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# Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: A narrative review

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## ABSTRACT

**Aims:** Rising prevalence of non-communicable diseases world-wide has made diabetes an important comorbidity in patients with coronavirus disease-19 (COVID-19). We sought to review the risk, severity and mortality in COVID-19 and its relation to the glycemic control, and role of anti-diabetic agents in patients with diabetes.

**Methods:** A Boolean search was made in PubMed, MedRxiv and Google Scholar database until May 10, 2020 and full articles with supplementary appendix were retrieved using the specific key words related to the topic.

**Results:** There is a high prevalence of diabetes in patients with COVID-19. Patients with diabetes had a significantly more severe variety of COVID-19 and increased mortality, compared to the groups without diabetes. Moreover, poor glycemic control is associated with a significantly higher severe COVID-19 and increased mortality, compared to the well-controlled glycemic groups. No data currently available for or against any anti-diabetic agents in COVID-19.

**Conclusions:** Diabetes, in particular poorly-controlled group is associated with a significantly higher risk of severe COVID-19 and mortality. This calls for an optimal glycemic control and an increased emphasis on future preventative therapies including the vaccination programs for these groups in addition to the traditional risk prevention such as social distancing and self-isolation.

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## 1. Introduction

The pandemic of coronavirus infectious disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has involved more than 4.2 million people accounting for nearly 300 thousand deaths world-wide, as of May 14, 2020 [1]. With the rising prevalence of cardiometabolic disorders globally, people with these

comorbidities are also expected to be increasingly inflicted with COVID-19. Uncontrolled diabetes (glycated hemoglobin [HbA1c] > 9%) has been linked to a nearly 60% increased risk of pneumonia-related hospitalization during the bacterial infection [2]. Like-wise, several past viral pandemics have witnessed an increased morbidity and mortality in patients with diabetes. Not only 50% of population was found to have diabetes during the Middle East Respiratory Syndrome Coron-

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avirus (MERS-CoV) outbreak in 2012, but patients with diabetes had an odds ratio (OR) of 7.2 to 15.7 for severe or critical type of MERS-CoV infection, with a relative high 35% rate of mortality, compared to the overall population [3–5]. Similarly, diabetes was associated with a 3-fold increased risk of hospitalization and the 4-fold risk of admission to intensive care unit (ICU), during the 2009 Influenza A (H1N1) outbreak [6]. Diabetes was also an independent risk factor for acute complications and death during the Severe Acute Respiratory Syndrome (SARS-CoV-1) outbreak in 2002–2003 [7].

Studies in patients with COVID-19 pandemic have also found people with diabetes, hypertension, obesity, cardiovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) to have a significant increased risk of severity as well as mortality, that is further compounded by higher mortality with increasing age and body mass index. Aim of this article is to report a narrative review of available literature to find the association between diabetes and COVID-19 in terms of risk, severity and mortality. Additionally, we also reviewed the relationship of glycemic control with the severity and mortality in COVID-19 and put a perspective on the impact of anti-diabetes drugs.

## 2. Methods

A Boolean search was carried out to find the literature in PubMed, MedRxiv and Google Scholar databases up till May 10, 2020 using the specific keywords that include “SARS-CoV2”, “COVID-19”, “risk”, “severity”, “mortality”, “glycemic control”, “diabetes”, “anti-diabetic drugs”, with interposition of “AND”. Full text of all the related articles in English language with supplementary appendix were retrieved. In addition, full text of relevant cross references was also retrieved. We noticed that several of these studies have collected the data from the same hospital, during the same time period, suggesting a significant overlap. Therefore, we carefully chose to describe the results mainly from the largest study that have reported the outcomes during the describing analysis, in addition to the other studies of high importance.

## 3. Risk, severity and mortality in patients with diabetes and COVID-19

### 3.1. Risk of COVID-19 in patients with diabetes

While the first case series of 41 patients hospitalized with COVID-19 in China, Huang et al. [8] reported that nearly 20% had diabetes, other retrospective Chinese studies that followed soon after, reported a prevalence of diabetes that varied from 7 to 21% [9–23]. From the larger case-series (n = 1099) of China, Guan et al. [24] reported a diabetes prevalence of nearly 7%, while the largest reported database (n = 20,982) from the Chinese Centre for Disease Control and Prevention (CCDC) showed an approximately 5% diabetes prevalence, in patients with COVID-19 [25]. Data from the 122,653 cases of COVID-19, CDC USA reported diabetes to be the commonest comorbidities in about 10%, amongst the 7162 patients with comorbidities [26]. Grasselli et al. [27] reported a diabetes prevalence of around 17% from the 1043

COVID-19 patients with comorbidities from Lombardy, Italy. Prospective observational data from UK reported uncomplicated diabetes in 19% of 16,749 COVID-19 cases [28]. The largest study conducted from Spain that reported data of 121,263 COVID-19 patients, had reported a diabetes prevalence of about 10% [29]. Bello-Chavolla et al. reported nearly 18% prevalence of diabetes from 15,529 cases, from Mexico [30]. Table 1 summarizes the proportion of diabetes observed in patients with COVID-19, world-wide.

Several meta-analyses have also reported the proportions of diabetes in COVID-19 patients. Earlier meta-analysis conducted by Li and colleagues [31] from the pooled data of 6 studies (n = 1527), reported a diabetes prevalence of nearly 10.0% (95% confidence interval [CI], 7.0–13.0%), while meta-analysis by Yang et al. [32] that included 9 studies (n = 46,248) reported a diabetes prevalence of 8.0% (95% CI, 6.0–11.0%). Meta-analysis by Emami et al. [33] that pooled 10 studies (n = 76,993) showed an estimated diabetes prevalence of nearly 8% (95% CI, 7.0–9.0%), Hu et al. [34] showed a diabetes prevalence of 10% (95% CI, 6.0–9.0%) from the pooled study of 21 studies (n = 47,344) with COVID-19. However, some caution is required while interpreting these results. First, almost all of these meta-analyses have pooled the data from majority of the studies that have reported either from a single or two centers from China that too during the same time period, therefore it is highly likely that many of these studies have the overlapped data, which may cause inaccurate results. Second, majority of these earlier meta-analysis were conducted from the pooled studies that was reported from the China and did not include data from the other part of the world. Finally, from these available data it is not yet clear whether chance of contracting COVID-19 is higher in patients with diabetes, since these reported prevalence or proportions could merely reflect the higher prevalence of diabetes across the globe. Interestingly, Wang et al. [35] reported that these prevalences of diabetes in COVID-19 are closely similar to the nationwide diabetes prevalence of around 11% of type 2 diabetes in China. Collectively, it is not yet clear whether presence of diabetes increases the risk of contracting COVID-19.

### 3.2. Severity of COVID-19 in patients with diabetes

To date, eight meta-analysis have assessed the severity of COVID-19 in patients with comorbidities including diabetes. While 5 of these meta-analysis that have calculated either a relative risk (RR) or an odds ratio (OR) found a significant 2- to 3-fold increase (Chen et al., OR 2.67; 95% CI, 1.91–3.74; Roncon et al., OR 2.79; 95% CI 1.85–4.22; Wang et al., OR 2.47; 95% CI, 1.67–3.66; Kumar et al., OR 2.75; 95% CI, 2.09–3.62, Huang et al., RR 2.45; 1.79–3.35) in severity; 2 meta-analysis have only found a non-significant trend (Li et al., RR 2.21; 95% CI 0.88–5.57; Yang et al., OR 2.07; 95% CI, 0.89–4.82) [31,32,36–40]. In one meta-analysis based on the pooled data from 6 studies, Hu et al. [34] reported a significantly higher percentage of critical cases (44.5%; 95% CI, 27.0–61.9%) in patients with diabetes and COVID-19. However, interpretation of these results needs some caution. Firstly, there was no uniformity in the definition of severity across the studies that was included in these meta-analyses and varied from study to study. Severe COVID-

**Table 1 – Proportion of diabetes in patients with COVID-19 from the largest cohort studies of each country.**

| Study, First author name, country  | Dates cases identified    | Location (study design)  | N                   | Age (yrs.)<br>(mean (SD)) | Male<br>n, (%) | Diabetes<br>n, (%) |
|------------------------------------|---------------------------|--|---------------------|---------------------------|----------------|--------------------|
| Guan et al. [24], China            | 11th Dec' 2019 – 29th Jan | 552 hospitals in 30 provinces, China<br>(Retrospective case-series)  | 1099                | 47 (35–58)*               | 640 (58.2)     | 81 (7.4)           |
| CCDCP [25], China                  | Dec' 2019 – 11th Feb      | 1386 counties in 31 provinces<br>(Retrospective cohort study)  | 20,982 <sup>^</sup> | NR                        | NR             | 1102 (5.3)         |
| CDC [26], USA                      | 12th Feb – 28th Mar       | Laboratory confirmed cases from 50<br>states, and 4 territories and affiliated<br>islands reported to CDC, USA<br>(Retrospective cohort study) | 7162 <sup>^</sup>   | NR                        | NR             | 784 (10.9)         |
| Grasselli et al. [27], Italy       | 20th Feb – 18th Mar       | 72 hospitals, Lombardy Region, Italy<br>(Retrospective case series)  | 1043 <sup>^</sup>   | 63 (56–70)*               | 1304 (82.0)    | 180 (17.3)         |
| Docherty et al. [28], UK           | 6th Feb – 18th April      | 166 UK hospitals, ISARIC-CCP-UK (<br>Prospective observational cohort study)   | 16,749              | 72 (57–82)*               | 7715 (60.2)    | 1204 (19.0)        |
| Prieto-Alhambra et al. [29], Spain | 15th March – 24th April   | Information System for Research in<br>Primary Care (SIDIAP), Catalonia, Spain<br>(Prospective observational cohort study)                      | 121,263             | NR (45–54) <sup>†</sup>   | 50,532 (41.7)  | 11,829 (9.8)       |
| Bello-Chavolla et al. [30], Mexico | Up to 27th April          | Dataset from the General Directorate of<br>Epidemiology of the Mexican Ministry of<br>Health   | 15,529              | 47 (15.5) <sup>#</sup>    | 8977 (57.8)    | 2831 (18.4)        |

Values are n (%) unless otherwise stated, CCDCP – Chinese Center for Disease Control and Prevention, CDC – Centers for Disease Control and Prevention, NR – not reported.  
\* Median (IQR).  
† Median (range).  
# Mean (S.D).  
^ N reporting co-morbidities.

19 has been defined by World Health Organization, if following is present: Respiratory frequency  $\geq 30$ /minute, blood oxygen saturation  $\leq 93\%$ , PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $< 300$ , and/or lung infiltrates  $> 50\%$  of the lung field within 24–48 h; while CCDC [25] defined severe COVID-19, if following is present: hypoxia, dyspnea,  $> 50\%$  lung involvement within 24–48 h. Second, as mentioned earlier many studies that was included in these meta-analyses have overlapped data. Third, all these meta-analyses have calculated the risk or odds ratio of severity, while comparing patients with diabetes who required mechanical ventilation or intensive care unit (ICU) admission, versus the patient with diabetes who did not require either of these. Thus, neither of these meta-analyses calculated the risk of severity between patients with diabetes versus without diabetes cohorts. Therefore, the conclusion from these meta-analyses only suggest that patients who had severe COVID-19 are more likely to have diabetes. Fourth, other comorbidities which is commonly associated with the diabetes that can also increase the severity such as hypertension, obesity, CVD, chronic kidney disease (CKD), were not adjusted while conducting these meta-analyses. Finally, these meta-analyses have not yet answered whether patients with diabetes have a higher chance of severe COVID-19, compared to the non-diabetic populations.

To this end, one retrospective study although a smaller one, looked for the severity in patients with diabetes and COVID-19, in the absence of other comorbidities, and compared to the groups without diabetes. Guo et al. [41] compared the hematological and biochemical profile of total 174 patients of COVID-19, of which 37 had diabetes compared to 137 without diabetes. Interestingly, both the hematological and biochemical parameters that are generally characterized as a marker of severe COVID-19, were significantly higher in patients with diabetes, compared to cohorts without diabetes. Significant decrease in lymphocyte, red blood cells (RBC), level of hemoglobin and a marked increase in neutrophils, erythrocyte sedimentation rate (ESR) and D-dimer was observed in patients with diabetes, compared to the cohorts without diabetes. Moreover, when the patients with diabetes were compared to without diabetes and without other comorbidities ( $n = 24$  vs.  $26$ , respectively), even then, the biochemical and hematological markers of severe COVID-19 were significantly higher in cohorts with diabetes. A significant increase in neutrophil, ESR,  $\alpha$ -hydroxybutyrate dehydrogenase, lactic dehydrogenase, alanine aminotransferase (ALT), fibrinogen, C-reactive protein, ferritin (CRP), interleukin-6 (IL-6) and a significant decrease in lymphocyte, hemoglobin, RBC and albumin was observed in patients with diabetes, compared to the cohorts without diabetes. These changes clearly point to a poor prognosis and suggests an excessive inflammatory response or cytokine storm, and increase hypercoagulability in patients with diabetes, compared to the groups without diabetes. Indeed, the computed tomography scan (CT-Scan) of the chest based on a scoring scale, also fared poorly suggestive of severe COVID-19 in patients with diabetes, compared to the cohorts without diabetes.

Another large retrospective study conducted by Zhu et al. [42] studied 7337 patients from 19 hospitals in China with COVID-19 and compared 810 patients with diabetes to 6385 cohorts without diabetes. This study found a significant

increase in leukocytosis, neutrophilia, D-dimer, ferritin, CRP, Procalcitonin, ALT, creatinine and a significant decrease in lymphocyte count, all suggestive of severe COVID-19 in patients with diabetes, compared to the cohorts without diabetes (all  $p < 0.001$ ). Similarly, Chest CT scan had significantly more unilateral and bilateral lesions in cohorts with diabetes, compared to patients without diabetes. Significant increase in acute respiratory syndrome (ARDS), septic shock, acute kidney injury, acute heart injury, requirement of oxygen inhalation and both non-invasive and invasive ventilation including extracorporeal membrane oxygenation (ECMO) were observed in patients with diabetes, compared to the groups without diabetes (all  $p < 0.001$ ).

### 3.3. Mortality in patients with diabetes with COVID-19

Odds ratio for in-hospital mortality was nearly 3-fold higher (OR 2.85, 95% CI, 1.35–6.05) in patients with diabetes with COVID-19, in a univariate analysis ( $n = 191$ ) conducted by Zhou et al. [43], although it was not significant in multivariate regression analysis. Similarly, in a bivariate cox regression analysis conducted by Wu et al. [22], a non-significant increase trend in hazard ratio (HR) for death (HR 1.58; 95% CI, 0.80–3.13) was observed in patients with diabetes with COVID-19. Nevertheless, the CCDC reported a case fatality rate (CFR) of 7.3% in patients with diabetes, compared to a CFR of 2.3% of overall population of 44,672 patients of COVID-19 [44].

Indeed, three meta-analysis that studied the mortality outcome have shown a significant 2–3-fold increase in mortality in patients with diabetes with COVID-19. While the meta-analysis by Roncon et al. [37] from the pooled data of 4 studies found a significantly higher risk of mortality (OR 3.21; 95% CI 1.82–5.64), Kumar et al. [39] similarly reported a significant increase in death (OR 1.90; 95% CI, 1.37–2.64) in patients with diabetes and COVID-19 from the pooled data of 9 studies. Huang and Colleagues [40] in a pooled data of 10 studies also found a significant increase in mortality (RR 2.12; 95% CI, 1.44–3.11). As mentioned earlier, these meta-analyses have two important limitation that include overlapping of data included in the studies and not analyzing the mortality between patients with diabetes to the cohorts without diabetes with COVID-19. Therefore, this meta-analysis only suggests that patients who died from COVID-19 are more likely to have diabetes, rather than suggesting that patients with diabetes are more likely to succumb to death, compared to the cohorts without diabetes.

Nevertheless, some of the recent studies have reported the mortality outcome of COVID-19 that compared patients with diabetes to the cohorts without diabetes. A retrospective observational study by Bode et al. [45] from 88 hospitals in USA involving 570 patients found a significantly higher mortality rate (28.8% vs. 6.2%,  $p < 0.001$ ) in patients with diabetes (HbA1c  $\geq 6.5\%$ ) and/or uncontrolled hyperglycemia (defined as  $\geq 2$  blood glucose value  $> 180$  mg/dL within any 24-hour period), compared to patients without diabetes or hyperglycemia. Moreover, amongst the patients who survived ( $n = 493$ ), the length of stay in hospital was significantly longer in patients with diabetes and uncontrolled hyperglycemia, compared to patients without diabetes or uncontrolled hyperglycemia



**Table 2 – Proposed mechanism of concerns and benefit of anti-diabetic drugs in patients with diabetes with COVID-19 [53–75].**

| Anti-diabetic drugs    | Relation to ACE2 expression in experimental models or humans                               | Harm or benefit in experimental studies  | Proposed concerns in COVID-19 patients                              | Past human studies during various infections  | Proposed benefit in COVID-19 patients  | Remarks  |
|------------------------|--|--|---|---|--|--|
| Metformin              | No such association  | Protective in pneumonia  | Chance of lactic acidosis in sick patients and renal dysfunction    | Reduction in mortality in tuberculosis, COPD and sepsis   | Potential cardiovascular benefit   | Can be continued in mild to moderate COVID-19. Avoid in severe/critical stage. |
| Pioglitazone           | Increased ACE2 expression in liver in mouse, decreased ADAM-17 in skeletal muscle in human | Reduction in markers of proinflammatory cytokines, reduction in lung injury              | Increased chance of COVID-19 infection through ACE2 overexpression. | Increase in LRTI and pneumonia  | Reduction in proinflammatory cytokines can reduce cytokine storm induced damage                        | Can be continued in mild to moderate COVID-19. Avoid in severe/critical stage. |
| Sulfonylureas          | No such association  | No such association  | Fear of hypoglycemia  | No increase. Older SUs like tolbutamide had anti-bacterial activity due to resemblance to sulfonamide antibiotics | Nothing specific   | Can be continued in mild to moderate COVID-19. Avoid in severe/critical case   |
| DPP-4 inhibitors       | No such association, severe MERS-CoV infection in transgenic mice expressing high DPP4     | Antibodies to DPP4 showed inhibition of MERS-CoV in vitro studies. No effect of DPP-4Is. | No concerns.  | No increase in pneumonia  | Anti-inflammatory activity. Proposed benefit if SARS-Cov-2 utilize DPP4 as entry receptor, if mutated. | Can be continued in mild to moderate COVID-19. Avoid in severe/critical case   |
| SGLT-2 inhibitors      | Increased ACE2 expression in kidney in human   | Favorable effect on reduction in oxidative stress, autophagy and inflammation            | Increase in EuDKA, hypovolemia                                      | No studies  | Beneficial cardio-renal outcomes observed may be protective. DARE-19 is ongoing.                       | Can be continued in mild to moderate COVID-19. Avoid in severe/critical case   |
| GLP-1 receptor agonist | Liraglutide increased ACE2 expression in lungs and heart in T1DM rats                      | Benefit on lungs and heart in T1DM rats  | GI side effects   | No studies  | Beneficial cardio-vascular effect observed may be protective   | Can be continued in mild to moderate COVID-19. Avoid in severe/critical case   |
| Insulin                | Increases intrarenal ACE2 expression by reducing renal ADAM-17 in diabetic mice            | Reduction in inflammatory markers  | No concern  | Beneficial effect due to anti-inflammatory action   | Anti-inflammatory and positive anabolic effects, makes insulin as a choice in any infections           | Can be continued at any stage.   |

ADAM-17: a disintegrin and metalloproteinase-17, ACE2: angiotensin converting enzyme-2, COVID-19: coronavirus disease-2019, SARS-CoV-2: severe acute respiratory syndrome-2, DPP-4: dipeptidyl peptidase-4, DPP-4Is: dipeptidyl peptidase-4 inhibitors, T1DM: type 1 diabetes mellitus, COPD: chronic obstructive pulmonary disease, LRTI: lower respiratory tract infection, EuDKA: euglycemic diabetic ketoacidosis, SUs: sulfonylureas, SGLT-2: sodium glucose co-transporter-2, GLP-1: glucagon-like peptide-1, DARE-19: dapagliflozin in respiratory failure in patients with COVID-19.

(5.7 vs 4.3 days,  $p < 0.001$ ). Guo et al. [41] reported ( $n = 174$ ) a significant increase in mortality (16.7% vs. 0%) in patients with diabetes, compared to the patients without diabetes. The COVID-19 Patient Notification System (CPNS) from the primary care electronic health records, on behalf of NHS England, have studied 17,425,445 adults from Feb 1 to April 25, 2020 and recorded 5683 COVID-19 deaths. This study suggested that patients with both controlled (HbA1c  $< 58$  mmol/mol) and uncontrolled diabetes (HbA1c  $\geq 58$  mmol/mol) with COVID-19, have a significant increase in death (HR 1.50; 95% CI, 1.40–1.60 and HR 2.36; 95% CI, 2.18–2.56; in controlled vs. uncontrolled diabetes, respectively), compared to the cohorts without diabetes even after the full adjustment of confounding factors [46]. In a large retrospective study ( $n = 7337$ ), Zhu et al. reported a significant 49% relative increase in all-cause mortality (HR 1.49; 95% CI, 1.13–1.96;  $p = 0.005$ ) in patients with diabetes ( $n = 810$ ), compared to the groups without diabetes ( $n = 6385$ ) and COVID-19, even after the adjustment of multiple confounding factors [42].

### 3.4. Relationship of glycemic control to severity and mortality in patients with diabetes and COVID-19

Previous viral pandemics of SARS-CoV-1, MERS-CoV and H1N1 influenza have suggested that patients with diabetes and poor glycemic control had a significant increased risk of complications and death.

Very limited number of studies to date have analyzed the outcomes of severity and mortality, stratified on the level of glycemia, in patients with diabetes and COVID-19. Interestingly, Bode et al. [45] reported a significantly higher percentage of death (41.7 vs. 14.8%,  $p < 0.001$ ) in patients with COVID-19 ( $n = 184$ ) who had uncontrolled hyperglycemia (defined as  $\geq 2$  blood glucose value,  $>180$  mg/dl within any 24-hour period) but were not diagnosed as diabetes (HbA1c  $< 6.5\%$ ), compared to the patients with diabetes (HbA1c  $\geq 6.5\%$ ). This suggests that stress hyperglycemia may have a worse outcome in ICU, compared to a known patient with diabetes. However, these findings are based on a very small number of cohorts. In a relatively large retrospective study of 810 patients with diabetes, Zhu et al. [42] reported a significant increase in septic shock (4.7% vs. 0.0%,  $p = 0.004$ ), ARDS (21.4% vs. 7.1%,  $p < 0.001$ ), acute kidney injury (3.8% vs. 0.7%,  $p = 0.019$ ) and acute heart injury (9.9% vs. 1.4%,  $p < 0.001$ ) in patients with poorly-controlled diabetes ( $n = 528$ ), defined as blood glucose  $>180$  mg/dL, compared to the well-controlled diabetes ( $n = 282$ ) groups, defined as blood glucose between 70 and 180 mg/dL. The adjusted HR for all-cause mortality was 0.13 (95% CI, 0.04–0.44,  $p < 0.001$ ) in patients with well-controlled vs. poorly-controlled diabetes. Interestingly, the increased signal of ARDS, acute kidney injury and acute heart injury remained highly significant in poorly controlled arm, even when compared in propensity score-matched groups (matched for other comorbidities that include hypertension, cardiovascular disease, cerebrovascular disease and chronic kidney disease). Moreover, the adjusted HR for all-cause mortality was 0.14 (95% CI, 0.03–0.60,  $p = 0.008$ ) in well-controlled group, compared to the

poorly controlled diabetes, even after the 1:1 propensity-matching.

Collectively, these findings suggest that poor-glycemic control (blood glucose  $>180$  mg/dl or  $>10$  mmol/L) is associated with a significantly higher risk of severity and mortality in people with or without diabetes, compared to the people with well-controlled blood glucose (blood glucose  $<180$  mg/dl or  $<10$  mmol/L).

## 4. Choosing anti-diabetic drugs during COVID-19

While no data is currently available for any differential effects of anti-diabetic drugs in patients with diabetes with COVID-19, several expert groups across the world have opined do's and don'ts with regards to choosing between them. Interestingly, all expert groups including us have proposed avoiding metformin and sodium glucose co-transporter-2 inhibitors (SGLT-2Is) in particular, in sicker patients with moderate to severe COVID-19, with an anticipation of increased lactic acidosis and euglycemic diabetic ketoacidosis (EuDKA) with both the drugs, respectively [47–52]. Others have also proposed some concerns in the light of interaction of angiotensin converting enzyme-2 (ACE2) to COVID-19, since some of these anti-diabetic drugs have been associated with overexpression of ACE2 in the different human organs [53]. However, there is no clear evidence that these drugs could be detrimental in patients with diabetes and COVID-19. Counterintuitively, it is also possible that the anticipated cardiovascular benefit of metformin and cardio-renal benefit of SGLT-2Is would no longer be there by stopping these drugs. Table 2 summarizes the expected concerns and possible benefit of anti-diabetic agents in patients with diabetes and COVID-19.

### 4.1. Metformin

Metformin by virtue of inducing AMP activated protein kinase, has an anticipated antiproliferative and immunomodulatory effects. In mouse model, metformin has shown its protective role in *legionella* pneumonia. Few human studies in the past have also examined the role of metformin in sepsis and lung diseases. Liang et al. [54] in a meta-analysis of 5 observational studies showed metformin use in patients with diabetes prior to admission had a significantly lower mortality rate (OR, 0.59; 95% CI, 0.43–0.79,  $P = 0.001$ ) during sepsis, compared to the non-users. In a meta-analysis of 17 observational studies, Zhang et al. [55] found people with diabetes on metformin had a significantly lower incidence of active tuberculosis (RR 0.51; 95% CI, 0.38–0.69,  $p < 0.001$ ) and mortality (RR 0.34; 95% CI, 0.20–0.57,  $p < 0.001$ ), compared to the non-users of metformin. Even after the adjustment for multiple confounding factors, Mendy et al. [56] found use of metformin ( $n = 5266$ ) had a significant decreased risk of mortality (HR 0.30; 95% CI, 0.10–0.93) in patients with COPD with diabetes, compared to the non-users, in a median 6.2 years of follow up. Similarly, Ho et al. [57] found a significantly lower risk of death in metformin users (HR 0.46; 95% CI, 0.23–0.92), compared to the non-users, in a 2-year follow up study of 4321 patients with diabetes and COPD.

Zhu et al. [42] reported that a significantly different proportion of patients with diabetes and COVID-19 were receiving metformin in a 1:1 propensity-matched, well-controlled group, compared to the poorly-controlled arm (39.2% vs. 26.4%,  $p = 0.003$ ) and still showed a significantly less severe COVID-19 and less mortality in the former group. This hints at no anticipated harm with metformin and perhaps a possible benefit, although that needs to be confirmed in further studies.

#### 4.2. Pioglitazone

Animal studies have suggested an increased ACE2 expression in liver tissues, one of the mechanisms by which pioglitazone reduces steatohepatitis [58]. Pioglitazone was also associated in causing downregulation of ADAM-17 (a disintegrin and metalloproteinase-17), an ACE2 cleaving enzymes in human skeletal muscles that can lead to increase ACE2. Indeed, this purported increase in ACE2 with pioglitazone led some researchers to propose avoiding this drug in patients with diabetes, in anticipation of theoretical increased chance of contracting COVID-19 [53]. Interestingly, few human studies showed an increased risk of pneumonia with thiazolidinediones (TZD) use, when compared to the sulfonylureas (SUs). A nested case-controlled study from a Spanish general practice research database that studied 1803 cases of community acquired pneumonia (CAP) from the total 76,009 cases, Gorricho et al. [59] found a 2-fold (adjusted OR 2.48; 95% CI 1.40–4.38) increase in CAP with TZD use, compared to the SUs. Singh et al. [60] in a meta-analysis of 10 randomized controlled trial ( $n = 17,627$ ) in patients with type 2 diabetes also showed a significantly higher risk of lower respiratory tract infection or pneumonia with TZD, compared to the placebo or other active treatment (RR 1.40, 95% CI 1.08 to 1.82).

In contrast, some experimental studies have found a protective effect of TZD on the lung inflammatory markers. Reduction in several inflammatory markers such as tumor necrosis alpha (TNF- $\alpha$ ), IL-6, IL-8, ferritin and a reduction in fibrotic lung reaction to silica-exposed rats with pioglitazone, may suggest a possible direct beneficial effect on lung inflammation [61]. Several studies in humans have also shown a significant reduction in proinflammatory cytokines including IL-1b, IL-6, IL-8, TNF- $\alpha$  and other markers of insulin resistance with pioglitazone [62]. These findings led some of the researchers to propose pioglitazone in patients with diabetes and COVID-19 [63].

#### 4.3. Sulfonylureas

No concern on overexpression of ACE2, thus theoretically no increased risk of COVID-19. Historically, older SUs such as tolbutamide have shown a significant reduction in *Pneumocystis carinii* pneumonia in experimental studies due to structural similarities with sulfonamide antibiotics, trimethoprim-sulfamethoxazole [64]. No increase in CAP has been observed with modern SUs compared to TZD, as reported by Gorricho et al. [59], as mentioned earlier. However, hypoglycemic potential warrants lower dosage.

#### 4.4. DPP-4 inhibitors

Since, lymphocyte protein CD26 is structurally similar to dipeptidyl peptidase-4 (DPP-4), there was expectedly some apprehension whether inhibition of DPP-4 by the DPP4-inhibitors (DPP-4Is) can be associated with an increased risk of infections. Although there was an initial report of increase in nasopharyngitis with the DPP-4Is during the phase 3 clinical development program, however, the later larger trials with their meta-analysis and the longer cardiovascular outcome trials (CVOTs) with these class did not show any such signals. Similarly, the UK-based Clinical Practice Research Datalink (CPRD) database that studied 103,159 patients of diabetes over 8-years that compared the respiratory tract infection with DPP-4Is to SUs, metformin, TZD and insulin, found no significant increase in risk [65]. These findings were further reassured by few studies conducted in immunocompromised patients with human immunodeficiency virus (HIV), showing no increase in infection with the DPP-4Is [66].

The role of DPP-4Is in COVID-19 have resurfaced in the light of association of DPP-4 with coronaviruses. Since DPP-4 served as the functional receptor for MERS-CoV, it was believed that DPP-4Is may have a potential to protect from MERS-CoV infection. Certain polymorphisms of DPP-4 have been associated with a reduced risk of MERS-CoV infection in an experimental study. It was also speculated that presence of protective polymorphisms of DPP-4 in Africans may explain the perplexing absence of MERS-CoV cases in Africa [67]. Interestingly, in vitro studies by Raj et al. found antibodies directed against the DPP4 inhibited the human coronavirus-Erasmus Medical Center (hCoV-EMC) infection of primary human bronchial epithelial cells and Huh-7 cells, although the application of DPP-4Is such as sitagliptin, vildagliptin and saxagliptin were not able to inhibit the hCoV-EMC infections [68].

A recent modeling study did not rule out interaction of SARS-CoV-2 with DPP4, despite ACE2 being the functional receptor [69]. One hypothesis suggested that just like other RNA viruses that inherit a high mutation rate, SARS-CoV-2 may continually mutate to adapt the changes in the environment including the types of invading cells. It is possible that SARS-CoV-2 can also mutate like another novel coronavirus, that can invade cells via coupling with DPP4, the principal receptor of MERS-CoV infections. This provoking theory proposed that because of these easy mutational characteristics of SARS-CoV-2, DPP-4Is can be an effective tool against the mutant coronavirus [70]. Similar optimism has been expressed previously suggesting DPP4 may represent a potential target for preventing and reducing the risk and the progression of the acute respiratory complications that type 2 diabetes may add to the COVID-19 infection [71]. This optimism was primarily based on potential anti-inflammatory effects of DPP-4Is that can possibly reduce the burden of cytokine storm in COVID-19. However, anti-inflammatory effect of DPP-4Is is equivocal to protect from ensuing cytokine storm in COVID-19 [66].

Although there is no adequate data with DPP-4Is currently in patients with diabetes with COVID-19, the study by Zhu



et al. [42] reported that a significantly different proportion of patients with diabetes and COVID-19 were receiving DPP-4Is in a propensity-matched well-controlled arm vs. poorly-controlled arm (11.2% vs. 4.4%,  $p = 0.008$ ) with a significantly less severe COVID-19 and lesser mortality in the former group. This might hint of a possible benefit of DPP-4Is, although that needs to be proven in further studies.

#### 4.5. SGLT-2 inhibitors

SGLT-2Is have been associated with an increase in ACE2 expression in kidney and therefore have theoretical concern to have a higher chance of COVID-19 [53]. Moreover, experts have recently recommended to avoid SGLT-2Is in patients with diabetes and moderate to severe COVID-19, in anticipation of EuDKA, especially in a background of poor food intake, dehydration and hypovolemia. However, counterintuitively, both pre-clinical and clinical studies have suggested that SGLT2i have a favorable effect on inflammation, tissue hypoxia, oxidative stress, autophagy and energy metabolism that can favorably impact the dysregulated processes in the setting of cytokine storm of COVID-19. Moreover, SGLT-2Is have already shown to have a significant cardio-renal benefit as seen in CVOTs in patients with diabetes and established cardiovascular disease, and thus SGLT-2Is may have some potential to offer a protection to the heart and kidney, in the setting of COVID-19. With these assumptions, recently an international, multicenter, randomized, double-blind, placebo-controlled, Phase 3 study (NCT04350593) named Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) has been initiated (on April 17, 2020) in 900 patients with moderate to severe manifestation of any duration but without the need for mechanical ventilator. DARE-19 will include patients with a history of at least one of the following: hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure and/or chronic kidney disease stage 3–4 ( $eGFR \geq 25 \text{ mL/min/1.73 m}^2$ ) that will receive 10 mg of dapagliflozin or placebo for 30-days. The primary objective of DARE-19 is time to first occurrence of either death from any cause or new/worsened organ dysfunction through 30 days of follow up, defined as at least one of the following - respiratory decompensation, new or worsening congestive heart failure, requirement for vasopressor therapy and/or inotropic or mechanical circulatory support, ventricular tachycardia or fibrillation lasting at least 30 s and/or associated with hemodynamic instability or pulseless electrical activity or resuscitated cardiac arrest and initiation of renal replacement therapy, with an expected completion by December 2020 [72].

There is a growing argument that dapagliflozin in particular has shown to decrease lactic acidosis and thus has the potential to reverse acid-base balance inside the cells during hypoxia, which can prevent cell injury during the cytokine storm of COVID-19 illness, in patients with diabetes [73].

#### 4.6. GLP-1 receptor agonists

GLP-1 receptor agonists (GLP-1RAs) such as liraglutide has shown to increase ACE2 expression in lungs and heart and has improved right ventricular hypertrophy in rats with type 1 diabetes [74]. Experimental study has also suggested an

anti-inflammatory effects and therapeutic benefit in acute lung injury with liraglutide [75]. However, this purported increase in ACE2 expression raise a theoretical concern in patients with COVID-19 [53]. Moreover, since GLP-1RAs have been associated with increased gastrointestinal adverse events, experts have suggested avoiding this class of drugs during the sick days. Nevertheless, since several GLP-1RAs have shown a significant cardiovascular benefit in CVOTs, stopping these drugs may be disadvantageous.

#### 4.7. Insulin

Insulin is always a preferred modality in any emergent situation irrespective of the degree of renal and hepatic dysfunction and thus it can be used at any stage of COVID-19. Subcutaneous (SC) insulin in patients with diabetes and mild to moderate COVID-19, in those taking food orally, is not a challenging issue. However, most hospitalized COVID-19 patient with diabetes with poor oral intake or on mechanical ventilator will eventually need intravenous insulin infusion with hourly or 2-hourly monitoring and frequent adjustment of infusion rates. This would increase the chance of exposure of health care providers (HCP). To minimize frequent exposure, use of SC short acting insulin analogues can be one approach, however, its role in critically ill patients is not fully known. Alternatively, to minimize the exposure, even a single per day SC dose of long-acting basal insulin could be an attractive option, as demonstrated in one study from Thailand that found a similar outcome when compared to continuous insulin infusion, in critically ill patients [76]. Models of Insulin pump or continuous subcutaneous insulin infusion (CSII), where insulin rates can be remotely adjusted via a Bluetooth can be useful to minimize exposure of HCP.

## 5. Conclusions

While increased prevalence of diabetes was noted across the studies and their meta-analysis, no data yet suggest that there is increased risk of contracting COVID-19 in people with diabetes. In general, prevalence appeared similar to the country-wise prevalence of diabetes. However, available studies clearly suggest that the patients with diabetes had a significantly higher severe variety of COVID-19 as well as increased mortality, compared to the cohorts without diabetes. Data also suggest that poorly-controlled diabetes or stress hyperglycemia (blood glucose  $>180 \text{ mg/dl}$  or  $>10 \text{ mmol/L}$ ) have a significantly higher risk of severe COVID-19 and increased mortality, compared to the patients with well-controlled blood glucose (blood glucose  $<180 \text{ mg/dl}$  or  $<10 \text{ mmol/L}$ ).

Collectively, these findings suggest that every clinician should strive to achieve a blood-glucose targets of  $<180 \text{ mg/dL}$ , without provoking hypoglycemia for most of patients with diabetes or stress hyperglycemia with COVID-19. Although no large data is currently available with regards to the role of anti-diabetic agents in patients with COVID-19, from the available evidence it is not yet fully clear that any specific drugs had a favorable or unfavorable effect in patients with

diabetes. Nonetheless, these findings call for an increased emphasis on future preventative therapies and vaccination programs in patients with diabetes, in addition to the traditional risk prevention such as social distancing and self-isolation.

### Authorship

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work. They confirm that this paper will not be published elsewhere in the same form, in English or in any other language, including electronically.

### Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work.

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### Author contributions

AKS and KK conceptualized; AKS wrote the first draft; KK revised the text; and both approved the final manuscript.

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