Diabetes and COVID-19 risk: an miRNA perspective

Paras K. Mishra,1 Ritesh Tandon,2 and Siddappa N. Byrareddy3
1Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, Nebraska; 2Department of Microbiology and Immunology, University of Mississippi Medical Center, Jackson, Mississippi; and 3Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, Nebraska

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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 proteasein 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).
IMPACT OF DIABETES ON SEVERITY AND MORTALITY OF COVID-19

A meta-analysis 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       |
| 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/NEJMct2018688        |
| 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/bmjdrce-2020-001343   |
| Prevalence and impact of diabetes among people infected with SARS-CoV-2 | Fadini et al.       | 2020 Mar 28      | PMID: 3222956                 |
| 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.
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.

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? | Gutteres 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.v912.9534 |
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.](AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00489.2020 • www.ajpheart.org)
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 represent the official views of the grant institutions.

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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