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Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 159–167

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Non-insulin anti-diabetic agents in patients with type 2 diabetes and COVID-19: A Critical Appraisal of Literature

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ARTICLE INFO

Article history:
Received 11 December 2020
Accepted 13 December 2020

Keywords:
Anti-diabetic drugs
Outcomes
Severity
Mortality
COVID-19
SARS-CoV-2

ABSTRACT

Background & aims: Several observational studies have recently reported the outcomes of non-insulin anti-diabetic agents (ADA) in patients with T2DM and coronavirus disease 2019 (COVID-19). We sought to review the literature to appraise the clinicians on these outcomes.
Methods: A literature search using the specific keywords was carried out in the database of PubMed, MedRxiv and Google Scholar up till December 11, 2020 applying Boolean method. Full text of all the relevant articles that reported the outcomes of ADA in patients with T2DM and COVID-19 were retrieved. Subsequently, an appraisal of literature report was narratively presented.
Results: Available studies that reported the outcomes of ADA are either case series or retrospective cohorts or prospective observational studies, in absence of the randomized controlled trials (RCTs). Results from these observational studies suggest that amongst all the non-insulin ADA, metformin users prior to the hospitalization had improved outcomes compared to the non-users. Data for dipeptidyl-peptidase-4 inhibitors (DPP-4i) are encouraging although inconsistent. No documentation of any harm or benefit has been observed for sulfonylureas (SUs), sodium glucose co-transporter-2 inhibitors (SGLT-2i) and glucagon-like peptide receptor agonists (GLP-1RAs). No data is yet available for pioglitazone.
Conclusion: Metformin and DPP-4i should be continued in patients with T2DM until hospitalization or unless contraindicated. No evidence of harm suggests that SUs, SGLT-2i or GLP-1RAs may not be stopped unless very sick, hospitalized or contraindicated. The results from RCTs are needed to claim any meaningful benefit with either metformin or DPP-4i in patients with T2DM and COVID-19.

1. Introduction

Since the pandemic of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread across the world, several expert groups from the field of diabetes and endocrinology have opined do's and don'ts with regards to choosing non-insulin anti-diabetic agents (ADA) in patients with type 2 diabetes mellitus (T2DM). In general, all expert groups have uniformly proposed avoiding metformin and sodium glucose co-transporter-2 inhibitors (SGLT-2i) in patients with moderate to severe COVID-19, with an anticipation of increased lactic acidosis and euglycemic diabetic ketoacidosis (EuDKA), respectively, beside other adverse effects [1–4]. Some authors proposed concerns in the light of angiotensin converting enzyme-2 (ACE2) overexpression with some of these ADA, since ACE-2 is the entry receptor for the SARS-CoV-2 in human [5]. However, these recommendations were made in the absence of any studies conducted in patients with T2DM and COVID-19 at that point of time. Interestingly, no class of ADA have shown any specific detrimental effect during the past coronavirus or with other viral and bacterial infections [6]. Indeed, some ADA such as metformin has shown an improved outcome during various pulmonary disease such as asthma, acute exacerbation of chronic obstructive pulmonary disease and pulmonary tuberculosis including sepsis [6]. In this comprehensive literature review, we sought to evaluate the outcomes with non-insulin anti-diabetes agents in patients of T2DM with COVID-19, and aimed to discuss all the available evidence

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https://doi.org/10.1016/j.dsx.2020.12.026
1871-4021/

gathered so far in the past one year ever since the first case of COVID-19 was diagnosed in Wuhan, China in November 2019.

2. Methods

A Boolean search was carried out in the database of PubMed, MedRxiv and Google Scholar up till December 11, 2020 using the specific keywords that include "SARS-CoV2", "COVID-19", "severity", "mortality", "diabetes", "anti-diabetic agents", "metformin", "DPP-4 inhibitors", "SGLT-2 inhibitors", "Sulfonylureas", "Pioglitazone", "GLP-1 receptor agonists" with interposition of "AND". After an initial screening of abstract, the full text of all the relevant articles in English language with supplementary appendix that reported the outcomes with anti-diabetes agents in patients with COVID-19 were retrieved. Full text of relevant cross references was also retrieved manually. An additional search in the database of ClinicalTrials.gov was made to find ongoing studies with all ADA in patients with T2DM and COVID-19. Subsequently, we reviewed the available literature systematically and presented it narratively.

3. Non-insulin anti-diabetic drugs in COVID-19

3.1. Metformin

Historically, host-directed anti-viral properties of metformin were utilized during the treatment of influenza outbreak in Philippines in 1949 [7]. In addition, metformin has shown an inhibitory effect on hepatitis B (HBV) and C (HCV) infection. *In vitro* study found metformin to have a notable inhibitory effect on hepatitis B surface antigen (HBsAg) production and a moderate inhibitory effect on HBeAg expression. Interestingly, metformin has been found to compliment the effect of interferon-α2b and lamivudine on HBsAg and HBeAg expression [8]. Indeed, viral clearance was significantly higher when metformin was combined with peg interferon and ribavirin, in the treatment of chronic HCV [9]. Metformin has also shown a beneficial effect in HIV-lipodystrophy [10]. Although the mechanism for anti-viral effect of metformin is not clearly known, it appears likely to be due to the reduction in insulin resistance which is increasingly associated with viral infections, in particular in both chronic HBV and HCV infections.

Metformin may have an ability to improve host-directed response by virtue of inducing adenosine monophosphate (AMP) activated protein kinase. Anti-inflammatory, anti-oxidative and immuno-modulatory effect of metformin include induction of autophagy, formation of M2 macrophages and CD8 memory T-regulatory cells, reduction in the expression of genes that encode chemokines and cytokines, and alteration of the activities of catalase and superoxide dismutase, besides altering the composition of gut microbiota [11–13]. Collectively, these anticipated beneficial properties concur with metformin ability to combat the cytokine storm induced host-directed damage in patients with diabetes and COVID-19, the reason researchers proposed metformin as a repurposed drug [14]. However, an anticipated increase in lactic acidosis with the use of metformin that would likely be compounded in the presence of concomitant tissue hypoxia, hypoxemia and hypoperfusion (especially in sicker patients with COVID-19) also needs to be kept in mind [15,16].

Meanwhile, several small to large retrospective studies and one large prospective study have reported the outcomes with metformin in patients of T2DM with COVID-19 [17–29]. While some studies [17–21] found neither any harm nor any benefit in metformin users when compared to non-users both in severity and mortality outcomes, majority [23–29] reported a significant reduction in mortality. Interestingly, one study reported even an increase in severity in metformin users [22]. In earlier part of pandemic, a study by Chen et al. [17] that analyzed 120 patients with diabetes and COVID-19 (including confirmed and unconfirmed but clinically diagnosed cases) showed metformin users (n = 43) had a significantly less increase in inflammatory markers such as interleukin-6 (4.1 *vs.* 11.1 pg/mL, respectively; p = 0.02) compared to the non-users (n = 77). A reduced trend of in-hospital deaths was also observed in metformin users, compared to the non-users (9.3 vs. 19.5%, respectively; p = 0.19) in this retrospective study. Subsequently, several small to moderately large retrospective studies [18–20] reported no difference in either severity of COVID-19 or death in metformin users as compared to the non-users. First prospective study of Coronavirus Disease and Diabetes Outcome (CORONADO) (n = 1317) was conducted in patients with diabetes and COVID-19. Interim report of this study showed no difference in outcomes (composite of tracheal intubation and death [primary outcome] and death [secondary outcome] at day 7) amongst different ADA. However, amongst all the ADA, only metformin users prior to the hospital admission had a lower rate of death compared to the non-users (OR 0.59; 95% CI, 0.42–0.84) in an unadjusted analysis, though no such difference in outcome observed in the multi-variate analysis [21]. Notably, Gao et al. [22] (n = 110) reported a significant increase in life-threatening complications in metformin users compared to the non-users (28.6% *vs.* 7.4%, respectively; p = 0.004). On the contrary, several other subsequent studies including their pooled meta-analysis, reported a favorable outcome of reduction in death in metformin users compared to the non-users. In a retrospective study, Luo et al. [23] analyzed the outcomes with metformin (104/283) in patients with diabetes versus non-users (179/283) and reported a significantly less in-hospital deaths in former as compared to the latter (2.9% vs. 12.3% in metformin-users vs. non-users, respectively; p = 0.01) despite a similar baseline patient characteristics (including age, sex and comorbidities, similar laboratory parameters, and a similar background treatment). Multi-variate analysis found a 4-fold decrease in in-hospital death in metformin users as compared to the non-users (OR 4.36; 95% CI, 1.22–15.59, p = 0.02) in this study. Interestingly, reduction in mortality was observed despite a significantly higher baseline fasting plasma glucose in metformin users compared to the non-users (9.19 mmol/L *vs.* 7.36 mmol/L respectively, p < 0.01), which hints of a direct beneficial effect of metformin in COVID-19 unrelated to the glycemic control. Similarly, two smaller retrospective study by Abu-Jamous et al. [24] and Crouse et al. [25] involving 411 and 239 patients with diabetes also showed an 81% (OR: 0.19 (0.05–0.70), p = not reported) and 67% (OR 0.33; 95% CI 0.13–0.84; p = 0.02) relative risk reduction of death, respectively, in those who were metformin users compared to the non-users. These findings were further replicated in a large multi-centric retrospective propensity-matched study from USA of 6256 patients with T2DM and COVID-19 by Bramante et al. [26] that found a relative 24% reduction in mortality (HR 0.76; 95% CI 0.60–0.96; p = 0.02) in metformin-users (2333/6256) as compared to the non-users (3923/6256). However, this mortality reduction was only limited to women and mainly ascribed to a significant reduction in TNF-α in women metformin users compared to non-users. Interestingly, gender difference in outcome amongst metformin users was further replicated in another multi-centric retrospective study from China by Jiang et al. [27] when compared to the non-users. This study showed a significant risk reduction in acute respiratory distress syndrome (ARDS) in metformin users (100/328) (adjusted OR 0.18; 95% CI, 0.05–0.62; p = 0.007)) compared to the non-users (228/328) but this benefit was restricted to females (51/100) (adjusted OR 0.13; 95% CI, 0.02–0.80; p = 0.03), compared to the males (49/100) (adjusted OR 0.21; 95% CI, 0.03–1.47; p = 0.12). Notably, propensity score-matched analysis (after removal of other confounding's) also

found a significant 84% relative reduction in ARDS amongst metformin users (adjusted OR 0.16; 95% CI, 0.04–0.72; p = 0.02) compared to the non-users, although no difference in 30-day all-cause mortality observed between the two groups. Another moderately large (n = 1213) retrospective study by Cheng et al. [28] showed a 41% relative risk reduction in heart failure in metformin users compared to the non-users (adjusted HR 0.59; 0.41,0.83, p = 0.003) in a propensity-matched cohort of COVID-19 patients, although no difference in mortality observed between the two arms. Of note, a significant (p = 0.04) increase in lactic acidosis (4-fold) was also observed in metformin users in this study but that was only limited to people with chronic kidney disease (CKD) having eGFR <60 ml/min/1.73 m^2. The most recently reported final result of prospective CORONADO study (n = 2794) in patients with diabetes and COVID-19 that analyzed the outcome of discharge or death within 28 days has shown a significant improvement in outcomes with metformin users when compared to the non-users. While there was a 46% higher chance of getting discharged from the hospital (OR 1.46; 95% CI, 1.25–1.71; p < 0.001), a significant 37% risk reduction in mortality (OR 0.63; 95% CI 0.52–0.77; p < 0.001) was also observed in metformin users (1553/2794) compared to the non-users, in an age-adjusted analysis. Moreover, the multivariate analysis found a significant 60% increase in discharge rate (OR 1.40; 95% CI, 1.08–1.81; p = nr) and 35% reduction in mortality (OR 0.65; 95% CI, 0.45–0.93; p = nr) in metformin users (1355/2794), when compared to the non-users [29]. Only available study with metformin by Bramante et al. [30] that analyzed the outcome with metformin in patients with non-alcoholic fatty liver disease (NAFLD) or steato-hepatitis (NASH) with COVID-19 without diabetes, has also shown a reduced risk of hospital admission in metformin users (36/6700) (OR 0.42; 95% CI, 0.18–1.01; p = 0.05) compared to the non-users, although it was nominally significant.

Additionally, several meta-analyses that included different number of studies as they evolved over the time – e.g., by Scheen AJ [31], Kow et al. [32] and Lukito et al. [33] – all have consistently shown a significant reduction in death amongst metformin users as compared to non-users – in patients with T2DM with COVID-19. Table 1 summarizes the effects of metformin in patients with diabetes with COVID-19.

3.2. Pioglitazone

Since pioglitazone causes downregulation of ADAM-17 (A Disintegrin And Metalloproteinase-17) an ACE2 cleaving enzymes in human skeletal muscles, it can lead to an increase in ACE2. Indeed, this led some researchers to propose avoiding pioglitazone in patients with diabetes and COVID-19 [5]. Interestingly, several human studies conducted in past found an increased risk of pneumonia with thiazolidinediones (TZD) use, when compared to the sulfonylureas (SUs) in patients with T2DM [34,35]. Contrarily, 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-α), 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 [36]. Several studies have also shown a significant reduction in proinflammatory cytokines including IL-1b, IL-6, IL-8, TNF-α and other markers of insulin resistance with pioglitazone in humans [37]. This finding led some researchers to propose pioglitazone in patients with diabetes and COVID-19 [38]. Unfortunately, no studies including CORONADO have yet reported the outcomes in pioglitazone users in patients with T2DM and COVID-19. Since pioglitazone users are small in numbers, it is unlikely that sufficient numbers will be available anytime in future to analyze the data meaningfully.

3.3. Sulfonylureas

Historically, older sulfonylureas (SUs) such as tolbutamide has shown a significant reduction in *Pneumocystis carinii* pneumonia in the experimental study owing to its structural similarities with trimethoprim-sulfamethoxozole, a sulfonamide antibiotic [39]. Gorricho et al. [34] found no increase in pneumonia in modern SUs users compared to TZD. Although no relation with overexpression of ACE2 exists with sulfonylureas, the hypoglycemic potential warrants caution in sick individuals. With regards to COVID-19, some retrospective studies have reported no harm or benefit in SU users. Dalan et al. [40] found no difference in intensive care unit (ICU) admissions (Adjusted RR 1.35; 95% CI, 0.50–3.68; p = 0.56) or mechanical ventilation (Adjusted RR 3.55; 95% CI, 0.46–27.33; p = 0.22) in SUs users (n = 33) vs. non-users, in a multi-variate analysis. In a multi-variate analysis of 1:1 propensity-matched cohorts, Kim et al. [18] reported no difference in severe disease (OR 1.16; 95% CI, 0.47–2.89; p = 0.74) or death (OR 0.84; 95% CI, 0.23–3.09; p = 0.79) in SUs users (n = 60) *vs.* non-users. Similarly, Izzi-Engbeaya et al. [20] reported no difference in primary outcome of ICU admissions or deaths within 30 days (OR 0.66; 95% CI, 0.30–1.52; p = 0.59) in SU-users (74/337), in a univariate analysis. Further the prospective study of patients with diabetes in COVID-19, CORONADO found neither detrimental nor beneficial effects on primary or secondary outcome in the combined groups of SU and glinides-users (n = 367) both in its interim report at day 7 and in final report of day 28 [21,29]. No difference in discharge rates (OR 1.13; 95% CI, 0.96–1.34; p = 0.15) or deaths (OR 0.83; 95% CI, 0.67–1.03; P = 0.09) within 28 days were observed with SU/glinides users (782/2794) in an age-adjusted analysis in CORONADO [29].

3.4. DPP-4 inhibitors

Dipeptidyl-peptidase-4 (DPP-4) had been the principal entry receptor for the past corona virus (Middle East Respiratory Syndrome [MERS-CoV] infection. Although the ACE2 is the principal entry point for SARS-CoV-2, a recent modeling study by Vankadari et al. [41] did not rule out the interaction of SARS-CoV-2 with the DPP-4. Indeed, a crystallographic study by Lee et al. [42] reported that both ACE2 and DPP-4 could be involved with the receptor-binding domain (RBD) of SARS-CoV-2. Moreover, recent developments suggest that while SARS-CoV-2 may not directly involve DPP-4, however their interaction with DPP-4 in conjunction with ACE2 and likely mutation leading to an involvement of DPP-4 cannot be entirely ruled out.

Several other propositions made DPP-4 inhibitors (DPP-4i) a potential repurposed agent in COVID-19. Firstly, *in vitro* studies showed antibodies directed against the DPP-4 can significantly inhibit the human coronavirus-Erasmus Medical Center (hCoV-EMC) infection of Huh-7 cells and human bronchial epithelial cells, though the application of DPP-4i with sitagliptin, vildagliptin and saxagliptin could not inhibit the hCoV-EMC infections [43]. Secondly, since a serine protease inhibitor camostat mesylate was found to efficiently suppress SARS-CoV-2 infection by inhibiting the transmembrane serine protease 2 (TMPRSS2), it was anticipated that DPP-4i might be useful by virtue of inhibiting another serine protease DPP-4. Other potential reasons that make DPP-4i a candidate agent in COVID-19 are its anti-inflammatory, antifibrotic and immunomodulator properties. Both experimental and human studies have shown that DPP-4i exerts a potent anti-inflammatory effect, by reducing pro-inflammatory cytokines. Intuitively, this may appear to help in curbing inflammatory storm in patients with COVID-19. However, DPP-4 inhibition may also alter the immunity offered by the effector T cells. Indeed, an increase association of

Table 1
Observational studies with metformin in patients with T2DM and COVID-19.

Study	Types of study	n/N	Odds ratio (95% CI)/Hazard ratio (95% CI)/%	Final results
Studies that suggested no harm or benefit with metformin in T2DM and COVID-19				
Chen et al.[17]	Retrospective	43/120	ACM, OR: 9.3% vs. 19.5%, p = 0.19	Lesser death in metformin users vs. non-users, although insignificant difference
Kim et al.[18]	Retrospective	113/235	Severe disease, OR: 0.49 (0.19–1.24), p = 0.13; Death, OR: 0.36 (0.10–1.23), p = 0.10	No harm or benefit in metformin users vs. non-users in 1:1 propensity matched cohort.
Philipose et al.[19]	Retrospective	100/159	ACM, OR: 1.39 (0.84–2.16), p = NR	No harm or benefit in metformin users vs. non-users
Izzi-Engbeaya et al.[20]	Retrospective	169/337	ICU admission or death, OR: 1.14 (0.74–1.76), p = 0.58	No harm or benefit with metformin users within 30 days of COVID-19 diagnosis in univariate analysis
CORONADO (Interim D-7), Cariou et al.[21]	Prospective	746/1317	ACM, OR: 0.59 (0.42–0.84), p = NR	Benefit observed in univariate but not in multivariate analysis.
Studies that suggested harm with metformin in T2DM and COVID-19				
Gao et al.[22]	Retrospective	56/110	Disease progression, OR: 3.96 (1.03–15.19), p = 0.04	Increased severity in metformin users as compared to non-users
Studies that found benefit with metformin in T2DM and COVID-19				
Luo et al.[23]	Retrospective	104/283	ACM, OR: 4.36 (1.22–15.59), p = 0.02	≈4-fold decrease in death in metformin users as compared to non-users
Abu-Jamous et al.[24]	Retrospective	23/411	ACM: OR: 0.19 (0.05–0.70), p = NR	Benefit in those receiving metformin within 21 days after the diagnosis of COVID-19
Crouse et al.[25]	Retrospective	76/239	ACM, OR: 0.33 (0.13–0.84), p = 0.02	≈3-fold decrease in death in metformin users as compared to non-users
Bramante et al.[26]	Retrospective	2333/6256	ACM, OR: 0.76 (0.60–0.96), p = 0.02	24% lesser risk of death in metformin users (only in females) as compared to non-users
Jiang et al.[27]	Retrospective	100/338	ARDS, Adjusted OR: 0.18 (0.05–0.62), p = 0.007 ARDS (PSM), Adjusted OR: 0.16 (0.04–0.72), p = 0.02 ACM, Adjusted OR: 0.48; 95% CI, 0.13–1.74, p = 0.26	84% relative risk reduction in ARDS in metformin users compared to non-users, in propensity matched cohorts but beneficial effect significant only in females. No significant reduction in 30-days all-cause mortality between metformin users vs. non-users.
Cheng et al.[28]	Retrospective	678/1213	ACM, HR: 1.65 (0.71–3.86), p = 0.25 HHF, HR: 0.59 (0.41–0.83), p = 0.003	No decrease in death but 41% decrease in HHF in metformin users as compared to non-users
Wargny et al.[29], CORONADO(Final D-28)	Prospective	1355/2794	ACM, OR: 0.65 (0.45–0.93), p = NR	35% relative risk reduction in metformin users compared to non-users in multi-variate analysis
Meta-analysis of retrospective studies				
Scheen et al.[31]	Meta-analysis of 4 studies	N = 7976	ACM, OR: 0.75 (0.67–0.85), p < 0.00001	25% relative risk reduction in mortality in metformin users
Kow et al.[32]	Meta-analysis of 5 studies	N = 8121	ACM, OR: 0.62 90.43–0.89), p = NR	38% relative risk reduction in mortality users vs. non-users (pooled data from adjusted analysis)
Lukito et al.[33]	Meta-analysis of 6 studies	N = 10,233	ACM, OR: 0.64 (0.43–0.97), p = 0.035	36% relative risk reduction in mortality in metformin users (pooled data from adjusted analysis)

n- Patients on metformin, N- Patients with diabetes, T2DM- Type 2 diabetes mellitus, ACM- All cause mortality, OR- Odds ratio, HR- Hazard ratio, RR- Risk ratio, CI- Confidence interval, HHF- Hospitalization due to heart failure, ARDS- Acute respiratory distress syndrome, ICU- Intensive care unit, NR- Not reported, PSM- Propensity score-matched.

DPP-4i with bullous pemphigoid and inflammatory bowel disease has been implicated to its T cell mediated effects [44,45]. Finally, since emerging data did suggest an increase in severity of COVID-19 particularly in elderly population, people with diabetes and or obesity (all of whom often exhibit a heightened DPP-4 activity), it was increasingly believed that DPP-4i could be an ideal candidate as a repurposed agent [46], although some researcher contested this opinion in absence of conclusive studies [47,48].

With regard to studies with DPP-4i in patients with T2DM and COVID-19, one prospective and few retrospective studies are currently available. Chen et al. [17] reported that the rate of in-hospital death (25% *vs.* 14% respectively, p = 0.31) and poor prognosis (75% *vs.* 65% respectively, p = 0.45) were similar in DPP-4i users (20/120) compared to the non-users in total 120 patients receiving different oral anti-diabetic agents. Further, multivariate logistic regression analysis found no significant difference in in-hospital death (Odds ratio [OR] 1.48; 95% CI, 0.40–5.53; p = 0.56) and poor prognosis (OR 1.81; 95% CI, 0.51–6.37; p = 0.36) between DPP-4i users compared to the non-users. Similarly, Izzi-Engbeaya et al. [20] reported no difference in primary outcome of ICU admissions or deaths withing 30 days (OR 1.27; 95% CI, 0.79–2.05; p = 0.39) in DPP-4i users (93/337) compared to the non-users in univariate analysis. In prospective CORONADO interim report where 285 patients were receiving DPP-4i, both primary outcome (tracheal intubation and or death evaluated within 7-days of admission; unadjusted OR 1.01; 95% CI, 0.75–1.34) and secondary outcome (death at day 7; unadjusted OR 0.85; 95% CI, 0.55–1.32) were similar in DPP-4i users compared to the non-users in an unadjusted analysis [21]. However, in CORONADO final analysis, rate of discharge from hospital was significantly 22% higher in DPP-4

users (615/2794) compared to the non-users (OR 1.22; 95% CI, 1.02–1.47; p = 0.03), although no difference in mortality (OR 0.83; 95% 0.65–1.05; p = 0.12) was noted within 28 days [29]. Fadini et al. [49] in an unadjusted analysis of a retrospective study of 85 patients with diabetes and COVID-19 (9 receiving DPP-4i) showed no difference either in the rate of ICU admissions (33.3% vs. 19.2% respectively, p = 0.33) or deaths (11.1% vs. 13.9% respectively, p = 0.82) between DPP-4i users vs. non-users. No difference in deaths or severe disease in DPP-4i users was reported by Strollo et al. [50] and Kim et al. [18] from Italy and Korea respectively. Notably, Dalan et al. [40] reported a 4-fold increased risk of ICU admission in DPP-4i users (27/76) compared to the non-users, in a multivariate analysis (RR 4.07; 95% CI 1.42–11.66, p = 0.009). On the contrary, in a French case series of 27 patients with diabetes (10 receiving DPP-4i), Montastruc et al. [51] reported a lower rate of intubation in DPP-4i users (43% *vs.* 81% respectively; p = not reported) compared to the non-users. First suggestion of significant benefit with DPP-4i emerged from the study by Rhee et al. [52] that reported the population-based study of 832 patients with diabetes and COVID-19 from a South Korean Medical insurance claim database, where 263 were taking DPP-4i. This study found a 64% lesser risk of severe COVID-19 in DPP-4i users (adjusted OR, 0.36; 95% CI, 0.14–0.97; p = nr) compared to the non-users, even after the adjustment of multiple confounders. The largest retrospective study of DPP-4i SIDIACO-RETRO (n = 334) by Solerte et al. [53] reported the outcome in patients with T2DM and COVID-19 that compared sitagliptin to standard-of-care receiving background insulin therapy. This study found a 56% relative decrease in all-cause mortality (HR 0.44; 95% CI 0.29–0.66; p = 0.0001) with sitagliptin. Similarly, in a case series (n = 90) Mirani et al. [54] reported a significant reduction in death in DPP-4i users, compared to the non-users (HR 0.13; 95% CI, 0.02–0.92; p = 0.04). Table 2 summarizes the results of DPP-4i in COVID-19 from all the available clinical studies.

3.5. SGLT-2 inhibitors

Since SGLT-2i increases ACE2 expression in kidney, some concern of increased risk was raised during COVID-19 [5]. As mentioned earlier, experts recommended avoiding SGLT-2is in patients with diabetes and COVID-19, in anticipation of EuDKA on the background of illness-associated dehydration, hypovolemia and poor food intake. Nevertheless, both pre-clinical and clinical studies have shown that SGLT-2i possess an anti-inflammatory property which can favorably effect tissue hypoxia, oxidative stress, autophagy as well as energy metabolism. All of these can have a positive impact on the dysregulated process of cytokine storm associated with COVID-19 [55]. Interestingly, dapagliflozin has shown to decrease lactic acidosis significantly and therefore, has the potential to reverse acid-base balance inside the cells during hypoxia [55]. Moreover, SGLT-2i have consistently shown a significant cardio-renal benefit in patients with T2DM with high cardiovascular risk and renal disease.

Only a few studies have reported the outcomes with SGLT-2i in patients with T2DM and COVID-19. In a 1:1 propensity-matched multivariate analysis, Kim et al. [18] reported no difference in outcomes of either disease severity (OR 1.75; 95% CI, 0.23–13.50; p = 0.59) or deaths (OR 5.05; 95% CI, 0.48–53.26); p = 0.18) in SGLT-2i users (8/235) compared to the non-users. Similarly, in a univariate analysis, Izzi-Engbeaya et al. [20] reported no difference in primary outcome of ICU admissions or deaths within 30 days (OR 0.66; 95% CI, 0.30–1.52; p = 0.40) amongst SGLT-2i users (24/337) compared to the non-users. On the contrary, in a multivariate analysis of a retrospective study by Dalan et al. [40], reported a nominally decreased risk of mechanical ventilation (Adjusted RR 0.03; 95% CI, 0.00–0.70; p = 0.03) in SGLT-2i users (16/26)

Table 2
Observational studies with DPP-4 inhibitors in patients with T2DM and COVID-19.

Author, Study Eponym	Types of study	N	Odds ratio (95% CI)/Hazard ratio (95% CI)/Risk ratio (95% CI)/%	Final results
Studies that found no harm or benefit with DPP-4 inhibitors in T2DM and COVID-19				
Chen et al.[17]	Retrospective	20/120	ACM, OR: 1.48 (0.40–5.53) p = 0.56; Poor prognosis, OR: 1.81 (0.51–6.37), p = 0.36	Similar outcome in DPP-4i users vs. nonusers
Kim et al.[18]	Retrospective	85/235	Severe disease, OR: 1.05 (0.44–2.49), p = 0.92; Death, OR: 1.47 (0.45–4.78), p = 0.52	Similar outcome of severe COVID-19 and death in DPP-4i users vs. nonusers in 1:1 propensity matched cohort.
Izzi-Engbeaya et al.[20]	Retrospective	93/337	ICU admission or death, OR: 1.27 (0.79–2.05), p = 0.39	No harm or benefit in DPP-4i users within 30 days of COVID-19 diagnosis in univariate analysis
Cariou et al.[21], CORONADO (Interim D-7)	Prospective	285/1317	Tracheal intubation and/or death, unadjusted OR: 1.01 (0.75–1.34), p = NR; ACM, unadjusted OR: 0.85 (0.55–1.32, p = NR.	No difference in primary and secondary outcomes in DPP-4i users vs. nonusers.
Fadini et al.[49]	Retrospective	9/85	ICU admission (33.3% vs. 19.2%), p = 0.33; Death (11.1% vs. 13.9%), p = 0.82	Similar outcome in DPP-4i users vs. nonusers respectively in unadjusted analysis.
Strollo et al.[50]	Retrospective	3351/3351	–	Similar outcome of death in DPP-4i users vs. nonusers
Studies that found harm with DPP-4 inhibitors in T2DM and COVID-19				
Dalan et al.[40]	Retrospective	27/76	ICU admission, RR: 4.07 (1.42, 11.66), p = 0.009	Increased risk of ICU admission in DPP-4i users vs. nonusers
Studies that found benefit with DPP-4 inhibitors in T2DM and COVID-19				
Montastruc et al.[51]	Case series	10/27	Intubation (43% vs. 81%, p = NR)	Lower rate of intubation in DPP-4i users vs. nonusers
Rhee et al.[52]	Retrospective	263/832	Severe COVID-19, adjusted OR: 0.36 (0.14–0.97), p = NR	Significantly lower severe COVID-19 in DPP-4i users vs. nonusers even after the adjustment of multiple confounder
Solerte et al.[53], SIDIACO-RETRO	Retrospective	169#/338	ACM, HR: 0.44 (0.29–0.66); p = 0.0001	Significant 56% relative risk reduction in sitagliptin users compared to SOC.
Mirani et al.[54]	Case series	90/387	ACM, HR 0.13 (0.02–0.92), p = 0.04	Significant reduction in death in DPP-4i users vs. nonusers.
Wargny et al.[29] CORONADO (Final D-28),	Prospective	615/2794	Discharge within 28 days, OR: 1.22 (1.02–1.47), p = 0.03 ACM, OR: 0.83 (0.65–1.05), p = 0.12	22% higher chance of getting discharged in DPP-4i users, although no difference in mortality outcome

n = patients on DPP-4 inhibitors, N = patients with diabetes, #- patients on sitagliptin, T2DM- Type 2 diabetes mellitus, ACM- All cause mortality, OR- Odds ratio, HR- Hazard ratio, RR- Risk ratio, CI- Confidence interval, ICU- Intensive care unit, NR- Not reported, DPP-4I- DPP-4 inhibitors, SOC- standard of care.

compared to the non-users. Intriguingly, prospective CORONADO study did not report the outcome in patients receiving SGLT-2i.

3.6. GLP-1 receptor agonists

In experimental studies, GLP-1 receptor agonists (GLP-1RAs) have been found to increase ACE2 expression in lungs and heart, improve right ventricular functions and exhibit anti-inflammatory effect during acute lung injury [56,57]. These findings of pulmonary renin angiotensin system modulation led many to propose GLP-1RAs as a repurposed agent in COVID-19 [58]. However, this purported increase in ACE2 expression raised an initial concern during COVID-19 [5]. Moreover, experts suggested avoiding this class of drugs during the sick days due to associated gastrointestinal adverse events [2]. Counterintuitively, stopping these drugs could also be disadvantageous since GLP-1RAs have shown to exhibit a significant cardiovascular benefit in patients of T2DM with high CV risk.

Very few studies have reported the outcomes in patients receiving GLP-1RAs. Scattered case reports have claimed good outcome with GLP-1RAs therapy in patients with T2DM and COVID-19 [59]. In a retrospective study, Izzi-Engbeaya et al. [20] reported no difference in primary outcome of ICU admissions or deaths within 30 days (OR 0.52; 95% CI, 0.09–2.60; p = 0.66) in GLP-1RA users (5/337), in a univariate analysis. Similarly, in CORONADO interim report where 123/1317 patients were receiving GLP-1RAs, both tracheal intubation and or death (unadjusted OR 1.36; 95% CI, 0.92–2.01) and death at day 7 (unadjusted OR 0.64; 95% CI, 0.32–1.29) were similar in GLP-1RA users, compared to the non-users in an unadjusted analysis [21]. Even the final report of CORONADO did not find any detrimental or beneficial effect of GLP-1RAs (254/2794) on either discharge rate from the hospital (OR 1.11; 95% CI, 0.85–1.45; p = 0.45) or the mortality (OR 0.78; 95% 0.53–1.15; p = 0.21) compared to the non-users, in an age-adjusted analysis within 28 days [29].

4. Discussion

The available evidence from the majority of these observational studies (from small to moderately large size), it has been increasingly apparent that a signal of reduction in mortality does appear to exist amongst metformin users, when compared to non-users in patients of T2DM with COVID-19. The data with DPP-4i is also encouraging but inconsistent at this moment and needs consideration on several issues, as aptly commented by Nauck and Meier recently [60]. Nevertheless, some additional caution is warranted before claiming any substantial benefit with both these classes of drugs for the following reasons - Firstly, despite the fact that many of these studies have been adjusted for multiple confounders and are propensity score-matched, even then several other inherent potential confounders cannot be fully eliminated which could interfere with the final results. It is highly likely that the non-users of metformin may represent those groups of patients with COVID-19 which precluded its such as older age, CKD, cardiovascular disease, and other comorbidities having poorer outcome by themselves and not necessarily related to the drug. It is also likely that few studies may not have excluded patients having contraindication to metformin therapy which may impart some biases to the final result. Secondly, majority of these studies including CORONADO analyzed the outcomes with ADA that were used prior to the hospitalization and therefore it is not exactly known whether continuing these drugs after the hospitalization would have yielded similar results. Moreover, it is also not known from these studies as to what should be the minimal duration of metformin or DPP-4i treatment that would offer protection. Furthermore, no clarity with regard to the optimal dose of metformin or DPP-4i is available that may show putative beneficial effect. Thirdly, even if the benefit in outcomes with metformin or DPP-4i are assumed to be true and not related to the direct glycemic lowering effect, it is not exactly known as to what extent this beneficial impact should be generalized to the non-diabetic individuals. Finally, the exact mechanism by which both metformin and DPP-4i might exert its beneficial effect is largely unknown, although various mechanisms have been hypothesized. Table 3 summarizes these immunomodulatory mechanisms of metformin and DPP-4i for purported benefit in relation to COVID-19 [61–72]. Nonetheless, to claim these mortality benefit and before recommending the use of metformin or DPP-4i meaningfully in patients with T2DM and COVID-19, we need positive results from randomized controlled trials (RCTs). Since metformin is an inexpensive drug and out of patent world-wide, no stakeholders would be very keen to conduct a well-powered and large RCT to demonstrate its effect in COVID-19.

To this end, very few randomized controlled trials with ADA have been planned currently. MET-Covid is an ongoing small (n = 70), quadruple-blinded, randomized, placebo-controlled clinical trial (NCT04510194) that is being conducted with metformin (1500 mg) for the outpatient treatment in patients with COVID-19, with or without diabetes, and evaluating the change in inflammatory markers, albumin and viral load as a primary outcome with a time frame of 10 days. However, results are not expected before September 2021 [73]. Similarly, three randomized controlled trials (RCTs) are currently evaluating the DPP-4i in patients with diabetes and COVID-19. Two studies are examining the effect of linagliptin 5 mg daily compared to the control in the background of insulin therapy. One study of linagliptin (NCT04371978) is evaluating 100 patients with diabetes and established COVID-19, with a primary objective of time to clinical change within 28-days. The clinical change is defined as 2 points reduction in the World Health Organization 8-point ordinal scale for clinical improvement of COVID-19 and is expected to be completed in September 2021 [74]. Another study (NCT04341935) is evaluating 20 patients with diabetes and confirmed COVID-19 comparing linagliptin 5 mg daily to the control with background insulin therapy. Although the primary outcome of this 14-day study is changes in glucose control, the secondary outcome includes changes in oxygen saturation (SpO2 levels), changes in interleukin-6 and changes in chest radiography, and is expected to be completed in December 2021 [75]. The RCT with sitagliptin (NCT04365517) shall be evaluating the effect of sitagliptin treatment (n = 170) in COVID-19 positive diabetic patients (SIDIACO-RCT) while comparing vs. placebo with or without background insulin therapy [76]. The primary endpoint is change in two-point clinical improvement on seven-category scale and clinical as well as biochemical changes in acute lung disease at 1-month time frame. This study is expected to be completed in December 2021. Unfortunately, only one RCT (NCT04371978) out of 3 has currently started recruiting patients at the time of writing this review. With regard to the SGLT-2i, a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study (NCT04350593) with Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) is currently under progress (n = 900) evaluating patients with moderate to severe COVID-19 of any duration not needing mechanical ventilation [77]. DARE-19 is being conducted with 10 mg of dapagliflozin vs. placebo for 30-days, not only in people with T2DM but also in patients with a history of any one of the following: hypertension, atherosclerotic cardiovascular disease, heart failure and/or chronic kidney disease stage 3–4 (eGFR ≥25 mL/min/1.73 m^2). 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 and is expected to be

Table 3
Proposed mechanisms by which metformin and DPP-4i may exert benefit in the context of COVID-19 beyond glucose control.

Anti-diabetic agents	Possible mechanisms of protection
Metformin[11-14,31,61-67]	i. Reduction in insulin resistance and body weight ii. Reduction in immune hyperactivation by inhibition of mTOR pathway iii. Induction of AMPK pathway leading to anti-inflammatory, anti-oxidant and immuno-modulatory effect – decrease in neutrophil, induction of autophagy, formation of M2 macrophages and CD8 memory T-regulatory cells, reduction in the expression of genes encoding chemokines and cytokines, alteration of catalase/superoxide dismutase activities and gut microbiota composition, and phosphorylation of ACE2 leading to inhibition of viral penetration iv. Suppression of mitochondrial ROS (reactive oxygen species) signaling via inhibition of mitochondrial complex 1 leading to less IL-6 (interleukin-6) release v. Effects on endosomal Na^+/H^+ exchanger leading to increase in cellular pH and thereby inhibiting viral endocytosis vi. Upregulation of protein expression of IL-10 and decrease in TNF-α (tumor necrosis factor-alpha) especially in females
DPP-4 inhibitors[46,60,68-72]	i. Reduction of the NLRP3 (NOD-like receptor 3) inflammasome and CRP (C-reactive protein), TNF-α (tumor necrosis factor-α), interleukin-6 (IL-6), IL-1β, and IL-18 ii. Reduction in mRNA expression of CD26 in mononuclear cells and suppression of activation of myelin basic protein-specific $CD4^+$ T cell clones iii. Inhibition of lung fibroblasts activation induced by TGF-β iv. Reduction of heightened DPP-4 activity in elderly, obesity and T2DM v. Increase in soluble DPP-4/CD26 level keep SARS-CoV-2 away from the target cell entry via membrane bound DPP-4/CD26 [60]

Table 4
Planned and ongoing randomized controlled trials with anti-diabetic agents in COVID-19[73–77].

Anti-diabetic drugs *vs.* Comparators	Study title (NCT number)	N	Place	Primary outcome (Time frame)	Secondary outcome (Time frame)	Estimated completion; Status at the time of writing
Metformin						
Metformin vs. Placebo	MET-Covid Trial: Metformin for Outpatient Treatment and Post-exposure Prophylaxis of COVID-19 (NCT04510194)	70	University of Minnesota, USA	i. Change in CRP ii. Change in albumin iii. Change in viral load (Time frame 10 days)	i. Emergency department utilization ii. Incidence of possible COVID-19 symptoms iii. WHO disease progression scale (Time frame 14–28 days)	September 2021; not yet recruiting
DPP-4 inhibitors						
Sitagliptin vs. Placebo (with or without insulin)	SIDIACO: The Effect of Sitagliptin Treatment in COVID-19 Positive Diabetic Patients (NCT04365517)	170	University of Milan, Italy	i. Time of clinical improvement ii. Clinical parameter of acute lung disease iii. Biochemical parameter of acute lung disease (Time frame 1 month)	i. Cytokine-inflammatory profile (Time frame 6 month)	December 2021; not yet recruiting
Linagliptin vs. Placebo in background insulin therapy (Hospital setting)	Effects of DPP-4 inhibition on COVID-19 (NCT04341935)	20	University of Miami, USA	i. Changes in glucose level (Time frame 14 days)	i. Changes in SpO2 levels ii. Changes in IL-6 iii. Changes in chest radiography (Time frame 14 days)	December 2021; not yet recruiting
	Efficacy and Safety of Dipeptidyl Peptidase-4 Inhibitors in Diabetic Patients With Established COVID-19 (NCT04371978)	100	Rabin Medical Center, Israel	i. Time to clinical changes in 8-point WHO Ordinal scale (Time frame 28 days)	i. Clinical improvement ii. Length of hospitalization iii. All-cause mortality iv. Mechanical ventilation use v. ICU admissions vi. Virological response (Time frame 28 days)	September 2021; recruiting
SGLT-2 inhibitors						
Dapagliflozin vs. Placebo	DARE-19: Dapagliflozin in Respiratory Failure in Patients With COVID-19 (NCT04350593)	900	Saint Lukes' Health System, USA	Time to first occurrence of death due to any cause or anyone new/worsened organ dysfunction – i. Mechanical ventilation ii. New or worsening HF iii. Vasopressor therapy iv. VT/VF v. Initiation of RRT (Time frame 30 days)	i. Composite outcome (all-cause death, new/worsening organ dysfunction, clinical status at day 30, time to discharge) ii. Time to hospital discharge iii. Time to death iv. Time to new/worsened organ dysfunction v. Time to acute kidney injury (Time frame 30 days)	December 2020, recruiting

HF- heart failure, VT- Ventricular tachycardia, VF- Ventricular fibrillation, RRT- Renal replacement therapy, SpO2- Oxygen saturation, IL-6- Interleukin-6, ICU- Intensive care unit.

completed by December 2020. Table 4 summarizes all RCTs being planned or currently ongoing with ADA in patients with COVID-19.

5. Conclusions

Evolving data from the observational studies have consistently shown a reduction in mortality in patients with T2DM with COVID-19 who were prior metformin users without any obvious safety signals. This would suggest continuing metformin therapy in patients with COVID-19, unless there is declining renal function or increasing hypoxemia or multiple organ failure. Similar conclusion can also be drawn for the DPP-4i use in T2DM with COVID-19,

although the beneficial effects are heterogeneous, inconsistent, and less robust compared to metformin. Nonetheless, in the presence of comorbidities that would preclude metformin use, DPP-4i may offer a good alternative. Clearly, DPP-4i did no harm to patients with T2DM and COVID-19. With regard to SGLT-2i and GLP-1RAs, there is no adequate available data at the moment that may suggest any significant harm or benefit and therefore, there is no evidence to recommend stopping these drugs until hospitalization. Preferebly, SGLT-2i should be discontinued in hospitalized sicker patients with multiple organ failure or in presence of other contraindication that may preclude SGLT-2i use. No data is currently available for pioglitazone and thus its safety in patients with T2DM and COVID-19 is not clearly known.

Funding

None.

Authors contribution

AKS searched the literature in medical database, RS wrote the first draft, AKS, BS and SM revised the manuscript. All authors agreed to submit the manuscript.

Declaration of competing interest

We hereby declare that we have no conflict of interest, related to this article titled “Non-insulin Anti-diabetic Agents in Patients with Type 2 Diabetes and COVID-19: A Critical Appraisal of Literature”.

Acknowledgment

None.

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