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REVIEW ARTICLE

IMPACT OF ANTIDIABETIC DRUGS ON RISK AND OUTCOME OF COVID-19 INFECTION: A REVIEW

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Summary

Based on many reports, an unmistakable link probably exists between diabetes mellitus and COVID-19. A major predisposing factor determining severity and mortality of COVID-19 is diabetes mellitus, diabetic patients were shown to be at higher risk for developing severe COVID-19 disease than non-diabetics; many recent studies reported a striking prevalence of DM in those diagnosed with COVID-19. Accordingly, antidiabetic drugs can possibly impact the clinical course and / or the outcome of this infection, either by alleviating diabetes-associated symptoms, minimizing its complications, or by mitigating or aggravating COVID-19 disease by effects independent from their direct antidiabetic effects. Several antidiabetic drug classes were shown to have varying effects, like blocking viral entry to cells, as well as having immunomodulatory, anti-inflammatory, antifibrotic, or cardioprotective effects; such effects could prove beneficial for COVID-19 patients. On the other hand, some antidiabetic agents may have adverse effects that aggravate patients' condition like hypoglycemia, fluid retention, increased weight or lactic acidosis, which require special consideration in patient management. Some of the drugs were found in observational studies to either reduce mortality from COVID-19 or pose no harm, but more solid evidence from clinical trials is still lacking.

Key words: COVID-19; diabetes; DPP4 inhibitors; metformin; SGLT2 inhibitors; sulfonylureas; thiazolidinediones

1. Introduction

1.1. SARS-CoV-2 virus

Coronavirus disease (known as COVID-19), an acute infection caused by SARS-CoV-2 virus, was first witnessed in September 2019 in Wuhan, China (1). It was till March,12th 2020 that the WHO declared the disease a pandemic (2). As of June, 2021, greater than 174 million cases and deaths of over 3.7 million were reported (3). This epidemic has affected subjects with many common pathological conditions of metabolic etiology, one of which is type 2 diabetes mellitus (T2DM) (4). Coronaviruses are pathogens etiologically involved in a range of respiratory illnesses (5). The culprit in the current pandemic, SARS-CoV-2, is a positive sense RNA virus, it belongs taxonomically to the genus betacoronavirus (6,7) which is part of the subfamily *Orthocoronavirinae* (8).

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1.2. Role of ACE2 in infection

Angiotensin-converting enzyme 2 (ACE2), part of the renin-angiotensin system (RAS), was identified as a key receptor implicated in binding and entry of SARS-CoV-2 into human cells (9), which occurs after the virus is attached to this receptor via its spike glycoprotein's receptor binding domain (RBD).

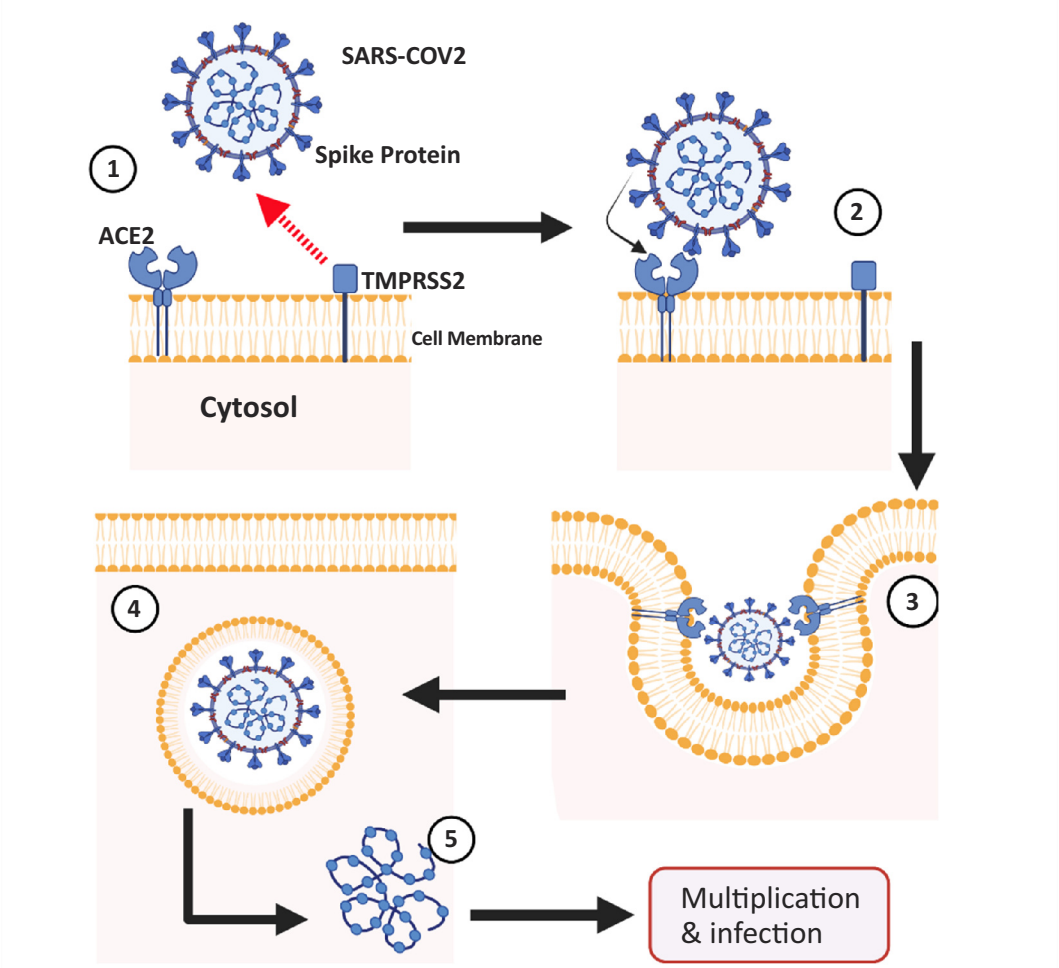

Figure 1. SARS-COV2 binding and entry into host cell with the following steps: Host TMPRSS2 first primes the spike protein inducing the latter's proteolytic cleavage. Binding of viral spike protein to host ACE2 occurs, viral and cellular membrane fusion and host entry by endocytic process occurs. The virus is internalized into an endosome in the cytosol, followed by release of viral genome into host cell, multiplication and further steps in infection later occur. TMPRSS2, type II transmembrane serine protease; ACE2, angiotensin converting enzyme 2. Created with BioRender.com.

ACE2 is a transmembrane protein, with an extracellular portion (N -domain) harboring the catalytic site and an intracellular C-domain (10). Two forms of ACE2 exist; full molecule mACE2 present on cell membrane, consisting of both the transmembrane and extracellular domains (11), this form serves as the target for viral binding and entry; the second form is a soluble (sACE2) present in the circulation (12). During viral entry to target cells, the S protein on the viral envelope undergoes cleavage into smaller subunits (S1 and S2) (13). While the second subunit (S2) undergoes no binding or interaction with the host receptor, it is functionally responsible for the viral membrane fusion. Receptor binding protein (RBD) is a part of S1 protein and S1 subunit interaction with its respective receptor is critical in the ability of the virus to infect the host. S1 protein attaches to the peptidase domain of host cell ACE2, thereby gaining cellular entry; to reach the cytosol, peptidase functionality of ACE2 is essential (14–16). S1 binding to its ACE2 receptor initiates the latter's disintegration (10, 17, 18); furthermore, a second host

molecule, type II transmembrane serine protease (TMPRSS2), also cleaves ACE2 at the intracellular (c-terminus) domain (17, 19); both of these events are critical for viral entry, but on the other hand will initiate shedding and thus loss of host reservoir of ACE2 (20). ACE2 is expressed in many tissues in the body, with high density in cardiovascular (CV) and lung alveolar epithelial sites (21, 22). Figure 1 shows viral binding and entry into host cells.

1.3. Diabetes mellitus and COVID-19: The link

One of the major predisposing factors determining severity and mortality of COVID-19 is diabetes mellitus (DM) (23–25), DM patients are at higher risk for developing severe COVID-19 disease than non-diabetics (26, 27). Diabetes, CV diseases and hypertension were shown in a meta-analysis to be prime cardiometabolic co-pathologies among hospitalized cases of COVID-19 (28). Similar findings were reported in a large scale study conducted on hospitalized COVID-19 patients, additionally, DM was reported as most common co-pathology at intensive care units (ICUs) (29, 30).

1.4. Prevalence of diabetes in COVID-19 patients

One-fifth of ICU COVID-19 admissions in early reports from Wuhan, China were diabetics (25), and in another study from Italy, over two-thirds of mortalities from COVID-19 had co-existing DM (31). In a nationwide Chinese study on about 1600 COVID-19 hospital admissions, 8 percent of them had pre-existing DM (32). Additionally, 2 data analyses, one on over 2100 , and one on over 1500 Chinese COVID-19 patients, revealed a 10 percent DM prevalence % (33). In another meta-analysis, a prevalence of 9.7 percent was reported (28). Another report on 46248 COVID-19 Chinese patients also reported a prevalence of DM of 8 percent, establishing the latter as the commonest comorbidity (34), another meta-analysis involving 19 studies (18 Chinese and 1 Australian) showed 11.9 prevalence of DM in these patients (35). A UK report on hospitalized COVID-19 patients found a prevalence of 21 percent for DM (36). In a long-term care institution, of 101 US patients hospitalized for COVID-19, 31 percent of those were diabetics (37). While prevalence is apparently variable in different studies, reflecting probably different demographics across different regions, however, DM appears to be a fairly common pre-morbidity or co-morbidity in those with COVID-19 (38). Since DM is a recognized risk factor for developing more serious cases (39), thus it has become increasingly urgent to explore the antidiabetic drugs effect on COVID-19 outcome (40). A link between the 2 morbidities apparently exists, and accordingly managing and controlling DM properly, could change the course of and reduce fatalities from COVID-19. This short narrative review aims to discuss the link between some of the major classes of antidiabetic drugs and risk of developing as well as outcome of COVID-19 disease.

2. Antidiabetic drugs and COVID-19

2.1. DPP4 inhibitors (Gliptins)

2.1.1. Mechanism of action and clinical effects

The serine protease dipeptidyl peptidase 4 (DPP4), also called CD26, is a trans-membrane glycoprotein, which holds a critical place in the homeostasis of glucose (41). Its major function of interest in DM is splitting the so-called incretin hormones, specifically, glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP) (42); degradation of GLP-1 via DPP-4 is a means for controlling post prandial glucose surge, the action of DPP-4 ultimately diminishes secretion of insulin (43). Incretin hormones (GLP-1 and GIP) stimulate about almost 70 % of insulin release after meals (44).

Dipeptidyl peptidase-4 inhibitors, also called gliptins, are antidiabetic drugs which are indicated for T2DM. As mentioned above, hypoglycemic effect is achieved by blocking DPP4-catalyzed breakdown of incretin hormones, primarily GLP1, the latter functions to enhance postprandial insulin release, diminishing hyperglycemia (45). By preventing their degradation, these drugs prolong incretins half-life (44). This class is not associated with gain of weight or hyperglycemic incidents (45).With risk of hypoglycemia being minimal and adequate glycemic control, gliptins currently have second line status for management of DM (46), utilized as an alternative therapy to insulin secretagogues, showing benefits in delaying introducing add-on insulin for T2DM patients, especially being useful for those with contraindications for other DM drug classes (47).

2.1.2. DPP4 inhibitors and viral entry and pathology

Although ACE2 is a major viral entry receptor protein for SARS-CoV-2 (48), evidence suggests that DPP-4 possibly functions as a co-receptor facilitating viral entry for SARS-CoV-2 (49) to host cells, also it was found that viral spike protein S1 domain has the potential to interact with host DPP4 molecules (49, 50). Partly, COVID-19 pathology may be attributed to DDP-4 distribution in airways enhancing entry to the lungs and thereby facilitating severe disease manifestations and consequences; thus, theoretically DPP4 inhibitors can counteract entry and later consequences of the virus in T2DM patients (51). In contrast to this notion, entry of the virus into cells was not blocked by gliptins in *in vitro* studies (52). ACE2, a principal component for the complementary RAS pathway, antagonizes the classical RAS pathway leading to conversion of (and hence inactivation) Ang II to Ang-(1-7) (53); COVID-19 infection is associated with decreased expression and hence bioactivity of ACE2 (54), the consequent imbalance in Ang II activity can potentiate COVID-19 severity; DPP4 inhibitors can decrease Ang II and thus reduce cardiac re-modelling and elevated blood pressure (BP) (55) and other related consequences.

2.1.3. Clinical effects in the context of COVID-19

DDP4 inhibitors may modulate certain immune aspects. DPP4 is expressed in many tissues and cells, including T-cell and macrophages, which suggests a modulating capacity for DPP4 inhibitors on innate and adaptive immune system (56). DPP4 is involved in T-cell activation (46) and functions as an activated T cells marker; additionally, it regulates the expression of several chemokines (57, 58). Type 1 helper T cell (Th1) response was reduced by gliptins and they upregulated the release of anti-inflammatory cytokines and downregulated the secretion of pro-inflammatory IL-7 (59).

Mast cells on mucosal surfaces release several substances which may aggravate patients' condition in COVID-19 infection (60), theoretically, by controlling mast cell migration via inhibition of DPP4-induced splitting of stromal derived factor 1 (SDF-1), DPP4 inhibitors may offer protection from COVID-19 disease (40). DDP-4 inhibitors can preserve endothelial function and protect vascular system and combat inflammation and oxidative distress (OS), all of which are of utility in managing COVID-19 disease (61). However, some reports indicated that these drugs were shown to have deleterious (62) or neutral (63) impact on endothelial function in diabetic patients.

In rodent models, several effects potentially beneficial for COVID-19 infections were reported for DPP4 inhibitors. Anti-inflammatory effect equivalent to aspirin was demonstrated for vildagliptin and saxagliptin in an inflammation model (64). Activation of inflammatory markers and rise in several interleukins, induced by DM, was ameliorated by saxagliptin (65).

2.1.4. DPP4 inhibitors and COVID-19 outcome

Whether the use of DPP4 inhibitors can offer protection from COVID-19 severe consequences is controversial (66). Frequency of infections (UTI and respiratory) were shown to be increased after DPP4 inhibitors use (67). Furthermore, increased upper respiratory tract infections in patients maintained on DPP4 inhibitor vs other DM drugs were reported (68), as well as worse outcome in another study, compared to other antidiabetic drugs (69).

In contrast, respiratory COVID-19 complications risk was reported by some authors to be mitigated by DPP4 inhibitors (66). Compared to placebo and other antidiabetic drugs, DDP4 inhibitors were found not to increase risk of respiratory infections (70). Similar results were reported in yet another study (71). A meta-analysis found similar results regarding sitagliptin prolonged use in T2DM patients (72), while another meta-analysis found this class not to increase susceptibility in general to infections in DM patients (70). DDP4 inhibitors use in DM patients developing COVID-19 disease was not found to be associated with safety concerns (43, 73). Furthermore, a recent study (74) found that adverse outcome of COVID-19 disease was not associated with use of this class of drugs as compared to other antidiabetic drugs; and sitagliptin was found to improve outcome and reduce mortality in hospitalized patients (75), another Italian study also demonstrated reduced mortality among those maintained on DPP4 inhibitors (76). In contrast to these studies, an Italian study found no evidence supporting drug use as a means to hinder COVID-19 progression or development (77).

In conclusion, cardioprotective and immune modulating merits that DPP4 inhibitors were shown to provide can possibly modulate COVID-19 disease course and mitigate its severity, however this needs further study to explore whether this is a class effect or confined to some gliptins only (22). No sufficient evidence currently supports discontinuing DPP4 inhibitors in those with moderate symptoms or those hospitalized, and it is recommended to continue using these drugs in non-critically ill COVID-19 patients (78). DPP4 inhibitors could be preferable therapy to maintain glycemic control, along with insulin, in hospitalized patients (79), but minimizing poor COVID-19 outcome via introducing these drugs to those T2DM patients exposed to the virus is not sufficiently supported by current evidence (80).

2.2. Sodium–glucose cotransporter 2 inhibitors

2.2.1. Mechanism of action

These drugs, also called gliflozins, are a new class of anti-diabetic drugs, which inhibit sodium–glucose cotransporter 2 (SGLT2) facilitative co-transporter of glucose, which is found in proximal convoluted tubule (PCT) of nephrons; this transporter promotes the urinary excretion of glucose, which in turn suppresses elevated plasma glucose levels in T2DM patients (81–83). The fall in glucose levels ushers an improvement in glycemic indices (84–86). The action of SGLT2 inhibitors relies on plasma levels of glucose whilst being independent of insulin effects. Thus, hypoglycemic risk is low and Beta cells are not functionally stressed (87). This unique mechanism sets the class apart from other DM drug classes as no interference with the incretin hormones or insulin endogenously released occurs (88). SGLT2 inhibitors also promote excretion of water and salt (natriuresis) from kidneys (89).

2.2.2 Class benefits in clinical conditions

Evidence indicates that this class confers substantial CV and renal benefits (90). SGLT2 inhibitors can bring about weight loss (91) with greater magnitude in long-standing DM and in those with high body weight (92). These drugs are preferable when T2DM patient has a high CV risk factor, e.g. heart failure (HF), coronary artery disease, renal dysfunction and proteinuria (93) as these drugs reduced CV mortality and hospitalization for HF patients with co-existing DM (94–96). Due to their natriuretic activity, SGLT2 inhibitors may show therapeutic benefit in hypertension (94). Significant BP reduction is reported in most studies on SGLT2 inhibitors (97), the effect occurs independently of their glycemic or weight-reducing effects (98). Such pleiotropic effects of SGLT2 inhibitors which extend beyond their glucose-modulating effects can ameliorate associated DM co-pathologies like HF, CV disease, chronic kidney disease (CKD); interestingly, these same co-morbidities enhance mortality risk in COVID-19 infection (99).

2.2.3. Anti-inflammatory and immune modulating effects

Evidence indicates that SGLT2 inhibitors mitigate inflammation both systemically and via direct action on renal, immune, endothelial and cardiac cells (96) . Empagliflozin, a member of the class, reduced inflammation, locally in the heart in an HF model (100) and systemically with reduced mortality in a sepsis model (101). Cardiac and kidney macrophage infiltration, in the context of HF and sepsis, was suppressed with empagliflozin treatment; additionally, secretion of TNF- α and IL-1β was reduced. This is potentially beneficial in case of COVID-19 infection which eventually cause immune activation and enhanced cytokine release (102). Anti-inflammatory effects of these drugs might ameliorate cytokine storm in the context of severe COVID-19 disease (103) and improve clinical outcome (102). Although significance of this claim has been questioned recently (104).

2.2.4. SGLT2 inhibitors effect in relation to lactate

This class of drugs has potential beneficial effects in relation to lactate. Lactate dehydrogenase (LDH) is a cytosolic enzyme catalyzing lactate formation from pyruvate and vice versa; SARS-CoV-2 virus may cause it to enter the circulation by disrupting cells and tissues (105, 106). During anaerobic conditions, e.g. compromised tissue oxygenation that the virus causes, the pathway for lactate formation from pyruvate is favored (107, 108); and resulting elevated levels of lactate stimulate secretion of pro-inflammatory mediators and OS (105). Dapagliflozin, a member of this class, has been shown to reduce levels of lactate. This drug is reported to lower tissue oxygen consumption, ultimately reducing generation of lactate, in addition to enhancing urinary excretion

of lactate (108,109). This has led to the hypothesis that dapagliflozin can alter the course of and prevent severe COVID-19 as it maintains cytosolic pH and diminishes virus load (105). Reduction of lactate levels is unlikely to be a class effect and only dapagliflozin possibly has such an effect (110).

2.2.5. Risk of diabetic ketoacidosis

A major problem when considering use of SGLT2 inhibitors is the increased risk for diabetic ketoacidosis (DKA) in DM patients in the setting of severe infections like COVID-19 (111, 112). These drugs are associated with a two-fold risk for DKA, vs other antidiabetic agents or placebo (113). Although DKA is relatively rare in T2DM patients, it may become a cause for concern during the present COVID-19 pandemic, as this infection may also precipitate DKA (114, 115). COVID-19 patients who develop DKA usually have concomitant severe hyperglycemia, which necessitates large doses of insulin (115) . In comparison, SGLT2 inhibitor may cause a euglycemic form of acidosis, as rise in glucose levels is suppressed by the drug-induced glucosuria (113), whether use of these drugs can increase COVID-19-associated DKA is unclear. Delay in resolution of ketoacidosis and high mortality in infected patients who develop DKA should discourage use of SGLT2 inhibitors for acute disease management in such patients (116, 117).

2.2.6. Class effect in relation to COVID-19

A few clinical studies were conducted on this class in the context of COVID-19. A study on diabetic hospitalized COVID-19 patients with severe pneumonia, who received SGLT2 inhibitor treatment upon admission, concluded that these drugs lack efficacy against disease progression or towards improving clinical outcome (118). However, Dalan *et al*., reported that in T2DM patients who developed the infection, those with prior SGLT2 inhibitor treatment had a lower risk for needing mechanical ventilation (MV) (69). This finding is important since patients developing acute respiratory distress (ARDS) who require MV usually have high rates of mortality (119).

2.2.7. Use in COVID-19 diabetic patients

Due to minimal untoward effects, outstanding safety and tolerance and multitude of beneficial effects, SGLT2 inhibitors could be potential candidates for management of COVID-19 patients with or without comorbidities (102). Many of the their effects mentioned earlier favorably modulate clinical outcome in those infected with SARS-CoV-2 virus (111). Those who have mild or asymptomatic infection should continue using these drugs with the aim of optimizing glycemic control, in addition to utilizing their beneficial pleiotropic effects. However in those who develop more severe infection requiring hospital admission, it will be wise to discontinue SGLT2 inhibitors in light of possibility of serious DKA, and insulin should be instituted together with good glycemic monitoring (111). Current evidence is still inconclusive for use of this class in this category of patients and their exact role is under study in an ongoing randomized clinical trial (RCT), DARE-19, investigating dapagliflozin in COVID-19 hospitalized patients to assess drug's efficacy to prevent all-cause mortality and related complications in this patient population (120). An individualized treatment algorithm is recommended, until results of studies like DARE-19 become available (121).

2.3. Thiazolidinediones

2.3.1. Mechanism of action

Peroxisome proliferator-activated receptor-γ (PPARγ) is a nuclear receptor expressed on many tissues. It has a regulatory role in the expression of genes related to lipid metabolism, lipogenesis, as well as insulin sensitivity, in addition to modulating gluconeogenesis and inflammation (122, 123). Thiazolidinediones (TZDs) are antidiabetic drugs that are agonists activating PPARγ, thereby boosting tissue sensitivity to insulin in muscle, liver and adipocytes, this decreases tissue insulin requirements and eventually glucose levels (124, 125).

2.3.2. Thiazolidinediones and ACE2 expression

SARS-CoV-2 binding to ACE2 elicits down-regulation of the latter (9), which functions primarily to rid of Ang II, thus action of Ang II continues unopposed, this in turn leads to acute injury in lung (126). Some animal

studies demonstrated that pioglitazone (a TZD) enhanced tissue expression of ACE2 (127), which suggested increased susceptibility to COVID-19 infection in addition to conveying protective effects by reducing lung injury (128). However, this upregulation was confined to insulin sensitive areas (129), while sparing alveolar tissue (128) and cardiac tissue (130).

2.3.3. Effect on insulin sensitivity

Pre-existing insulin resistance (IR) in T2DM patients could affect response to SARS-CoV-2 infections (131), via aggravating inflammatory status (132), eliciting a procoagulant state (133) and increasing CV risk (134), thus the benefits of TZDs in diminishing IR for these patients become evident.

2.3.4. Anti-inflammatory, anti-oxidant and immunomodulatory effects

PPAR-γ depresses inflammation and blocking it could be of utility in managing inflammation and excessive cytokine release in viral respiratory infections like COVID-19 (135), as biomarkers for inflammation are raised during the infection, PPAR-γ agonists like pioglitazone could prove to be of clinical value (136). Beneficial effects of this drug in late stages of severe COVID-19 disease are evident, e.g. as anti-inflammatory effects of pioglitazone were demonstrated through reducing IL-6 and TNFα in normoglycemic IR patients (137) and reducing C-reactive protein and IL-6 in males with advanced kidney disease (138). In addition, via modulating inflammation, it ameliorated lung damage in a mouse model (139), and improved lung status in terms of fibrosis and inflammation (140). By suppressing secretion of pro-inflammatory cytokines (141), notably in adipose tissue, as reported in animal studies (139), the agonists of PPAR-ɣ were suggested to have a beneficial modulatory role in cytokine storm-associated COVID-19 infection, however sufficient evidence from human studies is still lacking. TZDs immunomodulatory influence could theoretically slow COVID-19 progression in late severe stages (128, 131, 135). Based on their anti-oxidant and anti-inflammatory merits, in addition to improving insulin sensitivity and the anti-atherosclerotic potential they have (142–144), and since TZDs were shown to reduce BP in diabetics in clinical studies (145), and reduce stroke recurrence vs placebo in those with history of stroke (146), effectively conferring CV protection during management of COVID-19 (147), it was suggested that TZDs can improve prognosis in diabetic COVID-19 patients (131).

2.3.5. Role in COVID-19 management

The exact role of TZDs in managing COVID-19 in DM patients is, however, still debatable. They are not optimal agents for patients with severe COVID-19 especially those hospitalized, despite their presumed protective CV effects, this is due in part to their inclination to induce fluid retention, edema and increased weight, which are aggravating factor for such patients (146, 148), since COVID-19 may also injure kidney and myocardium (147, 149) and partly also as TZDs are not used in those with hemodynamic, hepatic or cardiac issues which are more likely to be encountered in severe COVID-19 cases (150). This has led some authors to recommend avoiding use of this class in hospitalized patients. In fact, those patients with more severe COVID-19 and those with HF, dropping this class may be warranted (151).Thus, insulin perhaps remains the hypoglycemic agent of choice in hospitalized COVID-19 patients, together with more strict blood glucose monitoring.

2.4. Biguanides

2.4.1. Historical overview

Roots of Biguanide usage as antidiabetic drugs can be traced back to medieval Europe, where parts of galega plant (*Galega officinalis*) were utilized as an early form of diabetes treatment (152). Galega was found to be rich in guanidine (153). Guanidine was found in 1920s to exert a glucose-lowering effect, however it was too toxic for human use (154), and this later led in 1920s to synthesis of mono-and diguanidine derivatives which also showed hypoglycemic effects (155). Metformin (dimethylbiguanide) is a member of the biguanides family of oral antidiabetic drugs (Song, 2016). Metformin was first prepared in 1922 thanks to Werner and Bell (156). It was reported by French physician Sterne in 1957 to treat T2DM (155), and in 1958 it became available in the UK (154). In 1957 and 1958 phenformin and buformin (metformin congeners) were reported to have a good glucose-lowering effect

(157, 158); they later gained popularity and were extensively employed as antidiabetic therapies. However, risk of lactic acidosis was found to be high with buformin and phenformin, with associated deaths reported, and as a result, these were withdrawn later in the late 1970s (154,155) from most markets. This tarnished metformin's reputation as a promising drug. In the 1980s and 1990s, various reports confirmed many of its potential benefits, and this helped regain confidence in its use (154,155). In most countries, metformin remains the only biguanide currently licensed for use.

2.4.2. Mechanism of action of metformin

By phosphorylating AMP-activated protein kinase (AMPK), metformin decreases hepatic gluconeogenesis, hence improving hyperglycemia (159). AMPK activation also enhances liver insulin sensitivity and gut microbiome (160). Metformin is suggested to act via both AMPK-dependent and -independent modes so its mode of improving hyperglycemia maybe more complex than once thought (160). Despite being an old drug, metformin continues to be a first-line option to manage hyperglycemia in T2DM (161), offering advantages like decreasing mortality especially in obese, newly diagnosed T2DM (162).

2.4.3. Metformin, viral entry, and protective lung effects

The safety of metformin as a first-line drug for T2DM during COVID-19 pandemic is still under scrutiny (163). Reducing viral binding by metformin can be theoretically beneficial in the context of COVID-19 disease. Viral entry to cells in the endocytic phase requires acidic pH (164), thus metformin may combat viral infection as it increases pH intracellularly thereby blocking endocytosis (165–167) and hence diminishes virus entry to target sites. Also, metformin-activated AMPK would phosphorylate ACE2 receptors thereby effecting conformational changes in them that hinder viral binding (168, 169). Furthermore, once the virus is inside, downregulation of ACE2 is initiated, which eventually activates pro-inflammatory pro-fibrotic arm of RAS, precipitating cardiopulmonary consequences of COVID-19 (170), hence the dual advantage of metformin (preventing viral entry and sequalae) becomes evident. In addition, some evidence suggests that established fibrotic changes to the lung can be reversed by metformin, leading some authors to speculate that it can be a cure for pulmonary fibrosis induced by COVID-19 (171, 172).

2.4.4. Anti-oxidant and anti-inflammatory effects

Metformin reduces inflammatory biomarker levels in DM patients (173). Poor prognosis of those with COVID-19 and disease severity and mortality are linked to so-called cytokine storm, induced by inflammation (174, 175); metformin have shown anti-inflammatory potential, with cytokine-blocking effects, regardless of diabetic status (176, 177), suggesting that it may improve outcome of DM patients hospitalized for SARS-CoV-2 infection (178–180). Metformin may diminish inflammation and activate adaptive/innate immune responses by various modes, like inducing autophagy, inducing generation of CD8 memory T-cells, M2 macrophages and downregulating gene expression of chemokines/cytokines linked to inflammation (181–183). By activation of AMPK, metformin can also confer protection against OS, (184), additionally, a potential anti-oxidant property of the drug is mediated by modulating catalase and superoxide dismutase (SOD) activities (185). By favorably affecting gut microbiota composition, it can also reduce inflammatory stress (173, 186). All these properties suggest that metformin can combat the cytokine storm and its subsequent tissue damage in diabetics who develop COVID-19 disease (180).

2.4.5. Metformin use and COVID-19 morbidity and mortality

Many cohort observational studies addressed mortality from the SARS-CoV-2 infection in DM patients taking metformin. In DM patients hospitalized for COVID-19 (CORONADO study) and compared to non-metformin users, metformin use prior to admission was associated with lower mortality rate, compared to other DM drugs (73). Lower risk was reported in other studies (187), and in a study on Chinese COVID-19 patients with DM, in-hospital mortality was four times lower among metformin users compared to non-users (188). Likewise, metformin therapy in DM patients who later developed COVID-19 was found in retrospective analysis of over 25 thousand patients to be linked to significant decrease in mortality (189), similar findings were reported in a large scale

meta-analysis (3); poor outcome for COVID-19 was not shown to be linked to use of this drug in another multi-study analysis (190), and in another meta-analysis as well (191). Similarly, reduced risk of death was found in a study on nursing home residents who developed COVID-19, in relation to use of metformin (192). In patients with COVID-19, those receiving metformin had lower hospitalization, ARDS and mortality than other subjects (193). Metformin therapy was found to be linked to significant enhancement of survival (194) in DM patients hospitalized for COVID-19. Thus it may be suggested that while DM is a major mortality risk factor in these patients, the risk appears to be substantially reduced in those taking metformin prior to diagnosis of the infection, hence some authors argued metformin may be protective in subjects with high risk (189). On the other hand, other studies failed to establish clear benefit. Kim *et al*. (195) found metformin not to impact disease severity; similarly, metformin therapy did not lower mortality risk in DM subjects who developed COVID-19 in a study in South Korea (196). Antidiabetic drugs taken at-home, including metformin alone or in combination, showed no association with mortality or adverse clinical outcome in T2DM subjects admitted due to COVID-19 (197). No harm could be attributed to drug use in DM patients with COVID-19 in yet other reports (198, 199).

2.4.6. Risk of COVID-19 progression and lactic acidosis

In contrast, metformin use was found to be linked to higher risk of COVID-19 progression in those with DM (200). Concerns about metformin use in patients with T2DM hospitalized for COVID-19 were raised, in particular in light of the possible risk of lactic acidosis in cases of multiple organ failure (201–203). Despite theoretical benefits at molecular level (discussed above) some authors considered metformin as not recommended in routine COVID-19 management, as dehydration from viral illness especially for DM patients may increase the likelihood of lactic acidosis and hyperglycemia (78), in addition to kidney injury (204). Metformin use was linked to greater incidence of acidosis in DM patients hospitalized for COVID-19 (205), and risk of lactic acidosis was related to developing more severe form of COVID-19 and poor renal function (190), thus those with severe infection should be closely monitored for developing lactic acidosis and deranged renal function (3), and some authors even stated that expert consensus suggests avoiding the drug due to these risks (206, 207); however, these early recommendations have no solid evidence of data or trials to support them currently (180). In contrast, some researchers suggested that risk of lactic acidosis in those with renal or hepatic dysfunction is relatively low, arguably making metformin a suitable candidate for managing infected patients (188), provided that continued use of the drug be coupled to close monitoring of kidney function.

2.5. Sulfonylureas

2.5.1. Mechanism of action

Sulfonylureas block the ATP-sensitive β-cell potassium channels, causing plasma membrane depolarization and enhanced calcium influx and thereby exocytosis of insulin, thus are insulin secretagogues (208). Theoretical grounds for protective effects by sulfonylurea use in COVID-19 patients were suggested by the in vitro observation that E protein, an ion channel on the virus, is blocked by gliclazide, a sulfonylurea (209).

2.5.2. Adverse effects of sulfonylureas

A very common adverse effect of these drugs is hypoglycemia, risk of which is increased in acute illness (210), the occurrence of hypoglycemia is also associated with inappropriate meal intake, which makes their use challenging in acute settings; however, when blood glucose monitoring is feasible, they may still be of use (211). Still, inadequate dietary intake during acute infections like COVID-19 may precipitate an episode of hypoglycemia in the drug users, especially in case of emergency admissions to ICUs (211). While risk of hypoglycemia is increased in patients with COVID-19 in ICUs due to restricted access to food, sulfonylureas can be used in those infected patients whose condition is sufficiently stable as to permit regular meals (212).

Non-selective sulfonylureas are not recommended in the setting of COVID-19, which is associated with risk of cardiac injury, as they bind to both pancreatic and cardiac receptors making the risk higher (213, 214). Selective, newer agents like gliclazide and glimepiride spare the cardiac tissue and could be safer (215).

2.5.3. Sulfonylureas effect on COVID-19 outcome

Several clinical studies explored the impact of this class on outcome of patients with COVID-19. In a retrospective study conducted by Charoenngam *et al*. (216) on adults hospitalized for COVID-19, lower mortality rate was observed for subjects on sulfonylureas, compared to non-users.

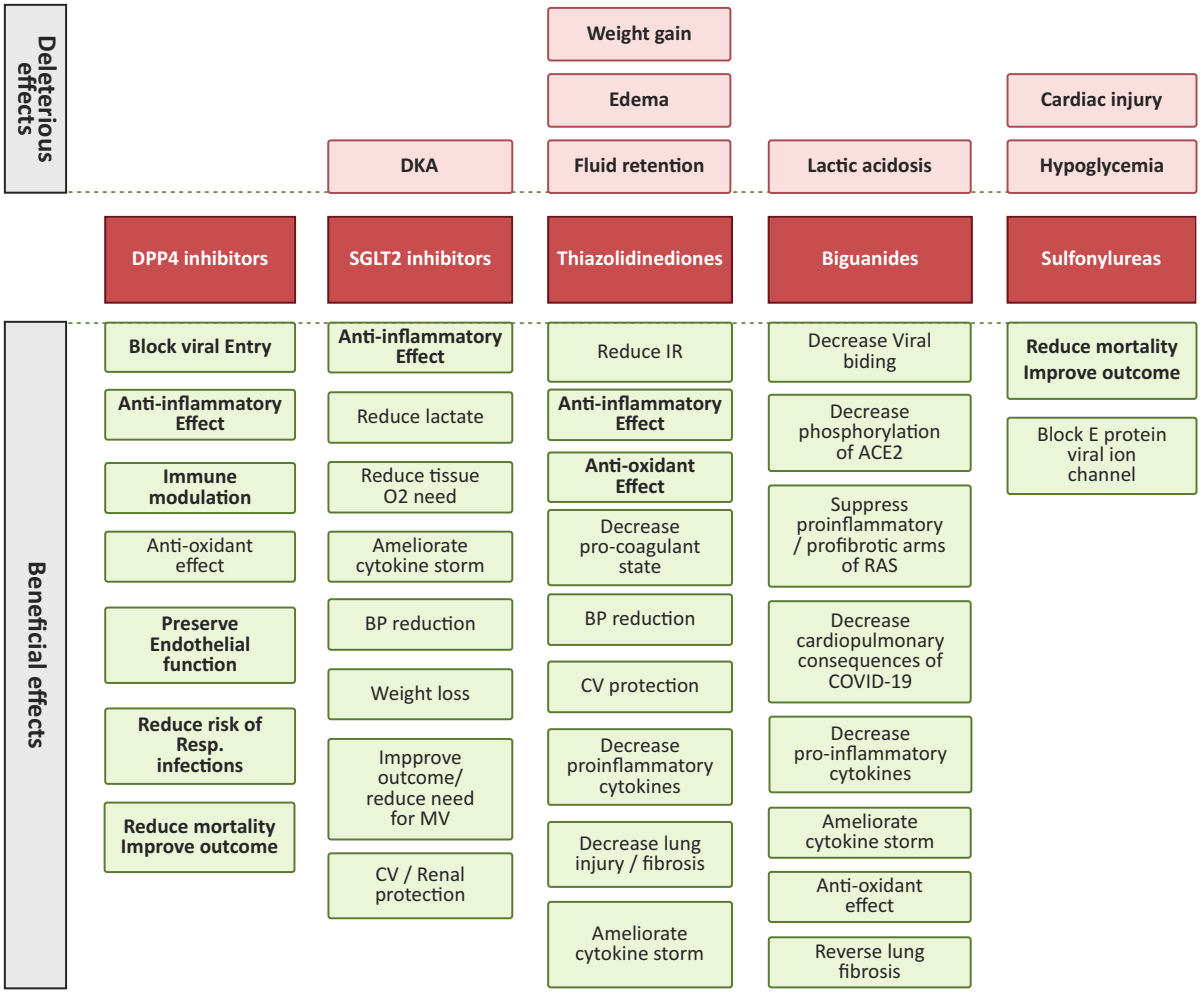

Figure 2. Potential beneficial/ deleterious mechanisms by which antidiabetic drugs impact COVID-19 disease course and outcome. Some effects lead to other listed effects, e.g. BP reduction confers CV protection. DKA, diabetic ketoacidosis; ACE2, angiotensin converting enzyme 2; RAS, renin angiotensin system; CV, cardiovascular; IR, insulin resistance; BP, blood pressure; MV, mechanical ventilation. Created with BioRender.com.

A large nationwide observational study involving entire T2DM population in England (a cohort of almost 2.9 million patients) reported lower risk of mortality from COVID-19 in sulfonylurea users (217). A meta-analysis involving almost 67 thousand patients spanning 31 studies was conducted to explore risk of death and poor outcome of COVID-19 in DM patients, it again found lower risk associated with sulfonylurea use (218).

In effect, this class appears not to increase mortality risk, or cause poor outcome in DM patients who develop this infection, however, studies done in this area are retrospective mostly, more prospective studies, mainly RCTs are required to explore true potential of these drugs. The potential beneficial / deleterious mechanisms by which antidiabetic drugs possibly affect COVID-19 disease and/or its outcome are shown in Figure 2.

3. Discussion and Conclusion

Knowledge about COVID-19 is still evolving, with many aspects yet to be unfolding, partly due to sufficient data lacking. The understanding of the association between glucose-lowering therapies and COVID-19-related death in people with T2DM is still at an early stage.

Discontinuing DPP-4 in case of moderate symptoms or in hospitalized patients is not supported by current evidence, they can be continued in those with non-critical COVID-19 disease (78); furthermore improving poor outcome by introducing DPP4 inhibitors in diabetics with exposure to the infection is also unsubstantiated by evidence (80). SGLT2 inhibitors class is a potential option for COVID-19 patients regardless of presence of co-morbidities (102). Those with mild /asymptomatic COVID-19 disease can carry on using those drugs, but a more severe condition usually prompts withdrawal of these drugs. TZDs place in COVID-19 management in diabetic patients remains controversial, being especially unsuitable for severe/ hospitalized COVID-19 cases despite their protective effects; furthermore, fluid retention, edema and weight gain can aggravate COVID-19 patient's condition; thus avoiding TZDs may actually be warranted.

Metformin diminishes viral binding to host cells, additionally, metformin-activated AMPK phosphorylates ACE2 receptors thereby effecting conformational changes in them that hinder viral binding (168,169). Metformin may reverse established fibrotic lung changes, leading to speculations that it can be a cure for pulmonary fibrosis induced by COVID-19 (171, 172). Anti-inflammatory effects, with cytokine-blocking consequences, were shown also by the drug (176, 177). Additionally, by favorably altering gut microbiota composition, metformin may mitigate inflammatory stress (173, 186); additionally, it can be protective against OS, (184). Thus metformin supposedly improves outcome of DM patients hospitalized for SARS-CoV-2 infection (178–180). Safety issues about metformin use in diabetics hospitalized for COVID-19 were raised, in particular in light of the possible risk of lactic acidosis, leading some authorities to not recommending its use in routine COVID-19 management, thus those with severe infection should be closely monitored for developing lactic acidosis and deranged renal function (3), however, no solid evidence exist to support avoiding metformin currently (180). Finally, sulfonylureas exhibit an extremely common adverse effect which is hypoglycemia, risk of which is increased in acute illnesses (210) like COVID-19. Additionally, non-selective sulfonylureas are not recommended in the setting of COVID-19, which is associated with risk of cardiac injury (213, 214). Clinical studies on this class showed lower risk of mortality from COVID-19 (217), and lower risk of death and poor outcome of COVID-19 in DM patients (218), thus this class appears not to increase mortality risk, or cause poor outcome in DM patients with COVID-19 infection.

In conclusion, currently, expert recommendations are no different from those concerning management of DM patients with severe infections (78). Optimum glycemic control may minimize severity of COVID-19 disease (199, 219). In daily practice, glycemic control and other benefits of DM drugs need not jeopardized by changing /removing DM drugs in an effort to improve outcome from COVID-19 infection (217). However, glycemic control for DM patients is challenging during acute/severe illness like SARS-CoV-2 infection, thus insulin may be considered instead under such circumstances (220, 221); insulin perhaps remains the hypoglycemic agent of choice in hospitalized COVID-19 patients, together with more strict blood glucose monitoring. Evidence of a particular hypoglycemic class being superior to others in management of DM patients who develop COVID-19 is still unsubstantial (222). Well-conducted observational studies, many of which are cited here, provide insufficient evidence for strong protective or deleterious associations. Thus, a dramatic change in current practices in managing patients with T2DM seems unwarranted, at least until double-blind RCTs providing more solid evidence are conducted.

Conflict of Interest

The authors have no conflicts of interest regarding the publication of this article.

Adherence to Ethical Standards

Not applicable. This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

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