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PERSPECTIVES | *Translational Physiology*

Diabetes and COVID-19 risk: an miRNA perspective

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Mishra PK, Tandon R, Byrareddy SN. Diabetes and COVID-19 risk: an miRNA perspective. *Am J Physiol Heart Circ Physiol* 88: H604–H609, 2020. First published August 7, 2020; doi:10.1152/ajpheart.00489.2020.—Coronavirus disease 2019 (COVID-19) and diabetes outcomes (CORONADO) trial revealed that 10.6% of patients with diabetes mellitus hospitalized for COVID-19 (COVID-19) die within 7 days. Several studies from New York, Italy, and China confirm that patients with diabetes are at a much higher risk for mortality due to COVID-19. Besides respiratory illness, COVID-19 increases cardiac injury and diabetic ketoacidosis. In the absence of specific guidelines for the prevention and treatment of COVID-19 for patients with diabetes, they remain at higher risk and are more susceptible to COVID-19. Furthermore, there is a scarcity of basic knowledge on how diabetes affects pathogenesis of severe acute respiratory coronavirus (SARS-CoV-2) infection. In patients with diabetes, impaired glucose use alters metabolic and consequently biological processes instigating pathological remodeling, which has detrimental effects on cardiovascular systems. A majority of biological processes are regulated by noncoding microRNAs (miRNAs), which have emerged as a promising therapeutic candidate for several diseases. In consideration of the higher risk of mortality in patients with diabetes and COVID-19, novel diagnostic test and treatment strategy are urgently warranted in post-COVID-19 era. Here, we describe potential roles of miRNA as a biomarker and therapeutic candidate, especially for heart failure, in patients with diabetes and COVID-19.

biomarker; cardiovascular disease; heart failure; noncoding RNA; therapeutic candidate; SARS-CoV-2

INTRODUCTION

Diabetes mellitus (hereafter diabetes) increases severity and mortality of coronavirus disease 2019 (COVID-19), and intriguingly, COVID-19 instigates onset of diabetic phenotypes, mainly ketoacidosis and insulin resistance (24, 44). The relationship of diabetes and COVID-19 is intertwined; however, both increase the risk of heart failure (2, 39). Nevertheless, very little is known about diagnosis and treatment of patients with diabetes and COVID-19, especially for heart failure.

The noncoding regulatory microRNAs (miRNAs) are a promising therapeutic candidate for cardiovascular diseases (32). They are differentially expressed in the diabetic heart (9). The pathophysiology of diabetes-induced heart failure is unique, and it relates to a metabolic disorder (27, 45). Because severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) perturbs energy metabolism (35, 42), it may exacerbate cardiac metabolic remodeling leading to heart failure. How heart failure happens in patients with diabetes and COVID-19 is poorly understood.

miRNAs could be a potential biomarker and therapeutic target for patients with COVID-19. Differential circulating levels of miRNAs could be a potential biomarker for cardiovascular diseases (55). Similarly, they could be a potential biomarker for severity of COVID-19 in patients with and without diabetes. miRNA targets genes and restricts their expression (3). Thus, miRNA could prevent SARS-CoV-2 infection by targeting its protein expressing genes. The single-stranded RNA genome of SARS-CoV-2 has 29,891 nucleotides (GenBank: MN975262.1), which encode for the structural and nonstructural proteins. More studies are needed to understand how miRNAs regulate SARS-CoV-2 gene expression in the host cells to control its amplifications. Furthermore, miRNAs can regulate immune cells and thereby improve immunity of patients with COVID-19. Thus, manipulating endogenous miRNA to improve immunity and decrease the risk of SARS-CoV-2 infection could be another avenue for further investigation.

BACKGROUND ON COVID-19

COVID-19 is caused by SARS-CoV-2. It was first discovered in Wuhan, China, and rapidly spread over the world (16). Currently, >612,829 people have died by COVID-19 worldwide (https://www.worldometers.info/coronavirus/coronavirus-death-toll/). The burden of mortality has been unfairly heavy on elderly (>60 yr) people with comorbidities such as diabetes, hypertension, respiratory disease, cardiovascular disease, and chronic kidney and lung disease (43). Moreover, these populations are more susceptible to SARS-CoV-2 infection and the resultant development of acute respiratory distress syndrome (ARDS) compared with general population (58). The receptor-binding domain of spike glycoprotein of SARS-CoV-2 binds to angiotensin-converting enzyme-2 (ACE2) receptors on cell surface, followed by furin cleavage of S1/S2 domain and priming by the serine proteinase TMPRSS2, facilitating virus entry into host cells (31). The coexpression of ACE2 and TMPRSS2 is a major determinant of permissiveness of a cell to SARS-CoV-2 infection. The binding affinity of SARS-CoV-2 envelope spikes to the cellular ACE2 receptor is 10–20 times higher as compared with that of SARS-CoV-1, probably explaining the high transmission rates and infectivity of SARS-CoV-2 in humans (52).

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IMPACT OF DIABETES ON SEVERITY AND MORTALITY OF COVID-19

A meta-analyses of 33 studies with 16,003 patients' data sets revealed that diabetes increases severity and mortality (2-fold) in patients with COVID-19 (24). In a Wuhan hospital, out of 193 patients with severe COVID-19, 48 (24.9%) were diabetic and their mortality rate was higher (81.3%, 39 out of 48 patients with diabetes) compared with patients without diabetes (47.6%, 69 out of 145 patients without diabetes). Moreover, severity of COVID-19 was also higher in patients with diabetes (56). Other studies in China also support higher mortality risk in patients with diabetes (19, 50, 54). Further studies showed that 33.9% of 86,499 patients with severe COVID-19 in Italy and 33.8% of 5,700 patients with severe COVID-19 in New York City had diabetes (14, 41). There are several studies demonstrating that diabetes is a comorbidity in patients with severe COVID-19 (Table 1). It has been suggested that arrhythmia and sudden cardiac arrest are associated with heart failure in patients with COVID-19 (15). However, the cause of heart failure in diabetic COVID-19 remains unclear. Recent COVID-19 and diabetes outcomes (CORONADO) trial (NCT04324736) in 53 French centers revealed increased vascular complications in >40% patients with diabetes. The primary purpose of this study was to evaluate combined mechanical ventilation and/or death within 7 days, which was found to be independently and positively associated with diabetes (6). Thus, diabetes is a significant comorbid condition in patients with COVID-19 that worsens the outcome of the disease (10).

Notably, patients with diabetes even with mild symptoms are more vulnerable to COVID-19 (21). One of the potential underlying mechanisms for increased risk is insulin inactivity that impairs glucose uptake causing metabolic derangement, which in turn increases cellular adaptive stress. In addition,

Table 1. *Selected recent peer-reviewed primary research publications implicating diabetes as a comorbidity in patients with COVID-19*

Title	Authors	Publication Date	DOI/PMID
Risk and predictors of in-hospital mortality from COVID-19 in patients with diabetes and cardiovascular disease	Hadith et al.	2020 Jul 6	10.1186/s13098-020-00565-9
Clinical and CT features of the COVID-19 infection: comparison among four different age groups	Li et al.	2020 Jul 13	10.1007/s41999-020-00356-5
The Relationship between Diabetes Mellitus and COVID-19 Prognosis: A Retrospective Cohort Study in Wuhan, China	Shang et al.	2020 Jul 9	10.1016/j.amjmed.2020.05.033
Health-related concerns and precautions during the COVID-19 pandemic: A comparison of Canadians with and without underlying health conditions	Ramage-Morin et al.	2020 Jul 2	10.25318/82-003-x202000500001-eng
The impact of type 2 diabetes and its management on the prognosis of patients with severe COVID-19	Xu et al.	2020 Jul 8	10.1111/1753-0407.13084
Clinical analysis of risk factors for patients with severe COVID-19 with type 2 diabetes	Zhang et al.	2020 Jun 29	10.1016/j.jdiacomp.2020.107666
Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy	Zangrillo et al.	2020 Apr 23	PMID: 32353223
Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis	Kumar et al.	2020 July–August	10.1016/j.dsx.2020.04.044
New-Onset Diabetes in Covid-19	Rubino et al.	2020 Jun 12	10.1056/NEJMc2018688
Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	Huang et al.	2020 Feb 15	10.1016/S0140-6736(20)30183-5
Cardiovascular disease and COVID-19	Manish Bansal	2020 May–Jun	10.1016/j.dsx.2020.03.013
Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China	Wang et al.	2020 Feb 7	10.1001/jama.2020.1585
Clinical characteristics and outcomes of patients with severe covid-19 with diabetes.	Yan et al.	2020 Apr 27	10.1136/bmjdrc-2020-001343
Prevalence and impact of diabetes among people infected with SARS-CoV-2	Fadini et al.	2020 Mar 28	PMID: 32222956
COVID-19 infection in Italian people with diabetes: Lessons learned for our future (an experience to be used)	Gentile et al.	2020 Apr	10.1016/j.diabres.2020.108137
Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature	Katulanda et al.	2020 Aug	10.1007/s00125-020-05164-x
Diabetes is a risk factor for the progression and prognosis of COVID-19	Guo et al.	2020 Mar	10.1002/dmrr.3319

This list is not comprehensive, and hypothetical models, individual case reports, and data mining reports have been excluded from this list. Updated through 2020 Jul 20.

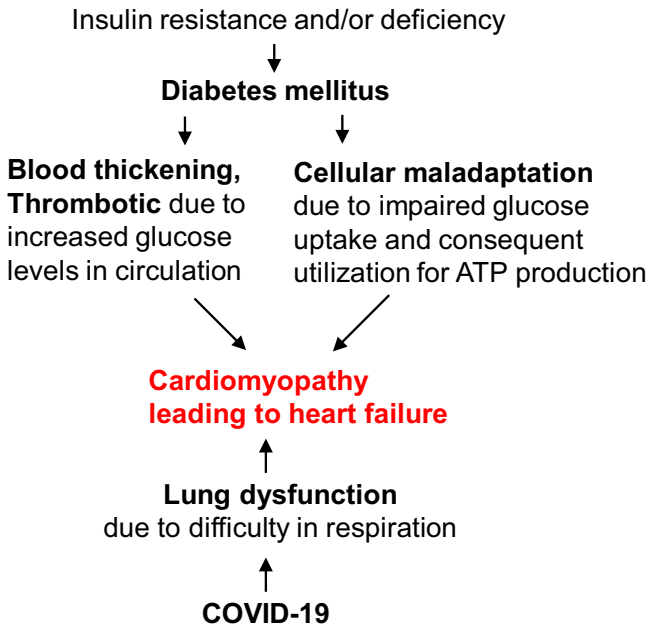

Fig. 1. Diabetes and coronavirus disease-19 (COVID-19) double the detrimental effects on the heart. Diabetes mellitus (DM) is caused by insulin resistance (type-2 DM) or deficiency (type-1 DM) or both at the advanced stage of the disease. High-glucose levels in the blood increases its viscosity and risk of thrombosis. Reduced glucose uptake at cellular levels causes metabolic remodeling due to impaired glucose oxidation. Moreover, increased fatty acid oxidation causes maladaptive changes and cellular stress that result in cell death instigating pathological cardiac remodeling leading to heart failure. In COVID-19 disease, severe acute respiratory coronavirus (SARS-CoV-2) infection damages lungs and compromises their function that reduces oxygen supply to the heart and ultimately causes heart failure.

increased circulating levels of glucose cause O-linked attachment of glycan moiety to proteins affecting their functional activity and induce adaptive modifications that instigate pathological remodeling in patients with diabetes (8, 40). Diabetes also increases inflammation and thrombotic tendency, which is exacerbated by SARS-CoV-2 infection (17, 49). Thus, diabetes increases thrombosis and cellular stress leading to heart failure, which is exacerbated by lung dysfunction due to COVID-19 infection (Fig. 1). Hypertension and diabetes are comorbid conditions in patients with COVID-19 (48). Patients with diabetes develop hypertension; however, an independent contribution of hypertension on severity of COVID-19 in patients with diabetes has not been demonstrated.

Diabetes does not increase the risk of SAR-CoV-2 infection (10). Therefore, the major effect of diabetes is on pathological remodeling leading to death in patients with COVID-19. Notably, the risk of heart failure in patients with diabetes is not decreased by glycemic control (7). Thus, controlling only glucose levels may not be adequate to decrease the risk of heart failure in patients with diabetes and COVID-19. Future studies focusing on the characterization of health failure and molecular mechanisms, especially underlying heart failure in patients with COVID-19, could provide insights for developing specific therapeutic candidates.

Low abundance of host-cell miRNAs is associated with increasing severity and mortality by COVID-19 in aged individuals (12). Aging increases the risk of diabetes. However, the role of miRNAs in patients with diabetes and COVID-19 is poorly understood.

MICRORNA IN TESTING AND TREATING DIABETIC COVID-19

Background of miRNA. miRNAs are a class of noncoding, endogenous, tiny regulatory RNAs that modulate gene expression either by mRNA degradation or translational repression. They are biosynthesized as a double-stranded primary miRNA in the nucleus and matured as a single-stranded RNA in cytoplasm, where they bind mostly at the 3′-untranslated region (3′-UTR) to control the majority of biological functions (3, 32). More than 2,000 miRNAs are present in our body, and more than 800 miRNAs are expressed in the heart (11, 26). Differentially expressed cardiac miRNAs are potential therapeutic candidates for heart failure with diabetes (22, 38). Several miRNAs are associated with SARS-CoV-2 infection. However, as of this date, only five studies have described the role of specific miRNAs in SARS-CoV-2 infection and pathogenesis (Table 2).

MicroRNA as a biomarker. miRNAs are excreted in circulation in microvesicles and exosomes. Differential levels of circulating miRNAs are a promising biomarker for heart failure (13, 46, 53). In diabetic conditions, the subclinical changes in the heart are difficult to diagnose with regular cardiovascular evaluations, and miRNA has great potential to serve as a diagnostic biomarker (25). In patients with diabetes and COVID-19, the mild symptoms have detrimental effects, and circulating miRNA profiling could offer an important strategy to determine disease severity. Furthermore, the subcategory of miRNA profiling could provide important information on severity of organ damage and dysfunction, including heart failure. Therefore, circulating miRNA profiling could be a new strategy to assess whether a patient with diabetes

Table 2. *List of recent publications discussing the role of microRNAs in SARS-CoV-2 infection*

Title	Authors	Publication Date	DOI
Computational analysis of microRNA-mediated interactions in SARS-CoV-2 infection	Demirici et al.	2020 Jun 5	10.7717/peerj.9369
COVID-19 Virulence in Aged Patients Might Be Impacted by the Host Cellular MicroRNAs Abundance/Profile	Fulzele et al.	29 Apr 2020	10.14336/AD.2020.0428
What is the potential function of microRNAs as biomarkers and therapeutic targets in COVID-19?	Guterres et al.	2020 Jun 8	10.1016/j.meegid.2020.104417
The Prediction of miRNAs in SARS-CoV-2 Genomes: hsa-miR Databases Identify 7 Key miRs Linked to Host Responses and Virus Pathogenicity-Related KEGG Pathways Significant for Comorbidities	Arisan et al.	2020 Jun 4	10.3390/v12060614
The impact of MicroRNAs (miRNAs) on the genotype of coronaviruses	Canatan et al.	2020 May 11	10.23750/abm.v91i2.9534

and with mild COVID-19 symptoms needs urgent attention/hospitalization. Thus, this miRNA testing strategy could prevent severe/detrimental consequences in patients with diabetes and with mild COVID-19 symptoms.

MicroRNA as a therapeutic target. Cellular/tissue levels of miRNAs alter in different disease, which is reviewed in Abdellatif (1). By targeting several genes in a biological network, an miRNA can trigger one or more biological processes and thereby maintains cellular homeostasis. Thus, manipulating the endogenous miRNA levels (increasing the downregulated miRNA by miRNA mimic and decreasing the upregulated miRNA by anti-miR treatment) has potential to ameliorate cardiovascular disease at least in preclinical models (32). Because of promising preclinical results, >900 clinical trials have been conducted on miRNAs (www.ClinicalTrial.Gov).

miRNAs could play crucial roles in preventing infection of SARS-CoV-2 by modulating gene expression levels and improving host immune system. An extensive review on miRNAs targeting SARS-CoV-2 genome, their target genes, and associated biological pathways has recently published (12). We postulate that miRNA could target virus genes and modulate their expression by degrading mRNA and inhibiting their translation. It has been shown that small viral RNAs contribute to SARS-CoV-2 pathogenesis (34), and miRNAs that regulate viral RNA could provide a molecular basis for SARS-CoV-2 infection (18, 28). Virus in COVID-19 disease belongs to the betacoronavirus family, and probably miRNAs are involved in regulating their replication and pathogenesis (4). Thus, by reducing the viral replication, miRNA could serve as potential therapeutic candidate to prevent the progression from mild to severe COVID-19 disease in patients with diabetes.

miRNA in patients with diabetes and COVID-19 could also optimize immune metabolism in the diabetic heart to ameliorate cardiomyopathy that leads to heart failure (33). Targeting inflammasome formation and cell death are other potential avenues for miRNA therapeutics that can be used to treat patients with diabetes and COVID-19 (57). Thus, miRNA can act at various levels to suppress virus infection and mitigate its pathological remodeling. It could serve as a biomarker for patients with diabetes and COVID-19 (Fig. 2).

In the heart, miRNAs involved in regulation of ACE2 expression, arrhythmia, and sudden cardiac arrest are of great interest for patients with COVID-19 due to their potential roles in SARS-CoV-2 protein expression and heart failure. It is found that miR-15b-5p decreased with age in coronary artery disease and that miR-30e-3p decreased with age in myocardial injury. Both of these miRNAs are predicted to target SARS-CoV-2 genome (12, 51, 59). Lipotoxicity and metabolic remodeling play a significant role in diabetic heart failure (27, 29). miRNAs involved in these pathways may have important roles in patients with diabetes and COVID-19. Our studies suggest that increasing the cardiac levels of miR-133a in the diabetic heart reduces cardiac lipid accumulation (20). Thus, miR-133a could regulate lipotoxicity and metabolic remodeling in the diabetic heart. Furthermore, it targets angiotensinogen and thus could be involved in regulation of ACE2 receptor function in congestive heart failure condition (47). It also modulates electrical repolarization caused due to pressure overload in the heart (30) and thus may be involved in controlling arrhythmia. miR-133a is one of the most abundant miRNAs in the human heart (26), which is downregulated in human diabetic and nondiabetic heart failure (5, 37). It is essential for adult heart function, and loss of miR-133a causes cardiac hypertrophy and dysfunction (5). Notably, overexpression of miR-133a does not have any detrimental effects; rather, it protects the heart against cardiac fibrosis after pressure

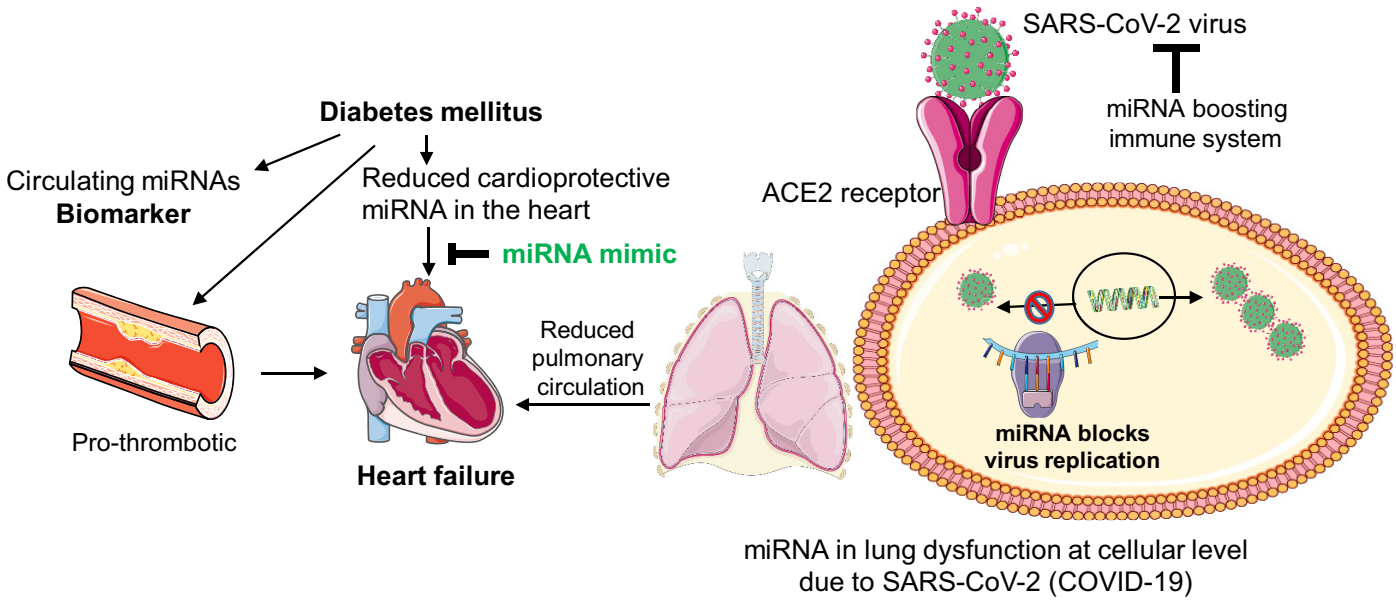

Fig. 2. MicroRNA (miRNA) as a biomarker and therapeutic candidate for patients with diabetes and coronavirus disease-19 (COVID-19). In diabetes, differential expression of circulating miRNAs could be a potential biomarker for severity of COVID-19 disease with and without cardiac dysfunction. Diabetes also increases thrombosis and reduces cardioprotective miRNAs such as miR-133a in the heart. Increasing the levels of cardioprotective miRNAs by miRNA mimic treatment mitigates diabetic heart failure. In COVID-19 infection, the severe acute respiratory coronavirus (SARS-CoV-2) virus enters lung cells by angiotensin-converting enzyme 2 (ACE2). They replicate inside the host cell to make more viruses. miRNA can restrict viral replication and boost immune system and thereby prevent lung deterioration and consequently improve cardiovascular outcomes. Thus, miRNA could be a potential therapeutic target and biomarker for patients with diabetes and COVID-19.

overload (30) and against impaired contractility caused by diabetes (38). Thus, miR-133a is a promising candidate for investigating its role in heart failure in patients with diabetes and COVID-19. Besides, miR-133a, miR-1, miR-208, miR-328, miR-21, miR-212, and miR-590 are involved in arrhythmia. The details of miRNA targets and their roles in cardiac conduction and arrhythmia have been recently elaborated (23).

SUMMARY AND FUTURE DIRECTIONS

Several studies from different parts of the world have confirmed that diabetes increases severity and mortality of COVID-19, plausibly by increasing inflammation and compromising immunity (36). The absence of specific guidelines to manage and treat patients with diabetes and COVID-19 and their increased mortality risk warrant new approaches to diagnose, manage, and treat the detrimental combination of diabetes and COVID-19 disease. We propose that investigating miRNAs in patients with diabetes and COVID-19 as a biomarker and a therapeutic candidate could open a new platform to assess mild to severely ill patients with diabetes and COVID-19 and may pave a way to prevent the progression of viral infection via restricting viral genome amplification and boosting immune system. Thus, miRNA could be a promising diagnostic biomarker and therapeutic target for patients with diabetes and COVID-19.

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DISCLAIMERS

The content is solely the responsibility of the authors and does not necessarily represents the official views of the grant institutions.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.K.M. conceived and designed research; P.K.M. prepared figures; P.K.M. drafted manuscript; P.K.M., R.T., and S.N.B. edited and revised manuscript; P.K.M., R.T., and S.N.B. approved final version of manuscript.

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