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Original Article

COVID-19 clinical outcomes in type-2 diabetic patients on DPP4-inhibitors

Atousa Najmaldin [1], Pardis Sadeghipour [2], Hoda Aryan [1], Homa Abri [2], Nahid Hashemi-Madani [3] *, Nadaer Tavakoli [4], Mohammad Ebrahim Khamseh [5]

[1] Department of Internal Medicine, Kowsar Hospital, Semnan University of Medical Medicine, Semnan, Iran
[2] Department of Internal Medicine, Firoozgar Hospital, Iran University of Medical Sciences, Tehran, Iran
[3] Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[4] Trauma and Injury Research Center, Iran University of Medical Sciences, Tehran, Iran
[5] Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran

* Correspondence to: Nahid Hashemi-Madani, Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran. Firouzeh St, Vali-asr Ave, Tehran, Iran. Phone: +98 21 88945435; Fax: +98 21 88945173; E-mail: Nahid.hashemimadani@gmail.com

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Abstract

It has been suggested that dipeptidyl peptidase 4 (DPP4) overexpression is associated with COVID-19 severity. We aimed to evaluate the clinical outcomes in people with COVID-19 infections and type 2 diabetes (T2DM) treated with DPP4 inhibitors in order to explore the impact of treatment with DPP4 inhibitors on adverse in-hospital outcomes. This retrospective multi-center study included 400 hospitalized people with T2DM and confirmed COVID-19 infection. The composite outcomes, including ICU admission, invasive ventilation and in-hospital mortality, were compared between patients who received DPP4 inhibitors before admission and those treated by other glucose-lowering drugs (GLDs), applying regression models. A total of 54 (13.5%) patients were treated with DPP4 inhibitors. Considering the potential confounders, the odds of the composite outcome of intensive care unit (ICU) admission, invasive ventilation, and death were significantly lower in patients treated with DPP4 inhibitors compared to their counterpart group (OR: 2.52, (1.05–6.01), P=0.04). Previous treatment with DPP4 inhibitors lowers the risk of adverse in-hospital outcomes in people with T2DM and COVID-19 infection.

Keywords: COVID-19 infection, ICU admission, mortality, severity, type 2 diabetes.

Introduction

Coronavirus disease 2019 (COVID-19) has affected approximately over 240 million people globally, with 5 million fatalities up to November 2022 [1]. The most frequent symptoms of severe acute respiratory syndromes are fever, cough, shortness of breath, and exhaustion [2]. Moreover, the most prevalent serious complication of COVID-19 exacerbation was acute respiratory distress syndrome (ARDS), respiratory failure, sepsis, acute cardiac damage, and heart failure [3].

According to the US Department of Health and Human Services and Centers for Disease Control and Prevention, people with T2DM and metabolic syndrome may have a tenfold increased risk of mortalities if they were infected with COVID-19 [4–6]. Given the increased mortality and higher risk of severe COVID-19 in patients with T2DM, good glycemic control is highly recommended [7]. Individualized blood glucose targets and treatment protocols are suggested for people with type 2 diabetes (T2DM) and COVID-19 infection.

COVID-19 infections are substantially connected to numerous metabolic disorders. In a recently published meta-analysis, which included 1,936 COVID-19 patients, hypertension, T2DM, and coronary heart disease had a major impact on the course of COVID-19 infection [8].

These patients are more prone to infections due to the negative impact of glucose and lipid metabolic disorders on the immune system.

On the other hand, recently published studies suggested that dipeptidyl peptidase 4 (DPP4) may act as a receptor for the virus [9]. Surprisingly, DPP4 overexpression has been linked to older age, respiratory or cardiovascular illnesses, and T2DM, all of which have been linked to an increase in COVID-19 severity and mortality [10]. DPP4 inhibitors were proposed to be advantageous to COVID-19 based on pathophysiological data [11]. Given the high mortality rate of COVID-19 infections among people with T2DM, it is critical to investigate the effect of DPP-4 inhibitors on COVID-19 outcomes. Thus, this retrospective research was conducted to explore the clinical characteristics, complications, and clinical outcomes in people with COVID-19 infection and T2DM treated with DPP4 inhibitors.

Material and methods

Study design

This retrospective multi-central study included 400 consecutive people with T2DM and confirmed COVID-19 infections admitted to the hospitals affiliated with the Iran University of Medical Sciences (IUMS) and Semnan University of Medical Sciences (SUMS) between February 2020 and August 2021. To document COVID-19 infection, we followed the rules of the World Health Organization (WHO)'s guidance. A confirmed case of COVID-19 infection was defined as a positive result on high-throughput sequencing or real-time reverse transcriptase polymerase chain reactions (RT-PCR) assay of nasal and pharyngeal swab specimens. In this study, a total of 54 (13.5%) patients with T2DM were treated with DPP4 inhibitors before admission.

Data acquisition

All demographic and clinical characteristics, including age, gender, hospitalization date, past medical histories and comorbidities, including hypertension, hyperlipidemia, cardiovascular diseases, renal diseases, and cancer, as well as drug history, including glucose-lowering drugs (GLDs), angiotensin-converting enzyme inhibitors (ACEin), and Statins, were collected. Also, all records related to the hospital course, including ICU admission, use of mechanical ventilation, and in-hospital mortality, were collected.

Statistical analysis

Categorical variables were described as frequency rates and percentages, and continuous variables were described using mean, median, and interquartile range (IQR). The means for continuous variables were compared using independent group t-tests when the data were normally distributed; otherwise, the Mann–Whitney U test was used. Proportions for categorical variables were compared using the $\chi 2$ test. Fisher's exact test was used when the data were limited. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc., USA). For unadjusted comparisons, a two-sided P value of less than 0.05 was considered to be statistically significant.

Results

Demographic and clinical characteristics

As shown in Table 1, 52.4% of the participants were male. The median (IQR) age was 65 (56–74) years. The median (IQR) BMI was 27.3 kg/m^2 (24.7–30.5). Among 400 enrolled individuals, 54 patients were treated with DPP4 inhibitors. The rate of insulin use and the presence of cardiovascular diseases were significantly lower in patients who received DPP4 inhibitors in comparison to patients who did not receive DPP4 inhibitors (9.4% *vs.* 35.3%; P<0.001 and 11.8% *vs.* 32.7%; P=0.002, respectively). Moreover, the presence of other comorbidities, the use of ACE/ARBs, and the duration of hospitalization did not differ between the groups.

COVID-19 clinical outcomes in patients treated with DPP4 inhibitors

We investigated the effect of DPP4 inhibitors on clinical outcomes of COVID-19 infection. Figure 1 shows that the rate of ICU admission was significantly lower in patients with DPP inhibitors (15.1%) compared to their counterparts (38.8%). In addition, the need for invasive ventilation was significantly lower in patients treated with DPP inhibitors (7.4%) in comparison to the other group (18.8%). Moreover, the composite incident outcome of ICU admission, use of mechanical ventilation, and in-hospital mortality were significantly lower in patients treated with DPP inhibitors (15.4%) compared to their counterpart group (42.1%). Finally, we observed that the mortality rate was significantly

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Table 1: Baseline characteristics of patients based on previous use of DPPIV- Inhibitor.

Variables	Total (n=400)	Not on DPP4-In (n=346)	On DPP4-In (n=54)	P-value
Sex (male), n (%)	208 (52.4%)	183 (53.2%)	25 (47.2%)	0.413
Age (year), median (IQR)	65 (56–74)	66 (57–75)	62 (55–69)	0.475
BMI (kg/m²), median (IQR)	27.3 (24.7–30.5)	27.3 (24.9–30.2)	26.4 (22.8–30.7)	0.429
T on admission, median (IQR)	37 (36.8–37.5)	37 (36.8–37.5)	37 (36.8–37.8)	0.601
RR on admission, median (IQR)	18 (15–20)	18 (15–20)	16 (15–19)	0.417
SBP on admission, median (IQR)	129 (120–140)	125 (120–140)	130 (120–140)	0.456
DBP on admission, median (IQR)	75 (70–80)	75 (70–80)	79 (70–82)	0.593
Ever Smoking (Yes), n (%)	39 (9.9%)	32 (9.4%)	7 (13.2%)	0.386
Opium addiction (Yes), n (%)	29 (7.3%)	25 (7.3%)	4 (7.5%)	0.946
Abnormal chest CT	358 (94.2%)	308 (93.9%)	50 (96.1%)	0.752
CVD (%)	114 (29.9%)	108 (32.7%)	6 (11.8%)	0.002
HF (%)	18 (4.7%)	16 (4.8%)	2 (3.9%)	0.772
CVA (%)	16 (4.2%)	15 (4.5%)	1 (2.0%)	0.706
CKD (%)	59 (15.3%)	53 (15.8%)	6 (11.8%)	0.453
Lung disease (%) (Asthma+ COPD)	14 (3.6%)	13 (3.9%)	1 (2.0%)	0.704
Insulin use (%)	125 (31.8%)	120 (35.3%)	5 (9.4%)	<0.001
ACE-In/ARB use (%)	48 (15.2%)	44 (15.7%)	4 (11.1%)	0.624
Malignancy (%)	7 (1.8%)	5 (1.5%)	2 (3.9%)	0.236
Duration of hospitalization, median (IQR)	6 (4–11)	7 (4–12)	6 (4–10)	0.164

Note: Chi-squared test and Mann-Whitney test for discrete and continuous variables, respectively.

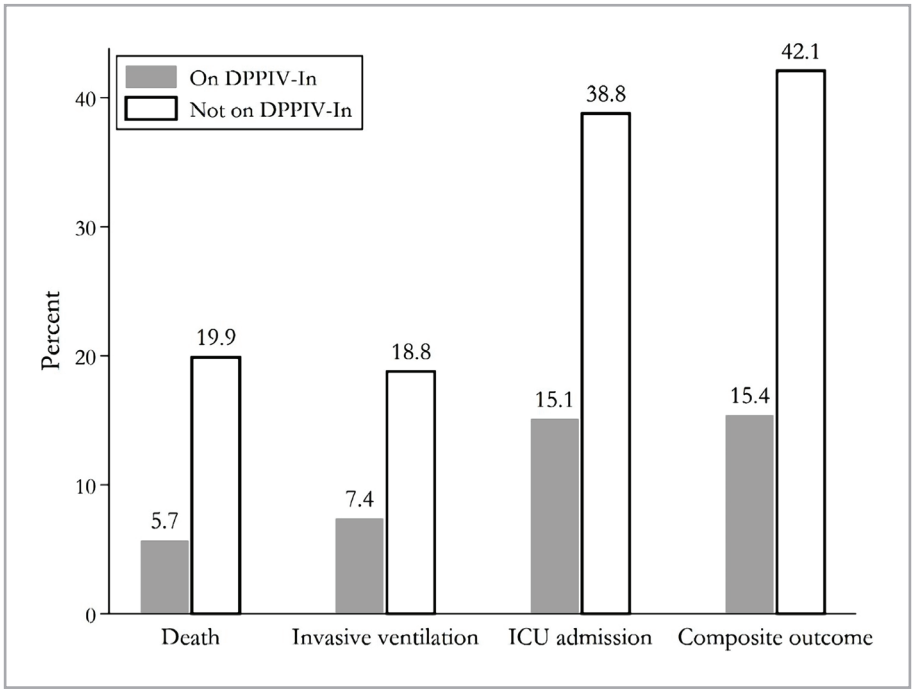

Figure 1: Clinical outcomes in patients with T2DM and COVID-19 were categorized based on previous use of DPPIV-inhibitor.

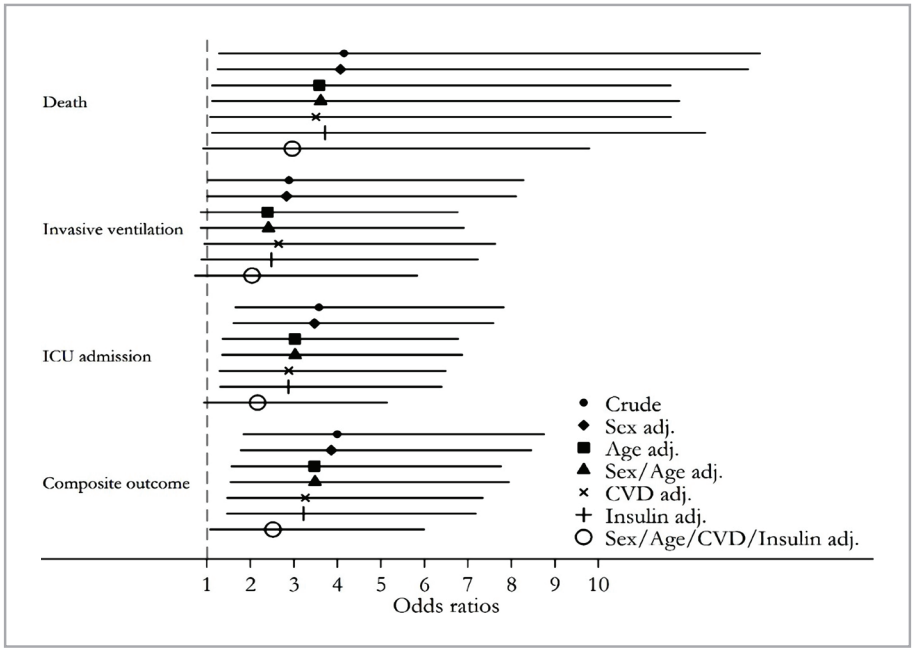

Figure 2: ORs of individual and composite outcomes in patients not on DPPIV-inhibitor comparing to those on DPPIV-inhibitor.

lower in the DPP inhibitors group (5.7%) in comparison to the other group (19.9%).

We further evaluated the odds ratio (OR) of clinical outcomes, including ICU admission, invasive ventilation, in-hospital mortality, and the composite outcome in patients who received DPP4 inhibitors compared to those not treated with DPP4 inhibitors. The results indicated significantly higher odds of ICU admission (OR: 3.57, (1.63–7.83), P=0.001), invasive ventilation (OR: 2.88, (1.00–8.29), P=0.05), in-hospital mortality (OR: 4.15, (1.25–13.73), P=0.02), and a composite of these outcomes (OR: 3.99, (1.82–8.76), P=0.001) in patients who did not receive DPP4 inhibitors before admission.

Upon adjustment for the potential confounders such as sex, age, cardiovascular disease (CVD), and insulin use, the odds of the composite outcomes, including ICU admission, invasive ventilation, and in-hospital mortality, were significantly higher in patients not treated with DPP4 inhibitors compared to those treated with DPP4 inhibitors before admission (OR: 2.52, (1.05–6.01), P=0.04). However, after adjusting for the potential risk factors, the odds of the individual adverse clinical outcomes indicated no significant difference in patients treated or not treated with DPP4 inhibitors (Figure 2).

Discussion

This study indicated that the use of DPP4 inhibitors is associated with a significantly lower risk of composite outcomes of ICU admission, invasive ventilation, and in-hospital mortality in patients with T2DM and COVID-19 infection.

It has been recently mentioned that DPP-4 inhibitor usage was not linked with unfavorable COVID-19-related outcomes in patients with T2DM in comparison to other antidiabetic medications [11]. In this regard, previous findings suggested a therapeutic significance with possible advantages associated with the use of DPP4 inhibitors in patients with T2DM and COVID-19 infection [9]. Meanwhile, previous reports showed that the use of DPP4 inhibitors could not decrease the rate of poor clinical outcomes in advanced and severe COVID-19 infection.

On the other hand, Strollo *et al.*, in a nationwide study of 3,818 patients with fatal COVID-19 infection, hypothesized that the geographical differences in DPP4 inhibitors did not correlate with diabetes prevalence among COVID-19 deaths. They suggested that DPP4 inhibition does not have any impact on COVID-19 infection development and progression [10]. However, based on molecular pathophysiology and the role of DPP4 inhibitors on the immune system, DPP4 may represent a potential target for preventing and reducing the risk and the progression of acute respiratory complications in people with T2DM and COVID-19 infection [11].

In a case-control study, Fadini *et al.* discovered that T2DM patients with COVID-19 infection had comparable clinical outcomes independent of DPP-4 inhibitors. Nonetheless, they recommend DPP-4 inhibitors are

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a viable therapy choice since they have a better safety profile than other GLDs. In contrast to previously mentioned studies, we observed that the use of DPP4 inhibitors before admission significantly decreases serious adverse outcomes of COVID-19 infection, including ICU admission, invasive ventilation and in-hospital mortality.

Apart from glucose-lowering effects, DPP-4 inhibitors have anti-inflammatory, anti-proliferative, and anti-fibrotic effects in various tissues. The paradigm of "one molecule, one target, one illness" changed toward multitarget medications capable of controlling complicated disorders around the end of the twentieth century.

The major limitation of this study was the retrospective nature of data collection. Therefore, a cause-and-effect relationship between drug therapy and survival should not be inferred. Main strengths include the relatively large number of participants and targeting hard endpoints in patients with COVID-19 infection. Randomized clinical trials evaluating the role of DPP4 inhibitors will be necessary before any conclusion can be reached regarding the potential benefit of these agents in patients with COVID-19 and T2DM.

Conclusion

DPP4 inhibitors significantly decrease the rate of composite outcome of ICU admission, invasive ventilation, and in-hospital mortality in people with T2DM and COVID-19 infection.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

All methods were performed in accordance with the Declaration of Helsinki. The study was approved by the ethics committees at the Iran University of Medical Sciences (IUMS) (IR.IUMS.REC.1398.526).

Consent to participate

Written informed consent was obtained from all participants.

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