Original Article

METFORMIN USE IN DIABETES PRIOR TO HOSPITALIZATION: EFFECTS ON MORTALITY IN COVID-19

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ABSTRACT

Objective: Although type 2 diabetes mellitus (T2DM) has been reported as a risk factor for coronavirus disease 2019 (COVID-19), the effect of pharmacologic agents used to treat T2DM, such as metformin, on COVID-19 outcomes remains unclear. Metformin increases the expression of angiotensin converting enzyme 2, a known receptor for severe acute respiratory syndrome coronavirus 2. Data from people with T2DM hospitalized for COVID-19 were used to test the hypothesis that metformin use is associated with improved survival in this population.

Methods: Retrospective analyses were performed on de-identified clinical data from a major hospital in Wuhan, China, that included patients with T2DM hospitalized for COVID-19 during the recent epidemic. One hundred and thirty-one patients diagnosed with COVID-19 and T2DM were used in this study. The primary outcome was mortality. Demographic, clinical characteristics, laboratory data, diabetes medications, and respiratory therapy data were also included in the analysis.

Results: Of these 131 patients, 37 used metformin with or without other antidiabetes medications. Among the 37 metformin-taking patients, 35 (94.6%) survived and 2 (5.4%) did not survive. The mortality rates in the metformin-taking group versus the non-metformin group were 5.4% (2/37) versus 22.3% (21/94). Using multivariate analysis, metformin was found to be an independent predictor of survival in this cohort ($P = .02$).

Conclusion: This study reveals a significant association between metformin use and survival in people with T2DM diagnosed with COVID-19. These clinical data are consistent with potential benefits of the use of metformin for COVID-19 patients with T2DM. **(Endocr Pract. 2020;26:1166-1172)**

Abbreviations:
ACE2 = angiotensin-converting enzyme 2; **AMPK** = AMP-activated protein kinase; **BMI** = body mass index; **COVID-19** = coronavirus disease 2019; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **T2DM** = type 2 diabetes mellitus

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has been a focus of intense interest and ongoing investigation. Established risk factors for poor outcomes of COVID-19 include age (>65 years old), chronic obstructive pulmonary disease, cardiovascular disease, hypertension, obesity, and type 2 diabetes mellitus (T2DM) (1). However, the mechanisms underlying these observations remain unclear. Due to the nature of the pandemic, the

execution of randomized trials is challenging. Thus, rigorous analyses of existing clinical data may be informative until more definitive data are available.

T2DM is a risk factor for many infectious diseases. The pathogenesis of immunosuppression is complex and likely related to hyperglycemia, oxidative stress, and other pathways (2-4). A retrospective study in Wuhan, China, indicated that poorly controlled blood glucose is associated with increased mortality (5). However, patients with well-controlled T2DM may be at risk for COVID-19 complications (6,7). Yet, the effects of antidiabetes pharmacotherapy on COVID-19 complications are unclear; therefore, studying the possible clinical outcomes of pharmacologic agents may provide important insights to drive further studies related to mitigating risk factors.

One common initial therapy for T2DM is metformin. In addition to its insulin sensitizing effect, metformin is associated with potential protective benefits against cardiovascular diseases, nonalcoholic fatty liver disease, cancers, and ventilator-induced lung injury (8-12). Interestingly, biguanides (which include metformin) were once used to treat the flu in the 1940s (12). The mechanisms underlying these benefits are likely complex and extend beyond simple anti-inflammatory or glucose regulation properties.

Metformin activates AMP-activated protein kinase (AMPK) in vitro and in vivo (13). In several lung injury rodent models, metformin activates AMPK to regulate angiotensin-converting enzyme 2 (ACE2) protein stability (13). ACE2 is a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into the host cells (14). However, metformin activation of ACE2 may have an important role in cardiopulmonary health (13,15). Given the risk of multiple system organ failure in severe lung injury and the potential role of cardiovascular dysfunction in mediating this process, the possibility that metformin improves outcomes in COVID-19 pneumonia merits investigation.

Based on this conceptual framework, we sought to test the hypothesis that metformin is associated with increased survival rate in those with COVID-19 and T2DM. To test this notion, data from a cohort in Wuhan, China, one of the epicenters of the COVID-19 outbreak, were analyzed.

METHODS

Study Population

This was a retrospective cohort study of 131 consecutive patients with COVID-19 pneumonia and T2DM hospitalized in Wuhan Red Cross Hospital (WRCH) in Wuhan, China from January 23, 2020, to March 19, 2020. COVID-19 was diagnosed using reverse transcription polymerase chain reaction to test for SARS-CoV-2 genes from nasopharyngeal swab samples, according to World Health Organization (WHO) interim guidance (16). The diagnosis of T2DM was determined using clinical records according

to the WHO diagnostic criteria for T2DM (17). The study protocol was approved by the WRCH Ethics Committee and written informed consent was obtained from the patients included in the study.

Procedures

A trained team of physicians reviewed and collected clinical and outcomes data from electronic medical records. All the individual components of the database were recorded and checked separately by 2 independent physicians. Patient confidentiality was protected by using a de-identified number. Demographic information (i.e., age, sex), medical history (i.e., cardiovascular disease, hyperlipidemia, the course of diabetes as well as the medications), clinical characteristics (i.e., body mass index (BMI), blood pressure, oxygen saturation), laboratory results, treatments (i.e., diabetes medications), duration of hospital stay, and outcomes were retrieved from the medical records. Data were summarized using a standardized database collection form. Two independent researchers then reviewed the database for accuracy. To account for potential bias of metformin use in early T2DM compared to insulin in late T2DM, outcomes for other oral agents typically given for early stage T2DM in China, such as acarbose, were also included in the analysis.

Outcomes

Our main outcome was mortality among patients with COVID-19 and T2DM during the hospitalization for COVID-19 pneumonia, up to 60 days after admission.

Statistical Analysis

The chi-squared test and Fisher exact test were used to compare univariate differences between survivors and nonsurvivors. Univariate logistic regression models were used to analyze the effects of continuous variables on mortality. Multivariate logistic regression models were also used to assess simultaneous effects of continuous, binomial, and categorical variables on survivability or mortality. Statistical significance was set at α (P value) of less than .05. Statistical analyses were performed using the R programming language or MATLAB.

RESULTS

Mortality Risk Factors for COVID-19 with T2DM

The characteristics of these 131 patients at admission, including age, BMI, serum glucose concentration, and oxygen saturation, are summarized in Table 1. Most patients had been on one or more diabetes medications prior to admission, including insulin, metformin, sulfonylureas, and acarbose. Some patients were managed with only diet control and lifestyle modification (Fig. 1 *A*).

To understand if clinical characteristics or diabetes medications were associated with COVID-19 survival

Table 1 Characteristics and Outcomes of COVID-19 Patients with Type 2 Diabetes		All	Survivor	Nonsurvivor	*P* value
Total, n (%)		131	108 (82.4)	23 (17.6)	
Gender					
	Male, n (%)	74	62 (83.8)	12 (16.2)	.7489
	Female, n (%)	57	46 (80.7)	11 (19.3)	
Age (mean ± SD)		66.8 ± 11.6	65.9 ± 11.5	71.5 ± 11.1	.0036[b]
Age (median)		66	65	75	
Weight (kg, mean ± SD)		66.0 ± 10.1	65.4 ± 10.5	69.3 ± 7.1	.0176[a]
BMI (mean ± SD)		24.23 ± 3.37	23.97 ± 3.28	25.66 ± 3.57	.0076[b]
O_2 saturation (mean ± SD)		0.91 ± 0.13	0.94 ± 0.08	0.74 ± 0.17	.0005[c]
Cholesterol (mmol/L, mean ± SD)		3.84 ± 1.09	3.52 ± 0.92	3.89 ± 1.11	.693
Triglyceride (mmol/L, mean ± SD)		1.32 ± 0.76	1.30 ± 0.78	1.42 ± 0.68	.0005[c]
HDL (mmol/L, mean ± SD)		0.95 ± 0.34	0.97 ± 0.35	0.86 ± 0.26	.445
LDL (mmol/L, mean ± SD)		2.41 ± 0.85	2.44 ± 0.86	2.18 ± 0.75	.372
HbA1c (mmol/L, mean ± SD)		7.89 ± 1.85	7.93 ± 1.89	7.15 ± 0.21	.571
Glucose (mmol/L, mean ± SD)		9.03 ± 4.45	8.50 ± 4.19	12.33 ± 4.71	.0069[b]
CRP (mg/L, mean ± SD)		49.37 ± 65.45	38.76 ± 57.07	104.1 ± 79.24	.000728[c]
D-dimers (mg/L, mean ± SD)		4.27 ± 12.16	2.22 ± 4.86	14.10 ± 25.58	.00129[b]
CAD, n (%)	Y	28	22 (78.6)	6 (21.4)	.579
	N	103	86 (83.4)	17 (16.5)	
Hypertension, n (%)	Y	78	62 (79.5)	16 (20.5)	.268
	N	53	46 (86.8)	7 (13.2)	
Hypertension med, n (%)	Y	45	40 (88.9)	5 (11.1)	.227
	N	86	68 (79.1)	18 (20.9)	
Hyperlipidemia, n (%)	Y	14	11 (78.6)	3 (21.4)	.736
	N	117	97 (82.9)	20 (17.1)	
Smoking, n (%)	Y	9	9 (100.0)	0 (0.0)	.124
	N	122	99 (81.1)	23 (18.9)	
Insulin, n (%)	Y	26	23 (88.5)	3 (11.5)	.557
	N	105	85 (81.0)	20 (19.0)	
Metformin, n (%)	Y	37	35 (94.6)	2 (5.4)	.0222[a]
	N	94	73 (77.7)	21 (22.3)	
Sulfonylureas, n (%)	Y	22	19 (86.4)	3 (13.6)	.417
	N	109	89 (81.7)	20 (18.3)	
Acarbose, n (%)	Y	38	35 (92.1)	3 (7.9)	.0779
	N	93	73 (78.5)	20 (18.3)	

Abbreviations: BMI = body mass index; CAD = coronary artery disease; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; HbA1c = hemoglobin A1c; HDL = high-density lipoproteins; LDL = low-density lipoproteins; med = medication; N = no; Y = yes.

Measurements were done using patients' blood samples obtained on the day of admission. *P* values indicate the level of significance in the relationship between each independent variable (e.g., metformin Y and N) and the dependent variable (recovered and death), as calculated by Fisher exact test, or, in case of continuous independent variable (e.g., CRP), by logical regression analysis.
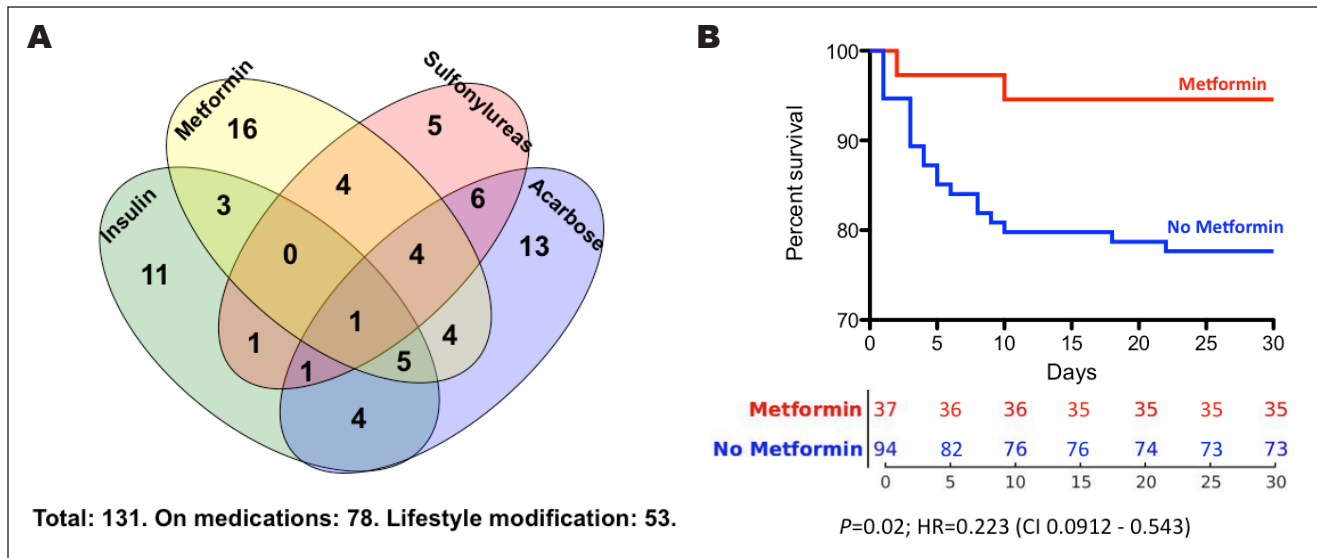
[a]*P*<.05; [b]*P*<.01; [c]*P*<.001.

Fig. 1. Metformin is associated with increased survival in people with T2DM diagnosed with COVID-19. *A*, A Venn diagram showing the number of patients taking diabetes medications. Of the total of 131 patients, 78 of them were on one or more medications, and 53 of them were on lifestyle modification only. Among the 78 patients with medications, 26 of them were on insulin, 37 of them were on metformin, 22 of them were on sulfonylureas, 38 of them were on acarbose. *B*, A Kaplan-Meier curve of survival probabilities for patients on metformin or not on metformin. Statistics were derived using MATLAB scripts. Hazard ratio (HR), 0.223, 95% confidence interval (CI), 0.0912 to 0.543; *P* = .02. *T2DM* = type 2 diabetes mellitus.

versus mortality, multivariate analysis of covariance was employed using mortality or survival as the outcome or dependent variable. The results indicate that mortality of this cohort was significantly positively associated with age, body weight, BMI, oxygen desaturation, glucose, triglyceride, C-reactive protein (CRP), and D-dimers (Table 1). Metformin use was significantly and positively associated with survival ($P = .02$). Certain variables were not associated with mortality, including gender, cholesterol, hemoglobin A1c, coronary artery disease, and hypertension. These results are by and large consistent with previous reports of mortality risks of other cohorts of COVID-19 patients (18).

Protective Effect of Metformin for COVID-19 Patients with T2DM

Among the 4 types of diabetes medications, metformin showed a significant association with survival. Of the 131 COVID-19 patients with diabetes, 37 were using metformin with or without other diabetes medications: only 2 (5.4%) of these 37 patients died and 35 (94.6%) survived. The survival of the metformin treated patients was significantly different ($P = .0222$) when compared with the 94 patients who were not on metformin, with 21 (22.3%) deaths and 73 (77.7%) recovered (Table 1). A Kaplan-Meier curve of survival probabilities also indicates that patients on metformin had a significantly better chance of survival compared with those not on metformin (Fig. 1 *B*).

The Effect of Metformin on Survival is Independent of Other Confounders

To rule out the possibility that other confounding factors, such as age and inflammatory conditions, were

disproportionately distributed in metformin users, we analyzed covariance with metformin use as a dependent variable. This analysis showed that metformin use versus no metformin use was not significantly different for a number of potentially important covariates (Table 2). For instance, the average ages of metformin and non-metformin users were 64.6 and 67.7 years, respectively, which were not significantly different ($P = .229$). In contrast, the age difference between all patients who survived versus those that did not survive was 65.9 and 71.5 years, respectively (Table 1). Thus, the potential efficacy of metformin in increasing survival was unlikely a function of age differences between groups. Other factors that may benefit from metformin administration, such as body weight and glucose concentration, were also not significantly different between metformin use or not in this cohort (Table 2), suggesting that the observed effect of metformin was not due to its glucose-lowering or body-weight reducing effect. Interestingly, these metformin users on average had higher concentrations of triglyceride, HbA1C, and CRP; factors that would be predicted to be associated with a higher mortality (Table 2). These analyses suggest that metformin use is associated with improved survival of COVID-19 patients with T2DM independent of its effects on lowering glucose concentration and body weight.

DISCUSSION

With ongoing studies in COVID-19 attempting to identify new therapeutic strategies, this study adds important information to the existing literature. The data from this cohort revealed a strong and independent association between prehospital metformin use for T2DM and lower

Table 2 Comparison of Patients with and without Metformin		All	Metformin	No metformin	*P* value
Total		131	37	94	
Survival	Survivor, n (%)	108	35 (94.6)	73 (77.7)	.0228[a]
	Nonsurvivor, n (%)	23	2 (5.4)	21 (22.3)	
Gender	Male, n (%)	74	22 (59.5)	52 (55.3)	.452
	Female, n (%)	57	15 (40.5)	42 (44.7)	
Age (mean ± SD)		66.8 ± 11.6	64.6 ± 11.2	67.7 ± 11.7	.229
Weight (kg, mean ± SD)		66.0 ± 10.1	66.0 ± 13.3	66.1 ± 8.6	.808
BMI (mean ± SD)		24.18 ± 3.33	24.24 ± 3.65	24.16 ± 3.21	.902
Hospital stay (survived; days)		17.26 ± 12.6	17.27 ± 9.49	17.25 ± 13.93	.995
O$_2$ saturation (mean ± SD)		0.91 ± 0.13	0.94 ± 0.08	0.89 ± 0.14	.163
Triglyceride (mmol/L, mean ± SD)		1.32 ± 0.76	1.40 ± 0.80	1.28 ± 0.75	.0005[c]
HbA1c (mmol/L, mean ± SD)		7.89 ± 1.85	9.23 ± 2.27	7.46 ± 1.49	.0032[b]
Glucose (mmol/L, mean ± SD)		9.01 ± 4.57	9.15 ± 4.64	8.95 ± 4.57	.929
CRP (mg/L, mean ± SD)		49.37 ± 65.45	57.78 ± 74.90	45.87 ± 61.12	.135
D-dimers (mg/L, mean ± SD)		4.27 ± 12.16	2.32 ± 5.83	5.12 ± 13.99	.242
CAD, n (%)	Y	28	7 (18.9)	21 (22.3)	.814
	N	103	30 (81.1)	73 (77.7)	
Hypertension, n (%)	Y	78	23 (62.2)	55 (58.5)	.844
	N	53	14 (37.8)	39 (41.5)	
Hypertension med, n (%)	Y	45	15 (40.5)	30 (31.9)	.415
	N	86	22 (59.5)	64 (68.1)	
Hyperlipidemia, n (%)	Y	14	3 (8.1)	11 (11.7)	.756
	N	117	34 (92.9)	83 (88.3)	
Smoking, n (%)	Y	9	2 (5.4)	7 (7.4)	.999
	N	122	35 (94.6)	87 (92.6)	
Insulin, n (%)	Y	26	9 (24.3)	17 (18.1)	.468
	N	105	28 (75.7)	77 (81.9)	
Secretagogues, n (%)	Y	22	9 (24.3)	13 (13.8)	.194
	N	109	28 (75.7)	81 (86.2)	
Acarbose, n (%)	Y	38	14 (37.8)	24 (25.5)	.2
	N	93	23 (62.2)	70 (74.5)	
Oxygen therapy/ventilation					.264
No ventilation, n (%)	Room air	26	6 (16.2)	20 (21.3)	
	NC	69	25 (67.6)	44 (46.8)	
	NRM	7	0 (0.0)	7 (7.4)	
	High flow	7	1 (2.7)	6 (6.4)	
Noninvasive ventilation, n (%)		19	4 (10.8)	15 (16.0)	
Invasive ventilation, n(%)		3	1 (2.7)	2 (2.1)	

Abbreviations: BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; HbA1c = hemoglobin A1c; med = medication; NC = nasal cannula; NRM = non-rebreathing mask.
Measurements were done using patients' blood samples obtained on the day of admission. *P* values indicate the level of significance in the relationship between each independent variable (e.g., insulin Y and N) and metformin versus no metformin, as calculated by Fisher exact test or chi-square test, or in case of continuous independent variable (e.g., CRP), by logical regression analysis.
[a]*P*<.05; [b]*P*<.01; [c]*P*<.001.

mortality among patients hospitalized with COVID-19 disease. This finding is of interest and should encourage subsequent research. Basic studies to understand the role of AMPK regulation of ACE2 in COVID-19 pathogenesis may reveal new therapeutic opportunities (19). Clinical randomized, controlled trials using metformin with or without T2DM could potentially be designed on the basis of our new findings.

Many empiric therapies of COVID-19 have been practiced but remain unproven and may have risk benefit profiles that may be deleterious. For example, remdesivir is an antiviral agent that has some promise based on early findings. However, the benefits are rather modest and conflicting results have been reported (20-22). Thus, adjunctive therapy will likely be required to have major benefits. Hydroxychloroquine with or without azithromycin has also been used in many institutions despite limited supportive data (23). These agents have been associated with a prolonged QTc interval, and professional societies have recently warned against their use in COVID-19 pneumonia outside of the context of a clinical trial (24,25). Tocilizumab has also been studied for COVID-19 based on its interleukin-6 receptor inhibition, but definitive outcome data are lacking (26). In addition, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are currently being used in trials with large cohorts (27). However, outcome data from these trials are limited and studies are ongoing.

We are highly supportive of ongoing research and view metformin as an attractive possibility. Metformin is safe, widely available, inexpensive, and has considerable use in various different clinical settings (15). Although some concerns exist regarding the adverse effect of metformin in causing lactic acidosis, this complication is extremely rare even with renal impairment (28). Although metformin may be helpful either as a monotherapy, or in combination with other medications, randomized trials using various drug combinations would need to be completed before definitive conclusions can be drawn.

The infectivity of SARS-CoV-2 relies on its binding to ACE2 in the host cells (14). Acting as the protective arm of the renin-angiotensin-aldosterone system, optimal expression of cellular ACE2 in the cardiopulmonary system is critical for homeostatic regulation in the lung, vasculature, kidney, and heart. The role of the ACE2 as a "friend-or-foe" in the context of COVID-19 is highly debatable (29-31). As a potent AMPK activator, we have previously shown that metformin increases the phosphorylation of ACE2 as well as the activity and expression levels of ACE2, in the mouse lung and vasculature (13). Thus, the therapeutic effects of metformin suggested by the current study might be partially due to the enhancement of ACE2 concentration in COVID-19 patients.

Despite the strengths of our study, there are some limitations to be mentioned. First, in the absence of a random-ized trial, these findings represent correlational rather than causal effects. This concern is true of all retrospective studies. Although the data analysis was controlled for known confounders, there may still be residual confounding. Metformin is generally a treatment for early stage T2DM, and as such, patients not taking metformin might have different disease severity or vulnerability. Other oral agents, such as acarbose (commonly used in China as initial therapy for diabetes), did not have a similar association with survival among patients in this cohort, suggesting that our findings are not spurious. Second, the sample size was relatively modest. Nonetheless, these findings are potentially important and perhaps will be a catalyst for a more definitive randomized trial. Furthermore, the observation that metformin may have important benefits could provide early guidance for novel therapeutic development. Third, although we have reported previously putative mechanisms underlying metformin effects (13,19), we have no means to study the causal pathways underlying our new observations in our participants. Thus, additional work is clearly needed. Despite these limitations, these findings provide a basis for further research and may be of interest until more definitive data emerge.

CONCLUSION

During our preparation of the manuscript, 2 observational studies (one prepublication release prior to peer review) became available which are consistent with our findings of potential beneficial effects of metformin in COVID-19 and T2DM patients (32,33). Our study identified metformin to be an independent predictor of survival in COVID-19 patients with T2DM. Further work is needed to give definitive clinical recommendations and to elucidate further underlying mechanisms.

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DISCLOSURE

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