *Life Sci* 2019; **239**: 117092 [PMID: 31760103 DOI: 10.1016/j.lfs.2019.117092]
- 71 **Ceolotto G**, Giannella A, Albiero M, Kuppusamy M, Radu C, Simioni P, Garlaschelli K, Baragetti A, Catapano AL, Iori E, Fadini GP, Avogaro A, Vigili de Kreutzenberg S. miR-30c-5p regulates macrophage-mediated inflammation and pro-atherosclerosis pathways. *Cardiovasc Res* 2017; **113**: 1627-1638 [PMID: 29016810 DOI: 10.1093/cvr/cvx157]
- 72 **Chen C**, Yang S, Li H, Yin Z, Fan J, Zhao Y, Gong W, Yan M, Wang DW. Mir30c Is Involved in Diabetic Cardiomyopathy through Regulation of Cardiac Autophagy via BECN1. *Mol Ther Nucleic Acids* 2017; **7**: 127-139 [PMID: 28624189 DOI: 10.1016/j.omtn.2017.03.005]
- 73 **Jiang H**, Toscano JF, Song SS, Schlick KH, Dumitrascu OM, Pan J, Lyden PD, Saver JL, Gonzalez

- NR. Differential expression of circulating exosomal microRNAs in refractory intracranial atherosclerosis associated with antiangiogenesis. *Sci Rep* 2019; **9**: 19429 [PMID: 31857618 DOI: 10.1038/s41598-019-54542-y]
- 74 **Hoekstra M**, van der Lans CA, Halvorsen B, Gullestad L, Kuiper J, Aukrust P, van Berkel TJ, Biessen EA. The peripheral blood mononuclear cell microRNA signature of coronary artery disease. *Biochem Biophys Res Commun* 2010; **394**: 792-797 [PMID: 20230787 DOI: 10.1016/j.bbrc.2010.03.075]
- 75 **Shi X**, Chen X. Effect of microRNA-370 on coronary atherosclerosis and its underlying mechanism. *Exp Ther Med* 2019; **17**: 115-122 [PMID: 30651771 DOI: 10.3892/etm.2018.6961]
- 76 **Qiang L**, Tsuchiya K, Kim-Muller JY, Lin HV, Welch C, Accili D. Increased atherosclerosis and endothelial dysfunction in mice bearing constitutively deacetylated alleles of Foxo1 gene. *J Biol Chem* 2012; **287**: 13944-13951 [PMID: 22389493 DOI: 10.1074/jbc.M111.332767]
- 77 **Kedenko L**, Lamina C, Kedenko I, Kollerits B, Kiesslich T, Iglseider B, Kronenberg F, Paulweber B. Genetic polymorphisms at SIRT1 and FOXO1 are associated with carotid atherosclerosis in the SAPHIR cohort. *BMC Med Genet* 2014; **15**: 112 [PMID: 25273948 DOI: 10.1186/s12881-014-0112-7]
- 78 **Gao W**, He HW, Wang ZM, Zhao H, Lian XQ, Wang YS, Zhu J, Yan JJ, Zhang DG, Yang ZJ, Wang LS. Plasma levels of lipometabolism-related miR-122 and miR-370 are increased in patients with hyperlipidemia and associated with coronary artery disease. *Lipids Health Dis* 2012; **11**: 55 [PMID: 22587332 DOI: 10.1186/1476-511X-11-55]
- 79 **Liu H**, Yang N, Fei Z, Qiu J, Ma D, Liu X, Cai G, Li S. Analysis of plasma miR-208a and miR-370 expression levels for early diagnosis of coronary artery disease. *Biomed Rep* 2016; **5**: 332-336 [PMID: 27602213 DOI: 10.3892/br.2016.726]
- 80 **Motawae TM**, Ismail MF, Shabayek MI, Selem MM. MicroRNAs 9 and 370 Association with Biochemical Markers in T2D and CAD Complication of T2D. *PLoS One* 2015; **10**: e0126957 [PMID: 25978320 DOI: 10.1371/journal.pone.0126957]
- 81 **Seleem M**, Shabayek M, Ewida HA. MicroRNAs 342 and 450 together with NOX-4 activity and their association with coronary artery disease in diabetes. *Diabetes Metab Res Rev* 2019; **35**: e3130 [PMID: 30681251 DOI: 10.1002/dmrr.3130]
- 82 **Chavali V**, Tyagi SC, Mishra PK. Differential expression of dicer, miRNAs, and inflammatory markers in diabetic Ins2^{+/-} Akita hearts. *Cell Biochem Biophys* 2014; **68**: 25-35 [PMID: 23797610 DOI: 10.1007/s12013-013-9679-4]
- 83 **Cheng S**, Cui Y, Fan L, Mu X, Hua Y. T2DM inhibition of endothelial miR-342-3p facilitates angiogenic dysfunction via repression of FGF11 signaling. *Biochem Biophys Res Commun* 2018; **503**: 71-78 [PMID: 29852165 DOI: 10.1016/j.bbrc.2018.05.179]
- 84 **Wei Y**, Nazari-Jahantigh M, Chan L, Zhu M, Heyll K, Corbalán-Campos J, Hartmann P, Thiemann A, Weber C, Schober A. The microRNA-342-5p fosters inflammatory macrophage activation through an Akt1- and microRNA-155-dependent pathway during atherosclerosis. *Circulation* 2013; **127**: 1609-1619 [PMID: 23513069 DOI: 10.1161/CIRCULATIONAHA.112.000736]
- 85 **Ikeda S**, He A, Kong SW, Lu J, Bejar R, Bodyak N, Lee KH, Ma Q, Kang PM, Golub TR, Pu WT. MicroRNA-1 negatively regulates expression of the hypertrophy-associated calmodulin and Mef2a genes. *Mol Cell Biol* 2009; **29**: 2193-2204 [PMID: 19188439 DOI: 10.1128/MCB.01222-08]
- 86 **Liu N**, Bezprozvannaya S, Williams AH, Qi X, Richardson JA, Bassel-Duby R, Olson EN. microRNA-133a regulates cardiomyocyte proliferation and suppresses smooth muscle gene expression in the heart. *Genes Dev* 2008; **22**: 3242-3254 [PMID: 19015276 DOI: 10.1101/gad.1738708]
- 87 **Al-Muhtareh HA**, Salem AH, Al-Kafaji G. Upregulation of Circulating Cardiomyocyte-Enriched miR-1 and miR-133 Associate with the Risk of Coronary Artery Disease in Type 2 Diabetes Patients and Serve as Potential Biomarkers. *J Cardiovasc Transl Res* 2019; **12**: 347-357 [PMID: 30610670 DOI: 10.1007/s12265-018-9857-2]
- 88 **Yang B**, Lin H, Xiao J, Lu Y, Luo X, Li B, Zhang Y, Xu C, Bai Y, Wang H, Chen G, Wang Z. The muscle-specific microRNA miR-1 regulates cardiac arrhythmogenic potential by targeting GJA1 and KCNJ2. *Nat Med* 2007; **13**: 486-491 [PMID: 17401374 DOI: 10.1038/nm1569]
- 89 **Nabialek E**, Wańha W, Kula D, Jadczyk T, Krajewska M, Kowalówka A, Dworowy S, Hrycek E, Włodarczyk W, Parma Z, Michalewska-Włodarczyk A, Pawłowski T, Ochała B, Jarzab B, Tendera M, Wojakowski W. Circulating microRNAs (miR-423-5p, miR-208a and miR-1) in acute myocardial infarction and stable coronary heart disease. *Minerva Cardioangiolog* 2013; **61**: 627-637 [PMID: 24253456]
- 90 **Toyoda M**, Shirato H, Nakajima K, Kojima M, Takahashi M, Kubota M, Suzuki-Migishima R, Motegi Y, Yokoyama M, Takeuchi T. jumonji downregulates cardiac cell proliferation by repressing cyclin D1 expression. *Dev Cell* 2003; **5**: 85-97 [PMID: 12852854 DOI: 10.1016/s1534-5807(03)00189-8]
- 91 **Liang D**, Li J, Wu Y, Zhen L, Li C, Qi M, Wang L, Deng F, Huang J, Lv F, Liu Y, Ma X, Yu Z, Zhang Y, Chen YH. miRNA-204 drives cardiomyocyte proliferation via targeting Jarid2. *Int J Cardiol* 2015; **201**: 38-48 [PMID: 26298346 DOI: 10.1016/j.ijcard.2015.06.163]
- 92 **Torella D**, Iaconetti C, Tarallo R, Marino F, Giurato G, Veneziano C, Aquila I, Scalise M, Mancuso T, Cianflone E, Valeriano C, Marotta P, Tammè L, Vicinanza C, Sasso FC, Cozzolino D, Torella M, Weisz A, Indolfi C. miRNA Regulation of the Hyperproliferative Phenotype of Vascular Smooth Muscle Cells in Diabetes. *Diabetes* 2018; **67**: 2554-2568 [PMID: 30257973 DOI: 10.2337/db170188]

- 10.2337/db17-1434]
- 93 **Wang N**, Yuan Y, Sun S, Liu G. microRNA-204-5p Participates in Atherosclerosis Via Targeting MMP-9. *Open Med (Wars)* 2020; **15**: 231-239 [PMID: 32266319 DOI: 10.1515/med-2020-0034]
- 94 **Ding YD**, Pei YQ, Rui-Wang, Yang JX, Zhao YX, Liu XL, Shen H, Ma Q, Zhang S, Ge HL. Association of Plasma MiRNA-204 and the Presence and Severity of Coronary Artery Calcification in Patients With Type 2 Diabetes. *Angiology* 2021; **72**: 451-458 [PMID: 33401931 DOI: 10.1177/0003319720984592]
- 95 **Cui RR**, Li SJ, Liu LJ, Yi L, Liang QH, Zhu X, Liu GY, Liu Y, Wu SS, Liao XB, Yuan LQ, Mao DA, Liao EY. MicroRNA-204 regulates vascular smooth muscle cell calcification *in vitro* and *in vivo*. *Cardiovasc Res* 2012; **96**: 320-329 [PMID: 22871591 DOI: 10.1093/cvr/cvs258]
- 96 **Lu H**, Buchan RJ, Cook SA. MicroRNA-223 regulates Glut4 expression and cardiomyocyte glucose metabolism. *Cardiovasc Res* 2010; **86**: 410-420 [PMID: 20080987 DOI: 10.1093/cvr/cvq010]
- 97 **Duan X**, Zhan Q, Song B, Zeng S, Zhou J, Long Y, Lu J, Li Z, Yuan M, Chen X, Yang Q, Xia J. Detection of platelet microRNA expression in patients with diabetes mellitus with or without ischemic stroke. *J Diabetes Complications* 2014; **28**: 705-710 [PMID: 24908639 DOI: 10.1016/j.jdiacomp.2014.04.012]
- 98 **Yang S**, Zhao J, Chen Y, Lei M. Biomarkers Associated with Ischemic Stroke in Diabetes Mellitus Patients. *Cardiovasc Toxicol* 2016; **16**: 213-222 [PMID: 26175178 DOI: 10.1007/s12012-015-9329-8]
- 99 **Long Y**, Zhan Q, Yuan M, Duan X, Zhou J, Lu J, Li Z, Yu F, Zhou X, Yang Q, Xia J. The Expression of microRNA-223 and FAM5C in Cerebral Infarction Patients with Diabetes Mellitus. *Cardiovasc Toxicol* 2017; **17**: 42-48 [PMID: 26717922 DOI: 10.1007/s12012-015-9354-7]
- 100 **Singh S**, de Ronde MWJ, Kok MGM, Beijl MA, De Winter RJ, van der Wal AC, Sondermeijer BM, Meijers JCM, Creemers EE, Pinto-Sietsma SJ. MiR-223-3p and miR-122-5p as circulating biomarkers for plaque instability. *Open Heart* 2020; **7** [PMID: 32487772 DOI: 10.1136/openhrt-2019-001223]
- 101 **Karolina DS**, Armugam A, Tavintharan S, Wong MT, Lim SC, Sum CF, Jeyaseelan K. MicroRNA 144 impairs insulin signaling by inhibiting the expression of insulin receptor substrate 1 in type 2 diabetes mellitus. *PLoS One* 2011; **6**: e22839 [PMID: 21829658 DOI: 10.1371/journal.pone.0022839]
- 102 **Thong FS**, Dugani CB, Klip A. Turning signals on and off: GLUT4 traffic in the insulin-signaling highway. *Physiology (Bethesda)* 2005; **20**: 271-284 [PMID: 16024515 DOI: 10.1152/physiol.00017.2005]
- 103 **Chen B**, Luo L, Wei X, Gong D, Jin L. Altered Plasma miR-144 as a Novel Biomarker for Coronary Artery Disease. *Ann Clin Lab Sci* 2018; **48**: 440-445 [PMID: 30143484]
- 104 **Cheng J**, Cheng A, Clifford BL, Wu X, Hedin U, Maegdefessel L, Pamir N, Sallam T, Tarling EJ, de Aguiar Vallim TQ. MicroRNA-144 Silencing Protects Against Atherosclerosis in Male, but Not Female Mice. *Arterioscler Thromb Vasc Biol* 2020; **40**: 412-425 [PMID: 31852219 DOI: 10.1161/ATVBAHA.119.313633]
- 105 **Tan KS**, Armugam A, Sepramaniam S, Lim KY, Setyowati KD, Wang CW, Jeyaseelan K. Expression profile of MicroRNAs in young stroke patients. *PLoS One* 2009; **4**: e7689 [PMID: 19888324 DOI: 10.1371/journal.pone.0007689]
- 106 **Giordano M**, Trotta MC, Ciarambino T, D'Amico M, Galdiero M, Schettini F, Paternosto D, Salzillo M, Alfano R, Andreone V, Malatino LS, Biolo G, Paolisso G, Adinolfi LE. Circulating MiRNA-195-5p and -451a in Diabetic Patients with Transient and Acute Ischemic Stroke in the Emergency Department. *Int J Mol Sci* 2020; **21** [PMID: 33076256 DOI: 10.3390/ijms21207615]
- 107 **Li P**, Teng F, Gao F, Zhang M, Wu J, Zhang C. Identification of circulating microRNAs as potential biomarkers for detecting acute ischemic stroke. *Cell Mol Neurobiol* 2015; **35**: 433-447 [PMID: 25410304 DOI: 10.1007/s10571-014-0139-5]
- 108 **Ding L**, Ai D, Wu R, Zhang T, Jing L, Lu J, Zhong L. Identification of the differential expression of serum microRNA in type 2 diabetes. *Biosci Biotechnol Biochem* 2016; **80**: 461-465 [PMID: 26554942 DOI: 10.1080/09168451.2015.1107460]
- 109 **Li S**, Lee C, Song J, Lu C, Liu J, Cui Y, Liang H, Cao C, Zhang F, Chen H. Circulating microRNAs as potential biomarkers for coronary plaque rupture. *Oncotarget* 2017; **8**: 48145-48156 [PMID: 28624816 DOI: 10.18632/oncotarget.18308]
- 110 **Ortega FJ**, Mercader JM, Moreno-Navarrete JM, Rovira O, Guerra E, Esteve E, Xifra G, Martínez C, Ricart W, Rieusset J, Rome S, Karczewska-Kupczewska M, Strackowski M, Fernández-Real JM. Profiling of circulating microRNAs reveals common microRNAs linked to type 2 diabetes that change with insulin sensitization. *Diabetes Care* 2014; **37**: 1375-1383 [PMID: 24478399 DOI: 10.2337/dc13-1847]
- 111 **Li SH**, Chen L, Pang XM, Su SY, Zhou X, Chen CY, Huang LG, Li JP, Liu JL. Decreased miR-146a expression in acute ischemic stroke directly targets the Fbx110 mRNA and is involved in modulating apoptosis. *Neurochem Int* 2017; **107**: 156-167 [PMID: 28202285 DOI: 10.1016/j.neuint.2017.01.011]
- 112 **Koth HG**, Ibrahim AH, Mohamed EF, Ali OM, Hassanein N, Badawy D, Abdelatty Aly E. The expression of microRNA 146a in patients with ischemic stroke: an observational study. *Int J Gen Med* 2019; **12**: 273-278 [PMID: 31496785 DOI: 10.2147/IJGM.S213535]
- 113 **Su ZF**, Sun ZW, Zhang Y, Wang S, Yu QG, Wu ZB. Regulatory effects of miR-146a/b on the function of endothelial progenitor cells in acute ischemic stroke in mice. *Kaohsiung J Med Sci* 2017;

- 33: 369-378 [PMID: 28811005 DOI: 10.1016/j.kjms.2017.05.010]
- 114 **Qu X**, Wang N, Cheng W, Xue Y, Chen W, Qi M. MicroRNA-146a protects against intracerebral hemorrhage by inhibiting inflammation and oxidative stress. *Exp Ther Med* 2019; **18**: 3920-3928 [PMID: 31656540 DOI: 10.3892/etm.2019.8060]
- 115 **Petrkova J**, Borucka J, Kalab M, Klevcova P, Michalek J, Taborsky M, Petrek M. Increased Expression of miR-146a in Valvular Tissue From Patients With Aortic Valve Stenosis. *Front Cardiovasc Med* 2019; **6**: 86 [PMID: 31294031 DOI: 10.3389/fcvm.2019.00086]
- 116 **Cheng HS**, Besla R, Li A, Chen Z, Shikatani EA, Nazari-Jahantigh M, Hammoutène A, Nguyen MA, Geoffrion M, Cai L, Khyzha N, Li T, MacParland SA, Husain M, Cybulsky MI, Boulanger CM, Temel RE, Schober A, Rayner KJ, Robbins CS, Fish JE. Paradoxical Suppression of Atherosclerosis in the Absence of microRNA-146a. *Circ Res* 2017; **121**: 354-367 [PMID: 28637783 DOI: 10.1161/CIRCRESAHA.116.310529]
- 117 **Nguyen MA**, Karunakaran D, Geoffrion M, Cheng HS, Tandoc K, Perisic Matic L, Hedin U, Maegdefessel L, Fish JE, Rayner KJ. Extracellular Vesicles Secreted by Atherogenic Macrophages Transfer MicroRNA to Inhibit Cell Migration. *Arterioscler Thromb Vasc Biol* 2018; **38**: 49-63 [PMID: 28882869 DOI: 10.1161/ATVBAHA.117.309795]
- 118 **Sheikhabaehi S**, Manizheh D, Mohammad S, Hasan TM, Saman N, Laleh R, Mahsa M, Sanaz AK, Shaghayegh HJ. Can MiR-503 be used as a marker in diabetic patients with ischemic stroke? *BMC Endocr Disord* 2019; **19**: 42 [PMID: 31035988 DOI: 10.1186/s12902-019-0371-6]
- 119 **Caporali A**, Meloni M, Völlenkle C, Bonci D, Sala-Newby GB, Addis R, Spinetti G, Losa S, Masson R, Baker AH, Agami R, le Sage C, Condorelli G, Madeddu P, Martelli F, Emanuoli C. Deregulation of microRNA-503 contributes to diabetes mellitus-induced impairment of endothelial function and reparative angiogenesis after limb ischemia. *Circulation* 2011; **123**: 282-291 [PMID: 21220732 DOI: 10.1161/CIRCULATIONAHA.110.952325]
- 120 **Bi R**, Ding F, He Y, Jiang L, Jiang Z, Mei J, Liu H. miR-503 inhibits platelet-derived growth factor-induced human aortic vascular smooth muscle cell proliferation and migration through targeting the insulin receptor. *Biomed Pharmacother* 2016; **84**: 1711-1716 [PMID: 27829550 DOI: 10.1016/j.biopha.2016.10.081]
- 121 **Hou LJ**, Han JJ, Liu Y. Up-regulation of microRNA-503 by high glucose reduces the migration and proliferation but promotes the apoptosis of human umbilical vein endothelial cells by inhibiting the expression of insulin-like growth factor-1 receptor. *Eur Rev Med Pharmacol Sci* 2018; **22**: 3515-3523 [PMID: 29917206 DOI: 10.26355/eurrev_201806_15178]
- 122 **Dunn J**, Qiu H, Kim S, Jjingo D, Hoffman R, Kim CW, Jang I, Son DJ, Kim D, Pan C, Fan Y, Jordan IK, Jo H. Flow-dependent epigenetic DNA methylation regulates endothelial gene expression and atherosclerosis. *J Clin Invest* 2014; **124**: 3187-3199 [PMID: 24865430 DOI: 10.1172/JCI74792]
- 123 **Lee HT**, Oh S, Ro DH, Yoo H, Kwon YW. The Key Role of DNA Methylation and Histone Acetylation in Epigenetics of Atherosclerosis. *J Lipid Atheroscler* 2020; **9**: 419-434 [PMID: 33024734 DOI: 10.12997/jla.2020.9.3.419]
- 124 **Hiltunen MO**, Turunen MP, Häkkinen TP, Rutanen J, Hedman M, Mäkinen K, Turunen AM, Aalto-Setälä K, Ylä-Herttua S. DNA hypomethylation and methyltransferase expression in atherosclerotic lesions. *Vasc Med* 2002; **7**: 5-11 [PMID: 12083735 DOI: 10.1191/1358863x02vm418oa]
- 125 **Kim MK**, Shin JM, Eun HC, Chung JH. The role of p300 histone acetyltransferase in UV-induced histone modifications and MMP-1 gene transcription. *PLoS One* 2009; **4**: e4864 [PMID: 19287485 DOI: 10.1371/journal.pone.0004864]
- 126 **Newby AC**. Metalloproteinases promote plaque rupture and myocardial infarction: A persuasive concept waiting for clinical translation. *Matrix Biol* 2015; **44-46**: 157-166 [PMID: 25636537 DOI: 10.1016/j.matbio.2015.01.015]
- 127 **Dje N'Guessan P**, Riediger F, Vardarova K, Scharf S, Eitel J, Opitz B, Slevogt H, Weichert W, Hocke AC, Schmeck B, Suttrop N, Hippenstiel S. Statins control oxidized LDL-mediated histone modifications and gene expression in cultured human endothelial cells. *Arterioscler Thromb Vasc Biol* 2009; **29**: 380-386 [PMID: 19122173 DOI: 10.1161/ATVBAHA.108.178319]
- 128 **Greißel A**, Culmes M, Burgkart R, Zimmermann A, Eckstein HH, Zerneck A, Pelisek J. Histone acetylation and methylation significantly change with severity of atherosclerosis in human carotid plaques. *Cardiovasc Pathol* 2016; **25**: 79-86 [PMID: 26764138 DOI: 10.1016/j.carpath.2015.11.001]
- 129 **Davegårdh C**, García-Calzón S, Bacos K, Ling C. DNA methylation in the pathogenesis of type 2 diabetes in humans. *Mol Metab* 2018; **14**: 12-25 [PMID: 29496428 DOI: 10.1016/j.molmet.2018.01.022]
- 130 **Yang BT**, Dayeh TA, Kirkpatrick CL, Taneera J, Kumar R, Groop L, Wollheim CB, Nitert MD, Ling C. Insulin promoter DNA methylation correlates negatively with insulin gene expression and positively with HbA(1c) levels in human pancreatic islets. *Diabetologia* 2011; **54**: 360-367 [PMID: 21104225 DOI: 10.1007/s00125-010-1967-6]
- 131 **Yang BT**, Dayeh TA, Volkov PA, Kirkpatrick CL, Malmgren S, Jing X, Renström E, Wollheim CB, Nitert MD, Ling C. Increased DNA methylation and decreased expression of PDX-1 in pancreatic islets from patients with type 2 diabetes. *Mol Endocrinol* 2012; **26**: 1203-1212 [PMID: 22570331 DOI: 10.1210/me.2012-1004]
- 132 **Zhu Y**, Liu Q, Zhou Z, Ikeda Y. PDX1, Neurogenin-3, and MAFA: critical transcription regulators for beta cell development and regeneration. *Stem Cell Res Ther* 2017; **8**: 240 [PMID: 29096722 DOI: 10.1186/s13287-017-0694-z]

- 133 **Ling C**, Del Guerra S, Lupi R, Rönn T, Granhall C, Luthman H, Masiello P, Marchetti P, Groop L, Del Prato S. Epigenetic regulation of PPARGC1A in human type 2 diabetic islets and effect on insulin secretion. *Diabetologia* 2008; **51**: 615-622 [PMID: 18270681 DOI: 10.1007/s00125-007-0916-5]
- 134 **Lai CQ**, Tucker KL, Parnell LD, Adiconis X, García-Bailo B, Griffith J, Meydani M, Ordovás JM. PPARGC1A variation associated with DNA damage, diabetes, and cardiovascular diseases: the Boston Puerto Rican Health Study. *Diabetes* 2008; **57**: 809-816 [PMID: 18162502 DOI: 10.2337/db07-1238]
- 135 **Hall E**, Dayeh T, Kirkpatrick CL, Wollheim CB, Dekker Nitert M, Ling C. DNA methylation of the glucagon-like peptide 1 receptor (GLP1R) in human pancreatic islets. *BMC Med Genet* 2013; **14**: 76 [PMID: 23879380 DOI: 10.1186/1471-2350-14-76]
- 136 **Tsalamandris S**, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, Deftereos S, Tousoulis D. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. *Eur Cardiol* 2019; **14**: 50-59 [PMID: 31131037 DOI: 10.15420/eur.2018.33.1]
- 137 **Ahmed M**, de Winther MPJ, Van den Bossche J. Epigenetic mechanisms of macrophage activation in type 2 diabetes. *Immunobiology* 2017; **222**: 937-943 [PMID: 27613200 DOI: 10.1016/j.imbio.2016.08.011]
- 138 **Babu M**, Durga Devi T, Mäkinen P, Kaikkonen M, Lesch HP, Junttila S, Laiho A, Ghimire B, Gyenesei A, Ylä-Herttua S. Differential Promoter Methylation of Macrophage Genes Is Associated With Impaired Vascular Growth in Ischemic Muscles of Hyperlipidemic and Type 2 Diabetic Mice: Genome-Wide Promoter Methylation Study. *Circ Res* 2015; **117**: 289-299 [PMID: 26085133 DOI: 10.1161/CIRCRESAHA.115.306424]
- 139 **Yang X**, Wang X, Liu D, Yu L, Xue B, Shi H. Epigenetic regulation of macrophage polarization by DNA methyltransferase 3b. *Mol Endocrinol* 2014; **28**: 565-574 [PMID: 24597547 DOI: 10.1210/me.2013-1293]
- 140 **Brasacchio D**, Okabe J, Tikellis C, Balcerzyk A, George P, Baker EK, Calkin AC, Brownlee M, Cooper ME, El-Osta A. Hyperglycemia induces a dynamic cooperativity of histone methylase and demethylase enzymes associated with gene-activating epigenetic marks that coexist on the lysine tail. *Diabetes* 2009; **58**: 1229-1236 [PMID: 19208907 DOI: 10.2337/db08-1666]
- 141 **Ea CK**, Baltimore D. Regulation of NF-kappaB activity through lysine monomethylation of p65. *Proc Natl Acad Sci USA* 2009; **106**: 18972-18977 [PMID: 19864627 DOI: 10.1073/pnas.0910439106]
- 142 **Dorrington MG**, Fraser IDC. NF-κB Signaling in Macrophages: Dynamics, Crosstalk, and Signal Integration. *Front Immunol* 2019; **10**: 705 [PMID: 31024544 DOI: 10.3389/fimmu.2019.00705]
- 143 **Barajas-Olmos F**, Centeno-Cruz F, Zerrweck C, Imaz-Rosshandler I, Martínez-Hernández A, Cordova EJ, Rangel-Escareño C, Gálvez F, Castillo A, Maydón H, Campos F, Maldonado-Pintado DG, Orozco L. Altered DNA methylation in liver and adipose tissues derived from individuals with obesity and type 2 diabetes. *BMC Med Genet* 2018; **19**: 28 [PMID: 29466957 DOI: 10.1186/s12881-018-0542-8]
- 144 **Nilsson E**, Jansson PA, Perfilyev A, Volkov P, Pedersen M, Svensson MK, Poulsen P, Ribel-Madsen R, Pedersen NL, Almgren P, Fadista J, Rönn T, Klarlund Pedersen B, Scheele C, Vaag A, Ling C. Altered DNA methylation and differential expression of genes influencing metabolism and inflammation in adipose tissue from subjects with type 2 diabetes. *Diabetes* 2014; **63**: 2962-2976 [PMID: 24812430 DOI: 10.2337/db13-1459]
- 145 **Simar D**, Verstehe S, Donkin I, Liu J, Hesson L, Nylander V, Fossum A, Barrès R. DNA methylation is altered in B and NK lymphocytes in obese and type 2 diabetic human. *Metabolism* 2014; **63**: 1188-1197 [PMID: 24996265 DOI: 10.1016/j.metabol.2014.05.014]
- 146 **Zhao J**, Goldberg J, Bremner JD, Vaccarino V. Global DNA methylation is associated with insulin resistance: a monozygotic twin study. *Diabetes* 2012; **61**: 542-546 [PMID: 22210312 DOI: 10.2337/db11-1048]
- 147 **El-Osta A**, Brasacchio D, Yao D, Poci A, Jones PL, Roeder RG, Cooper ME, Brownlee M. Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia. *J Exp Med* 2008; **205**: 2409-2417 [PMID: 18809715 DOI: 10.1084/jem.20081188]
- 148 **Bijli KM**, Fazal F, Rahman A. Regulation of RelA/p65 and endothelial cell inflammation by proline-rich tyrosine kinase 2. *Am J Respir Cell Mol Biol* 2012; **47**: 660-668 [PMID: 22842493 DOI: 10.1165/ajrmb.2012-0047OC]
- 149 **Johansen OE**, Birkeland KI. Preventing macrovascular disease in patients with type 2 diabetes mellitus. *Am J Cardiovasc Drugs* 2003; **3**: 283-297 [PMID: 14728081 DOI: 10.2165/00129784-200303040-00007]
- 150 **American Diabetes Association**. *Standards of Medical Care in Diabetes-2020* Abridged for Primary Care Providers. *Clin Diabetes* 2020; **38**: 10-38 [PMID: 31975748 DOI: 10.2337/cd20-as01]
- 151 **Cosentino F**, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41**: 255-323 [PMID: 31497854 DOI: 10.1093/eurheartj/ehz486]
- 152 **Mannino GC**, Andreozzi F, Sesti G. Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine. *Diabetes Metab Res Rev* 2019; **35**: e3109 [PMID: 30515958 DOI: 10.1002/dm.201900007]

- 10.1002/dmrr.3109]
- 153 **Fontana V**, Luizon MR, Sandrim VC. An update on the pharmacogenetics of treating hypertension. *J Hum Hypertens* 2015; **29**: 283-291 [PMID: 25355012 DOI: 10.1038/jhh.2014.76]
- 154 **Kitzmler JP**, Mikulik EB, Dauki AM, Murkherjee C, Luzum JA. Pharmacogenomics of statins: understanding susceptibility to adverse effects. *Pharmgenomics Pers Med* 2016; **9**: 97-106 [PMID: 27757045 DOI: 10.2147/PGPM.S86013]
- 155 **Nasykhova YA**, Tonyan ZN, Mikhailova AA, Danilova MM, Glotov AS. Pharmacogenetics of Type 2 Diabetes-Progress and Prospects. *Int J Mol Sci* 2020; **21** [PMID: 32961860 DOI: 10.3390/ijms21186842]
- 156 **Yanai H**. Metabolic Syndrome and COVID-19. *Cardiol Res* 2020; **11**: 360-365 [PMID: 33224380 DOI: 10.14740/cr1181]
- 157 **Gregory JM**, Slaughter JC, Duffus SH, Smith TJ, LeStourgeon LM, Jaser SS, McCoy AB, Luther JM, Giovannetti ER, Boeder S, Pettus JH, Moore DJ. COVID-19 Severity Is Tripled in the Diabetes Community: A Prospective Analysis of the Pandemic's Impact in Type 1 and Type 2 Diabetes. *Diabetes Care* 2021; **44**: 526-532 [PMID: 33268335 DOI: 10.2337/dc20-2260]
- 158 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]
- 159 **Apicella M**, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; **8**: 782-792 [PMID: 32687793 DOI: 10.1016/S2213-8587(20)30238-2]
- 160 **Sardu C**, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? *J Clin Med* 2020; **9** [PMID: 32403217 DOI: 10.3390/jcm9051417]
- 161 **Walls AC**, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020; **181**: 281-292.e6 [PMID: 32155444 DOI: 10.1016/j.cell.2020.02.058]
- 162 **Devaux CA**, Rolain JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. *J Microbiol Immunol Infect* 2020; **53**: 425-435 [PMID: 32414646 DOI: 10.1016/j.jmii.2020.04.015]
- 163 **Bakhshandeh B**, Sorboni SG, Javanmard AR, Mottaghi SS, Mehrabi MR, Sorouri F, Abbasi A, Jahanafrooz Z. Variants in ACE2; potential influences on virus infection and COVID-19 severity. *Infect Genet Evol* 2021; **90**: 104773 [PMID: 33607284 DOI: 10.1016/j.meegid.2021.104773]
- 164 **Sardu C**, Maggi P, Messina V, Iuliano P, Sardu A, Iovinella V, Paolisso G, Marfella R. Could Anti-Hypertensive Drug Therapy Affect the Clinical Prognosis of Hypertensive Patients With COVID-19 Infection? *J Am Heart Assoc* 2020; **9**: e016948 [PMID: 32633594 DOI: 10.1161/JAHA.120.016948]
- 165 **Yang JK**, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* 2010; **47**: 193-199 [PMID: 19333547 DOI: 10.1007/s00592-009-0109-4]
- 166 **Figani D**, Licata G, Brusco N, Nigi L, Grieco GE, Marselli L, Overbergh L, Gysemans C, Colli ML, Marchetti P, Mathieu C, Eizirik DL, Sebastiani G, Dotta F. SARS-CoV-2 Receptor Angiotensin I-Converting Enzyme Type 2 (ACE2) Is Expressed in Human Pancreatic β -Cells and in the Human Pancreas Microvasculature. *Front Endocrinol (Lausanne)* 2020; **11**: 596898 [PMID: 33281748 DOI: 10.3389/fendo.2020.596898]
- 167 **Bernardi S**, Tikellis C, Candido R, Tsorotes D, Pickering RJ, Bossi F, Carretta R, Fabris B, Cooper ME, Thomas MC. ACE2 deficiency shifts energy metabolism towards glucose utilization. *Metabolism* 2015; **64**: 406-415 [PMID: 25484288 DOI: 10.1016/j.metabol.2014.11.004]
- 168 **Yamamoto K**, Ohishi M, Katsuya T, Ito N, Ikushima M, Kaibe M, Tataru Y, Shiota A, Sugano S, Takeda S, Rakugi H, Ogihara T. Deletion of angiotensin-converting enzyme 2 accelerates pressure overload-induced cardiac dysfunction by increasing local angiotensin II. *Hypertension* 2006; **47**: 718-726 [PMID: 16505206 DOI: 10.1161/01.HYP.0000205833.89478.5b]
- 169 **Rabelo LA**, Todiras M, Nunes-Souza V, Qadri F, Szijártó IA, Gollasch M, Penninger JM, Bader M, Santos RA, Alenina N. Genetic Deletion of ACE2 Induces Vascular Dysfunction in C57BL/6 Mice: Role of Nitric Oxide Imbalance and Oxidative Stress. *PLoS One* 2016; **11**: e0150255 [PMID: 27070147 DOI: 10.1371/journal.pone.0150255]
- 170 **Bindom SM**, Hans CP, Xia H, Boulares AH, Lazartigues E. Angiotensin I-converting enzyme type 2 (ACE2) gene therapy improves glycemic control in diabetic mice. *Diabetes* 2010; **59**: 2540-2548 [PMID: 20660625 DOI: 10.2337/db09-0782]
- 171 **Karahalil B**, Elkama A. The impact of ACE2 gene polymorphism in the development of COVID-19 disease. *Gazi Med J* 2020; **31** [DOI: 10.12996/gmj.2020.121]
- 172 **Shikov AE**, Barbitoff YA, Glotov AS, Danilova MM, Tonyan ZN, Nasykhova YA, Mikhailova AA, Bespalova ON, Kalinin RS, Mirzorstamova AM, Kogan IY, Baranov VS, Chernov AN, Pavlovich DM, Azarenko SV, Fedyakov MA, Tsay VV, Eismont YA, Romanova OV, Hobotnikov DN, Vologzhanin DA, Mosenko SV, Ponomareva TA, Talts YA, Anisenkova AU, Lisovets DG, Sarana AM, Urazov SP, Scherbak SG, Glotov OS. Analysis of the Spectrum of ACE2 Variation Suggests a Possible Influence of Rare and Common Variants on Susceptibility to COVID-19 and Severity of Outcome. *Front Genet* 2020; **11**: 551220 [PMID: 33133145 DOI: 10.3389/fgene.2020.551220]
- 173 **Stawiski EW**, Diwanji D, Suryamohan K, Gupta R, Fellouse FA, Sathirapongsasuti JF, Liu J, Jiang

YP, Ratan A, Mis M, Santhosh D, Somasekar S, Mohan S, Phalke S, Kuriakose B, Antony A, Junutula JR, Schuster SC, Jura N, Seshagiri S. Human ACE2 receptor polymorphisms predict SARS-CoV-2 susceptibility. 2020 Preprint. Available from: bioRxiv:2020.04.07.024752 [DOI: [10.1101/2020.04.07.024752](https://doi.org/10.1101/2020.04.07.024752)]

- 174 **Pedersen KB**, Chhabra KH, Nguyen VK, Xia H, Lazartigues E. The transcription factor HNF1 α induces expression of angiotensin-converting enzyme 2 (ACE2) in pancreatic islets from evolutionarily conserved promoter motifs. *Biochim Biophys Acta* 2013; **1829**: 1225-1235 [PMID: [24100303](https://pubmed.ncbi.nlm.nih.gov/24100303/) DOI: [10.1016/j.bbagra.2013.09.007](https://doi.org/10.1016/j.bbagra.2013.09.007)]
- 175 **Chaudhary M**. COVID-19 susceptibility: potential of ACE2 polymorphisms. *Egypt J Med Human Genet* 2020; **21**: 54 [DOI: [10.1186/s43042-020-00099-9](https://doi.org/10.1186/s43042-020-00099-9)]
- 176 **Ali S**, Dornhorst A. Diabetes in pregnancy: health risks and management. *Postgrad Med J* 2011; **87**: 417-427 [PMID: [21368321](https://pubmed.ncbi.nlm.nih.gov/21368321/) DOI: [10.1136/pgmj.2010.109157](https://doi.org/10.1136/pgmj.2010.109157)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

