



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations



Awadhesh Kumar Singh ^{a,*}, Ritesh Gupta ^b, Amerta Ghosh ^b, Anoop Misra ^{b, c, d}

^a G.D Hospital and Diabetes Institute, Kolkata, India

^b Fortis CDOC Hospital, Chirag Enclave, New Delhi, India

^c National Diabetes, Obesity and Cholesterol Foundation, New Delhi, India

^d Diabetes Foundation, New Delhi, India

ARTICLE INFO

Article history:

Received 3 April 2020

Received in revised form

4 April 2020

Accepted 4 April 2020

ABSTRACT

Background and aims: High prevalence of diabetes makes it an important comorbidity in patients with COVID-19. We sought to review and analyze the data regarding the association between diabetes and COVID-19, pathophysiology of the disease in diabetes and management of patients with diabetes who develop COVID-19 infection.

Methods: PubMed database and Google Scholar were searched using the key terms 'COVID-19', 'SARS-CoV-2', 'diabetes', 'antidiabetic therapy' up to April 2, 2020. Full texts of the retrieved articles were accessed.

Results: There is evidence of increased incidence and severity of COVID-19 in patients with diabetes. COVID-19 could have effect on the pathophysiology of diabetes. Blood glucose control is important not only for patients who are infected with COVID-19, but also for those without the disease. Innovations like telemedicine are useful to treat patients with diabetes in today's times.

© 2020 Diabetes India. Published by Elsevier Ltd. All rights reserved.

1. Background

The disease burden of coronavirus infectious disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) has been increasing continuously with more than a million confirmed patients and more than 45 thousand deaths globally [1]. With a high prevalence of diabetes, it is important to understand the special aspects of COVID-19 infection in people with diabetes. This becomes even more important, as most parts of the world are seeing restrictions on mobility of patients in order to contain the pandemic. Recently our group has published an article highlighting special considerations in the management of diabetes in today's times with COVID-19 pandemic [2]. Much more data from various parts of world has accumulated since then about the association between diabetes and COVID-19, management of diabetes in those with COVID-19 infection, and innovative strategies for medical consultation in view of limited access to healthcare facilities for patients with chronic diseases.

2. Aims of the review

This review aims to collate currently available data about diabetes and COVID-19 infection. It specifically looks at the relation between diabetes and COVID-19 in terms of epidemiology, pathophysiology and therapeutics. The review is updated till the time of writing; however, the data is evolving, and the conclusions made here might change later.

3. Methods

We searched PubMed database and Google Scholar using the key terms 'COVID-19', 'SARS-CoV-2', 'diabetes', 'antidiabetic therapy' up to April 2, 2020. Full texts of the retrieved articles were accessed.

4. Association of diabetes with acute viral pandemics in the past

Diabetes and associated complications can increase the risk of morbidity and mortality during acute infections due to suppressed innate and humoral immune functions. The levels of glycosylated

* Corresponding author.

E-mail address: draksingh_2001@yahoo.com (A.K. Singh).

hemoglobin (HbA1c) > 9% have been linked to a 60% increased risk of hospitalization and pneumonia-related severity during bacterial infection [3]. Past viral pandemics have witnessed the association of diabetes to increased morbidity and mortality. Diabetes was considered as independent risk factor for complications and death during 2002–2003 outbreak of Severe Acute Respiratory Syndrome (SARS-CoV-1) [4]. Similarly, the presence of diabetes tripled the risk of hospitalization and quadrupled the risk of intensive care unit (ICU) admission during Influenza A (H1N1) infection outbreak in 2009 [5]. During the 2012 outbreak of Middle East Respiratory Syndrome Coronavirus (MERS-CoV), diabetes was prevalent in nearly 50% of population and the odds ratio (OR) for severe or critical MERS-CoV ranged from 7.2 to 15.7 in diabetic cohort [6] as compared to overall population. Mortality rate in patients with MERS who had diabetes was 35% [7,8].

5. Association of diabetes in COVID-19 patients

Emerging data suggests that COVID-19 is common in patients with diabetes, hypertension, and cardiovascular disease (CVD), although the prevalence rate varied in different studies as well in country-wise data. In the pooled data from the 10 Chinese studies (n = 2209) on characteristics of comorbidities in patients with COVID-19, Singh et al. [9] have reported a prevalence of hypertension, diabetes and CVD in 21%, 11%, and 7% patients, respectively. Similarly, in a meta-analysis of 8 trials that included 46,248 COVID-19 patients, Yang et al. [10] reported a prevalence of 17%, 8%, and 5% for hypertension, diabetes and CVD respectively, in patients with COVID-19. Epidemiology Working Group of Chinese Center for Disease Control and Prevention that investigated 20,982 patients of COVID-19 have shown that hypertension, diabetes and CVD were associated in nearly 13%, 5% and 4% of patients respectively [11]. In contrast, an Italian study by Onder et al. found diabetes in nearly 36%, while CVD was associated in nearly 43% of 355 patients admitted with COVID-19 [12]. Similarly, in a small study of 24 patients from United States, Bhatraju et al. [13] reported diabetes to be associated with 58.0% patient with COVID-19. While the study from the COVID-19 surveillance group of Italy (n = 481) has shown that 34% patients with COVID-19 had diabetes who died, the COVID-19 response team from Centers for Disease Control and Prevention

(CDC), USA reported a prevalence of 11% from the data of 7162 COVID-19 patients [14,15]. Table 1 summarizes the prevalence of these comorbidities in all available studies to-date in patients with COVID-19 [11–27].

It should be noted here that these findings could be a mere reflection of the high prevalence of diabetes across the globe including China (being the diabetes capital of the world), and thus causality cannot be inferred from the observed elevated proportions.

6. Morbidity and mortality in diabetic cohorts with COVID-19

Evolving data also suggest that patients of COVID-19 with diabetes are more often associated with severe or critical disease varying from 14 to 32% in different studies [15–18,20,22,24]. Wang et al. [20] in a study of 138 patients reported that 72% patients of COVID-19 with comorbidities including diabetes required admission in ICU, compared to 37% of patients without comorbidities. In an analysis of 201 patients with COVID-19, Wu et al. [24] found that diabetic patients had a hazard ratio (HR) of 2.34 (95% CI, 1.35 to 4.05; p = 0.002) for acute respiratory syndrome (ARDS). However, in the meta-analysis of 8 studies (n = 46,248) by Yang et al. [10] the odds ratio (OR) of severe COVID-19 was not significantly higher in patients with diabetes (OR, 2.07; 95% CI, 0.89 to 4.82), unlike hypertension (OR, 2.36; 95% CI, 1.46 to 3.83) and CVD (OR, 3.42; 95% CI, 1.88 to 6.22). Another metanalysis of 9 studies from China (n = 1936) by Chen et al. [28] found a significant correlation between COVID-19 severity and diabetes (OR, 2.67, 95% CI; 1.91 to 3.74; p < 0.01). Table 2 summarizes the prevalence of non-severe (mild to moderate) to severe or critical disease in patients with diabetes with COVID-19. Fig. 1 illustrates the graphical representation of non-severe and severe COVID-19 in patients with diabetes.

Interestingly, the prevalence of non-survivors was also higher in diabetic subjects with COVID-19 and it varied from 22 to 31% in different studies [17,21,23,24,27]. Table 3 summarizes the prevalence of survivors and non-survivors among patients with diabetes and COVID-19. Fig. 2 depicts the graphical representation of these data. In a univariate analysis of 191 patients with COVID-19, Zhou et al. [21] found diabetes to have an OR of 2.85 (95% CI, 1.35 to 6.05; p < 0.001) for in-hospital mortality. However, this association of

Table 1
Prevalence of diabetes, hypertension and other co-morbidities in COVID-19.

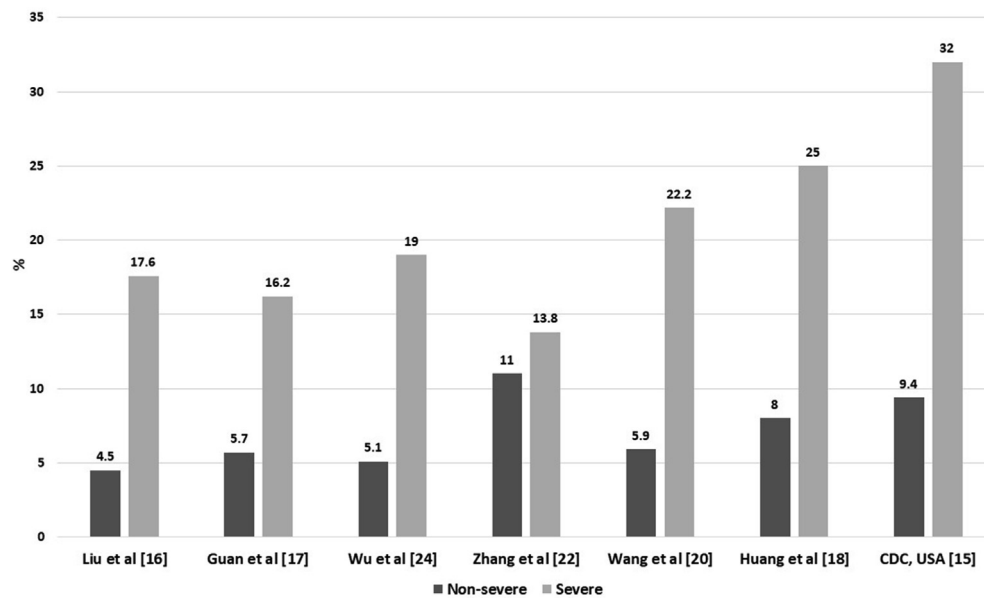
First author	n	Smokers, %	HTN, %	Diabetes, %	CVD, %	COPD, %	CKD, %	CLD, %	Ref.
<i>COVID-19 in China</i>									
Liu et al.	61	6.6	19.7	8.2	1.6	8.2	NR	NR	[16]
Guan et al.	1099	12.6	15.0	7.4	3.8	1.1	0.7	NR	[17]
Huang et al.	41	7.3	14.6	19.5	15.0	2.4	NR	2.4	[18]
Chen et al.	99	NR	NR	12.1	40.0	1.0	NR	NR	[19]
Wang et al.	138	NR	31.2	10.1	19.6	2.9	2.9	2.9	[20]
Zhou et al.	191	6.0	30	19.0	8.0 [#]	3.0	1.0	NR	[21]
Zhang et al.	140	NR	30	12.1	8.6	1.4	1.4	NR	[22]
Yang et al.	52	4.0	NR	17.0	23.0	8.0	NR	NR	[23]
Wu et al.	201	NR	19.4	10.9	4.0	2.5	1.0	3.5	[24]
Guo et al.	187	9.6	32.6	15.0	11.2 [#]	2.1	3.2	NR	[25]
Liu et al.	137	NR	9.5	10.2	7.3	1.5	NR	NR	[26]
Chen et al.	274	7.0%	34.0	17.0	8.0	7.0	1.0	NR	[27]
CCDCP, China	20,982	NR	12.8	5.3	4.2	2.4	NR	NR	[11]
<i>COVID-19 in Italy</i>									
Onder et al.	355	NR	NR	35.5	42.5	NR	NR	NR	[12]
Covid-19 surveillance group, Italy	481*	NR	73.8	33.9	30.1 [#]	13.7	20.2	3.7	[14]
<i>COVID-19 in USA</i>									
Bhatraju et al.	24	22	NR	58.0	NR	4.0	21.0	NR	[13]
CDC COVID-19 Response Team, USA	7162	3.6	NR	10.9	9.0	9.2	3.0	0.6	[15]

[#] reported coronary heart disease only, * COVID-19 patients who died, HTN- hypertension, CVD-cardiovascular disease, COPD-chronic obstructive pulmonary disease, CKD-chronic kidney disease, CLD-chronic liver disease, NR-not reported, Ref.- references, CCDCP- Chinese Center for Disease Control and Prevention, CDC- Centers for Disease Control and Prevention.

Table 2
Prevalence of non-severe versus severe COVID-19 in patients with diabetes.

Study	n	DM (n, %)	Non-severe/Non-ICU care [Mild/moderate] (%)*	ICU care [Severe/Critical] (%)*	p value between non-severe vs. severe COVID-19	Ref.
Liu et al.	61	5 (8.2%)	4.5%	17.6%	0.094	[16]
Guan et al.	1099	81 (7.4%)	5.7%	16.2%	NR	[17]
Wang et al.	138	14 (10.1%)	5.9%	22.2%	0.009	[20]
Wu et al.	201	22 (10.9%)	5.1%	19.0%	0.002	[24]
Zhang et al.	140	17 (12.1%)	11.0%	13.8%	0.615	[22]
Huang et al.	41	8 (15%)	8.0%	25.0%	0.16	[18]
CDC COVID-19 Response Team, USA	7162	784 (10.9%)	9.4%	32.0%	NR	[15]

DM-diabetes mellitus, NR-not reported, ICU- intensive care unit, Ref. References, CDC- Centers for Disease Control and Prevention. * % is calculated from total population having either Non-severe or Severe COVID-19 infection.

**Fig. 1.** Prevalence (%) of severe vs. non-severe COVID-19 in patients with diabetes.**Table 3**
Prevalence of survivor versus non-survivor in COVID-19 patients with diabetes.

Study	n	DM (n, %)	Survivor of COVID-19 (%)*	Non-survivor of COVID-19 (%)*	p value Between non-severe vs. severe	Mortality rate	Ref.
Yang et al.	52	9 (17%)	10%	22%	NR	NR	[23]
Zhou et al.	191	36 (19.0%)	14.0%	31.0%	0.0051	OR 2.85; 95% CI, 1.35 to 6.05; p < 0.001	[21]
Wu et al.	88	16 [#] (18.2%)	12.5%	25.0%	NR	HR 1.58; 95% CI, 0.80 to 3.13, p = 0.19	[24]
Chen et al.	274	47 (17.0%)	14.0%	21.0%	NR	NR	[27]
Guan et al.	1099	81 (7.4%) [@]	6.1% [@]	26.9% [@]	NR	NR	[17]

with ARDS – acute respiratory distress syndrome; [@]Primary composite end point includes admission to intensive care unit, use of mechanical ventilator, or death, OR-odds ratio, HR-hazard ratio, NR-not reported, DM-diabetes mellitus, Ref.- references, * % is calculated from total population either Survived or Non-survived.

diabetes and mortality was no longer significant after a multivariate regression analysis. Nevertheless, in a bivariate cox regression analysis, Wu et al. [24] demonstrated a HR of 1.58 (95% CI, 0.80 to 3.13, p = 0.19) for death in patients with diabetes with COVID-19.

In a summary report of 44,672 patients of COVID-19, The Chinese Center for Disease Control and Prevention reported a case fatality rate (CFR) of 2.3% (1023 deaths among 44,672 confirmed cases). However, the CFR was as high as 10.5% in patients with CVD, 7.3% in diabetes and 6.0% in hypertension [29]. Based on these findings and acknowledging the higher morbidities and mortality associated with comorbidities, researchers have recently proposed that the course of treatment and prognosis of COVID-19 should be

stratified based on the absence or presence of co-morbidities in to type A, B and C. While Type A represents COVID-19 patients with pneumonia with no comorbidities, Type B denotes COVID-19 pneumonia with comorbidities; and Type C denotes COVID-19 pneumonia with multi-organ dysfunction [30].

7. Special aspects of pathophysiology of diabetes and relationship of anti-diabetic drugs in the context of COVID-19

SARS CoV-2, like SARS CoV-1 utilises ACE-2 as receptor for entry into cell [31]. ACE-2 is expressed not only in the type I and II alveolar epithelial cells in the lungs and upper respiratory tract, but

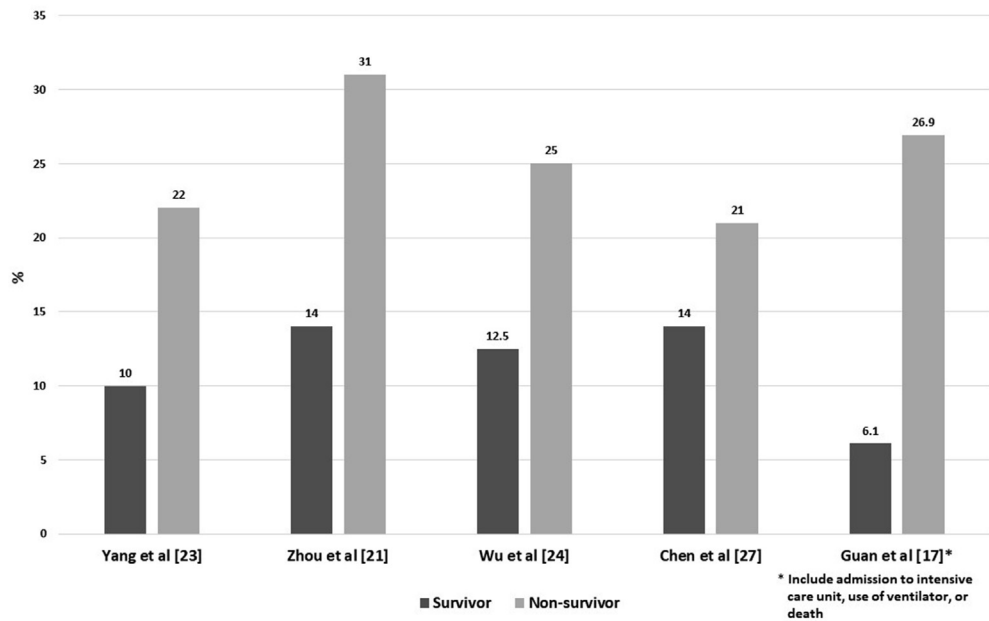


Fig. 2. Prevalence (%) of non-survivor vs. survivor in patients with COVID-19 with diabetes.

also several other locations like heart, endothelium, renal tubular epithelium, intestinal epithelium, and pancreas. S-glycoprotein on the surface of SARS CoV-2 binds to ACE-2 and causes a conformational change in the S-glycoprotein. This allows proteolytic digestion by host cell proteases (TMPRSS2 and Furin) ultimately leading to internalization of the virion [32]. Cellular entry of the virus triggers inflammatory response with recruitment of T helper cells which produce interferon γ . This leads of recruitment of other inflammatory cells leading to a 'cytokine storm' which could lead to organ damage and multi-organ failure seen in severe disease.

As discussed, diabetes is associated with poorer outcomes in COVID-19. A study in 161 patients with COVID-19 in Wuhan found increased time for viral clearance in patients with diabetes [33]. Apart from the usual mechanisms (impaired neutrophil chemotaxis and phagocytosis) by which diabetes predisposes to infections in general, there are several specific factors responsible for increased risk and severity of infection with SARS CoV2 in diabetes.

- Increased ACE-2 Expression:** Diabetic mice have been found to have increased expression of ACE-2 in renal cortex, liver and pancreas, but not in lungs [34]. Recently, a phenome-wide Mendelian randomization study found diabetes to be causally related to ACE-2 expression [35]. Though the significance of these observations is not clear at present, increased ACE-2 expression might predispose people with diabetes to infection with SARS CoV2.
- Increased Furin:** Diabetes is associated with an increase in furin, which is a type-1 membrane-bound protease, belonging to the proprotein convertase subtilisin/kexin family (PCSK). It is involved in the entry of coronaviruses into the cell and increased Furin has been reported in diabetes, which might facilitate viral replication [36].
- Impaired T-Cell function:** Alterations in CD4 lymphocytes have been reported in animal models with MERS [37]. Lymphocytopenia has been observed in patients with COVID-19 and correlated with prognosis [17].
- Increased Interleukin-6 (IL-6):** Several cytokines are increased in COVID-19 infection. Amongst these, IL-6 is increased in diabetes and may play a more deleterious role in Covid-19

infection [38]. Monoclonal antibody against IL-6 receptor (tocilizumab) is being tested in a trial in COVID-19 [39].

7.1. Effect of SARS CoV-2 on blood glucose

ACE-2 receptors are expressed in pancreatic islets and infection with SARS CoV-1 has been seen to cause hyperglycaemia in people without pre-existing diabetes. Hyperglycaemia was seen to persist for 3 years after recovery from SARS indicating a transient damage to beta cells [40]. Though the similar effect has not been reported in COVID-19, it may be important to monitor blood glucose levels in acute stage and during follow up.

7.2. Role of antidiabetic drugs in current context

There is no data on the differential effects of oral antidiabetic drugs on the disease course in COVID-19. Metformin has anti-proliferative and immunomodulatory effects by virtue of inhibition of AMP activated protein kinase and has shown protective role in pneumonia in mouse models [41]. In one study in patients with tuberculosis, patients treated with metformin had better survival than those who did not receive metformin [42]. In a median 6.2 years of follow up of 5266 patients with diabetes, Mendy et al. [43] showed that metformin was significantly associated with a decreased risk of mortality in patients with chronic lower respiratory diseases (HR: 0.30, 95% CI, 0.10 to 0.93), even after the adjustment for multiple confounding factors. In a study of 4321 patients with a follow up of 2-year period, Ho et al. [44] showed metformin users had a significantly lower risk of death (HR, 0.46; 95% CI, 0.23 to 0.92), compared with non-metformin users, in patients with coexistent chronic obstructive pulmonary disease and diabetes. Thiazolidinediones (TZD) seen to increase the risk of pneumonia in a study when compared to sulfonylureas [45]. Experimental studies suggest that pioglitazone reduces steatohepatitis by increasing the ACE-2 expression in liver tissues [46]. This purported increase in ACE-2 expression and its relation to COVID-19 has led some researchers to propose avoiding TZD in patients with diabetes and COVID-19. Experimental studies also suggest that

liraglutide, a GLP-1 receptor agonist increases the ACE-2 expression in lungs in type 1 diabetic rat and improves right ventricular hypertrophy [47]. Implications of these findings in the current context of COVID-19 and its relation to anti-diabetic drugs is not yet fully clear.

7.3. Role of DPP4 enzyme and DPP4 inhibitors

Dipeptidyl peptidase-4 (DPP4) are tissue oligopeptides involved in multiple biological processes that include control of the activity of growth factors, chemokines and bioactive peptides and T-cell activation beside regulating glucose metabolism [48]. The relationship of coronavirus to this cellular type-II transmembrane protein DPP4 (CD26) has generated a great interest recently. DPP4 serves as the receptor for MERS-CoV, in the same way as ACE-2 is the receptor for SARS CoV and SARS CoV2 [49,50]. Experimental studies have suggested that certain polymorphisms of DPP-4 are associated with reduced chance of MERS-CoV infection [51]. This finding might explain the perplexing absence of MERS-CoV cases in Africa, despite the presence of virus in camels, presumably because of frequent presence of protective polymorphisms of DPP-4 in Africans [51]. Moreover, this has generated an immense interest whether use of DPP4 inhibitors (DPP4i) can reduce the viral entry of MERS-CoV. In one *in vitro* study, sitagliptin, vildagliptin and saxagliptin could not block the coronavirus viral entry into cells [52].

Though ACE-2 is recognized as the main receptor for SARS CoV-2, a recent modeling study did not rule out its interaction with CD26 or DPP4 [53]. Moreover, a possible interaction of DPP4 and renin-angiotensin system (RAS) pathways seems to be plausible, although not completely studied. Interestingly, dipeptidyl aminopeptidase I-III cleaves the Angiotensin II (1–8) to Angiotensin III (2–8) and IV (3–8) which has cascading favorable effect through Angiotensin-4 (AT-4) receptors. Similarly, various endo- and oligopeptidase cleaves Angiotensin I (1–10) directly to Angiotensin (1–7) which has a very favorable cascading effect. This suggest that a plausible interaction of non-specific DPP-4i with ACE-2 is theoretically possible, and therefore, this area needs a future research.

In this regard, some of the studies found that co-administration of angiotensin-converting enzyme inhibitors (ACE-I) with DPP4 inhibitors led to an increased sympathetic tone and a consequent adverse hemodynamic effect [54–56]. There has been an interaction observed between ACE-I and vildagliptin where a 4- to 5-folds increased risk of angioedema was noted, possibly due to the diminished degradation of bradykinin or substance P [57]. In contrast, in the experimental study, sitagliptin was shown to inhibit ACE which could partially explain the purported beneficial CV effects [58].

DPP4 inhibitors have been associated with an increased risk of upper respiratory infections, however these agents have not been shown to lead to increased risk of pneumonia [45]. At present, there is insufficient evidence either for or against the use of DPP-4i in patients with diabetes and COVID-19 [59].

8. Special aspects of management of diabetes with COVID-19

8.1. Glycemic control

Glycemic control is important in any patient who has COVID-19. Though there is limited data about the association of blood glucose levels with disease course in COVID-19 at present, data from other infections like SARS and influenza H1N1 has shown that patients with poor glycemic control have increased risk of complications and death [60,61]. Most patients with mild infection and with normal oral intake can continue the usual antihyperglycemic medications. However, it is advisable to discontinue SGLT-2

inhibitors because of the risk of dehydration and euglycemic ketosis. Metformin may also need to be stopped if there is vomiting or poor oral intake. Doses of other antihyperglycemic drugs like sulfonylureas and insulin may have to be altered depending upon the blood glucose levels.

Most hospitalised patient with COVID-19, especially those with respiratory distress, would require insulin. Ideally, patients with very poor oral intake or those on mechanical ventilation would require intravenous insulin infusion with frequent monitoring of blood glucose (every hour or every 2 h, see next section). However, the adjustment of infusion rates would necessitate visit to the patient and increase exposure to the medical personnel. There is a need to explore alternate insulin administration strategies. One of these is use of subcutaneous short acting insulin analogues, an approach which has been used successfully in mild to moderate diabetic ketoacidosis; however, its safety in critically ill patients is less clear [62,63]. Secondly, single dose of basal insulin has been attempted in critically ill patients as in one study from Thailand. This could be an attractive option as it would reduce contact with the patient considerably [64] but needs more research especially in critically sick patients. Finally, insulin pump or continuous subcutaneous insulin infusion (CSII) could be an option and some models have the advantage of altering the insulin rates remotely via Bluetooth [65]. Fully automated closed-loop glucose control has been tried in critical illness and if feasible, could be useful in treating patients with COVID-19 [66].

8.2. Blood glucose monitoring

Blood glucose monitoring poses a special challenge as it necessitates frequent visits to patient's bedside, especially if the patient is critically ill and receiving intravenous insulin. However, attempts could be made to minimize exposure. If the patient is not critically ill, he/she may be given a glucose testing device and self-monitoring may be taught. Blood glucose readings can then be communicated on phone and necessary action taken. Continuous glucose monitoring (CGM) could be of help, especially the systems where the data can be remotely accessed without visiting the patient. Though, there is some evidence of CGM interference with commonly prescribed medications like acetaminophen, atenolol and lisinopril, it has been shown to be useful and reliable in critically ill patients [67,68].

8.3. Role of ACE/ARBs

Treatment with ACE inhibitors and ARB has the potential to cause up regulation of ACE-2 [69]. Mice with coronavirus induced lung injury showed improvement when treated with an angiotensin receptor blocker, losartan [70]. A retrospective analysis showed reduced rates of death and endotracheal intubation in patients with viral pneumonia who were continued on ACE inhibitors [71]. However, a contrary view is that increased expression of ACE-2 could theoretically increase the risk of infection with SARS CoV-2. This could be a concern in people with diabetes who are at already elevated risk of infections because of many other factors. However, there is no evidence to support this hypothesis currently. In a retrospective analysis of 112 COVID-19 hospitalised patients with cardiovascular disease in Wuhan, there was no significant difference in the proportion of ACEI/ARB medication between non-survivors and survivors [72]. In view of lack of robust evidence for either benefit or harm, it is reasonable for patients to continue using ACE inhibitors and ARB, as recommended by European Society of Cardiology Council on Hypertension, European Society of Hypertension and American Heart Association [73–75].

8.4. Role of statins, calcium channel blockers and aspirin

There are several studies about the protective effect of statins in pneumonia [76]. Statins are known to increase ACE-2 levels and may protect against viral entry of SARS CoV-2 [77]. However, this increase in ACE-2 could be counterintuitive in the current context. Nevertheless, statins are known to inhibit Nuclear factor kappa B (NFκB) activation and might help in blunting the cytokine storm [78].

Calcium channel blockers (CCB) have been shown to reduce severity of disease and mortality in patients with pneumonia, presumably by inhibiting calcium influx into the cell [79]. The precise role of these agents in COVID-19 has not been studied, however it seems safe to continue these drugs for control of blood pressure in hypertensive patients. Since CCB has no effect on ACE2 expression, some researchers have proposed its preferable use in patients with COVID-19 and hypertension [80].

Though aspirin has anti-inflammatory properties, it may not be advisable to continue it in patients with sepsis and disseminated intravascular coagulation. However, in patients with underlying coronary artery disease, it needs to be continued as anticoagulant unless otherwise contraindicated.

9. Treatment of diabetes in times of COVID-19 pandemic

Treatment of diabetes poses challenge in the current times when the world is going through an unprecedented pandemic. There are ‘lockdowns’ in most places with people confined at home. Opportunities for exercise are limited and regular walks and visits to gyms or swimming pools are not possible. There is also considerable mental stress because of the unpredictability of the disease as well as social immobility. Alterations in the daily routine affect the dietary intake as well. Stress could lead to inappropriate eating. Access to fresh fruits and vegetables could be limited and there may be a tendency to eat packaged foods high in calories, saturated fat and *trans*-fat. Patients may find it difficult to procure medicines, insulin, needles and glucose strips etc. because of partial or complete lockdowns. The problem becomes more pronounced with elderly who are living alone. All these factors could cause glucose dysregulation and could predispose the patients to complications like infections, hyperosmolar coma, ketoacidosis and even acute cardiac events.

9.1. Measures for good health in patients with diabetes

1. Patients with diabetes need to maintain regularity in daily diet. Care should be taken not to vary the calorie intake markedly. Healthy balanced diet with good amount of protein, fiber and limitation of saturated fats is important to maintain a good glycemic control.
2. Exercise should be continued. Home based exercise like cycling, treadmill, stationary jogging and resistance exercise with small weights are beneficial.
3. Regular intake of antidiabetic drugs and insulin is important and should be emphasized.
4. Telemedicine can be very helpful in these times. Patients can consult their physician via telemedicine and appropriate advice about treatment can be given [81]. An article dealing with telemedicine is under publication in the special issue.
5. Care of feet should be emphasized in order to avoid foot related complications. There are telemedicine temperature mats which can screen for inflammation without having to visit the clinic. The patients who show inflammation can then be called to the clinic [82].

6. Patients need to be educated about the need to visit the hospital urgently in emergency situations like vomiting, drowsiness, shortness of breath, chest pain, weakness of limbs, altered sensorium etc.

10. Conclusion

Diabetes is associated with increased incidence and severity of COVID-19. There is experimental evidence of the effect of diabetes on viral entry into cell and inflammatory response to the infection. It is important to control blood glucose in patients who are infected with COVID-19. Treating diabetes at present with restrictions on movement is challenging; however, innovations like telemedicine can be useful in these trying times.

Declaration of competing interest

We hereby declare that we have no conflict of interest related to this article.

References

- [1] World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report - 73 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_2
- [2] Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr* 2020 Mar 10;14(3):211–2. <https://doi.org/10.1016/j.dsx.2020.03.002>.
- [3] Akbar DH. Bacterial pneumonia: comparison between diabetics and non-diabetics. *Acta Diabetol* 2001;38:77–82.
- [4] Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006;23(6):623–8.
- [5] Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. *Diabetes Care* 2010;33(7):1491–3.
- [6] Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis* 2016;49:129–33.
- [7] Al-Tawfiq JA, Hinedi K, Ghandour J, Khairalla H, Musleh S, Ujayli A, et al. Middle East respiratory syndrome coronavirus: a case–control study of hospitalized patients. *Clin Infect Dis* 2014;59:160–5.
- [8] Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, et al. Risk factors for primary Middle East respiratory syndrome coronavirus illness in humans. *Saudi Arabia 2014 Emerg Infect Dis* 2016;22:49–55.
- [9] Singh AK, Gupta R, Misra A. Comorbidities in COVID-19: outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. *Diabetes Metabol Syndrome Res Rev* 2020. <https://doi.org/10.1016/j.dsx.2020.03.016>. Accepted article in press.
- [10] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis* 2020 Mar 12. <https://doi.org/10.1016/j.ijid.2020.03.017>. pii: S1201-9712(20)30136-3.
- [11] Epidemiology Working Group for Ncip Epidemic Response. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Chin J Epidemiol* 2020;41(2):145–51.
- [12] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *J Am Med Assoc* 2020 Mar 23. <https://doi.org/10.1001/jama.2020.4683>.
- [13] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the seattle region — case series. *NEJM.org* 2020. <https://doi.org/10.1056/NEJMoa2004500>. Published on March 30.
- [14] Covid-19 surveillance group, Italy. https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf.
- [15] Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 — United States, february 12–march 28, 2020. CDC COVID-19 response team. <https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm>.
- [16] Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-Lymphocyte ratio predicts severe illness patients with 2019 novel coronavirus in the early stage. <https://www.medrxiv.org/content/10.1101/2020.02.10.20021584v1>.
- [17] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. <https://www.nejm.org/doi/full/10.1056/NEJMoa2002032>.
- [18] Huang C, Xiang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506.
- [19] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in

- Wuhan, China: a descriptive study. *Lancet* 2020;395:507–13.
- [20] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in wuhan, China. *J Am Med Assoc* 2020;323(11):1061–9.
- [21] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Published Online March 2020;9. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3).
- [22] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020 Feb 19. <https://doi.org/10.1111/all.14238> [Epub ahead of print].
- [23] Yang X, Yu Y, Shu H, Xia J, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020. [https://doi.org/10.1016/S2213-2600\(20\)30079-5](https://doi.org/10.1016/S2213-2600(20)30079-5). Published Online February 21, 2020. [Accessed 27 March 2020].
- [24] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in wuhan, China. *JAMA Intern Med*. Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994 (Accessed on March 31, 2020)
- [25] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. doi:10.1001/jamacardio.2020.1017. Published online March 31, 2020.
- [26] Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J* 2020. <https://doi.org/10.1097/CM9.0000000000000744>. 00:00–00.
- [27] Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020;368:m109. <https://doi.org/10.1136/bmj.m1091>.
- [28] Chen Y, Gong X, Guo J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. <https://www.medrxiv.org/content/10.1101/2020.03.25.20043133v1>.
- [29] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *J Am Med Assoc* 2020 Feb 24. <https://doi.org/10.1001/jama.2020.2648>.
- [30] Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, Jiang B. Comorbidities and multi-organ injuries in the treatment of COVID-19. Published Online March 9, [https://doi.org/10.1016/S0140-6736\(20\)30558-4](https://doi.org/10.1016/S0140-6736(20)30558-4). [Accessed 31 March 2020].
- [31] Vaduganathan M, Vardeny O, Michel T, McMurray JVV, Pfeffer MA, Solomon SD. Renin–angiotensin–aldosterone system inhibitors in patients with covid-19. *N Engl J Med* March 30, 2020. <https://doi.org/10.1056/NEJMs2005760>.
- [32] Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *bioRxiv* 2020;2020.01.31.929042.
- [33] Chen X, Hu W, Ling J, Mo P, et al. Hypertension and diabetes delay the viral clearance in COVID-19 patients. *medRxiv* 2020;2020.2022.20040774.
- [34] Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE and ACE2 287 expression within different organs of the NOD mouse. *Int J Mol Sci* 2017;18.
- [35] Rao S, Lau A, and So H-C. Exploring diseases/traits and blood proteins causally related to 284 expression of ACE2, the putative receptor of 2019-nCoV: a Mendelian Randomization analysis. vol. 285 *medRxiv*: 2020.2003.2004.20031237, 2020.
- [36] Fernandez C, Rysa J, Almgren P, Nilsson J, Engstrom G, Orho-Melander M, Ruskoaho H, Melander O. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. *J Intern Med* 2018;284:377–87.
- [37] Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. *JCI Insight* 2019;4(20):131774. <https://doi.org/10.1172/jci.insight.131774>. pii.
- [38] Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. *Diabetes Metab Res Rev* 2020 Mar 31. <https://doi.org/10.1002/dmrr.3321>. e33213321.
- [39] Chinese Clinical Trial Registry. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). 2020. <http://www.chictr.org.cn/%0Dshowprojen.aspx?proj=49409>. [Accessed 6 March 2020].
- [40] Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* 2010;47(3):193–9. <https://doi.org/10.1007/s00592-009-0109-4>.
- [41] Kajiwara C, Kusaka Y, Kimura S, Yamaguchi T, et al. Metformin mediates protection against Legionella pneumonia through activation of AMPK and mitochondrial reactive oxygen species. *J Immunol* 2018;200(2):623–31. <https://doi.org/10.4049/jimmunol.1700474>.
- [42] Zhang M, He JQ. Impacts of metformin on tuberculosis incidence and clinical outcomes in patients with diabetes: a systematic review and meta-analysis. *Eur J Clin Pharmacol* 2020 Feb;76(2):149–59. <https://doi.org/10.1007/s00228-019-02786-y>.
- [43] Mendy A, Gopal R, Alcorn JF, Forno E. Reduced mortality from lower respiratory tract disease in adult diabetic patients treated with metformin. *Respirology* 2019 Jul;24(7):646–51.
- [44] Ho T, Huang C, Tsai Y, et al. Metformin use mitigates the adverse prognostic effect of diabetes mellitus in chronic obstructive pulmonary disease. *Respir Res* 2019;20:69. <https://doi.org/10.1186/s12931-019-1035-9>.
- [45] Gorricho J, Garjón J, Alonso A, Celaya MC, et al. Use of oral antidiabetic agents and risk of community-acquired pneumonia: a nested case-control study. *Br J Clin Pharmacol* 2017;83(9):2034–44. <https://doi.org/10.1111/bcp.13288>.
- [46] Zhang W, Xu YZ, Liu B, Wu R, Yang YY, Xiao XQ, Zhang X. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. *Sci World J* 2014 Jan 14;2014:603409. <https://doi.org/10.1155/2014/603409>.
- [47] Romani-Pérez M, Outeiriño-Iglesias V, Moya CM, Santisteban P, González-Matías LC, Vigo E, Mallo F. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. *Endocrinology* 2015 Oct;156(10):3559–69.
- [48] Mentlein R. Dipeptidyl-peptidase IV (CD26)—role in the inactivation of regulatory peptides. *Regul Pept* 1999 Nov 30;85(1):9–24.
- [49] Gierer S, Bertram S, Kaup F, et al. The spike protein of the emerging beta-coronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2, and is targeted by neutralizing antibodies. *J Virol* 2013 May;87(10):5502–11.
- [50] Qian Z, Dominguez SR, Holmes KV. Role of the spike glycoprotein of human Middle East respiratory syndrome coronavirus (MERS-CoV) in virus entry and syncytia formation. *PLoS One* 2013;8(10):e76469. <https://doi.org/10.1371/journal.pone.0076469>.
- [51] Kleine-Weber H, Schroeder S, Krüger N, Prokscha A, Naim HY, Marcel A, et al. Polymorphisms in dipeptidyl peptidase 4 reduce host cell entry of Middle East respiratory syndrome coronavirus. *Emerg Microb Infect* 2020;9(1):155–68.
- [52] Raj VS, Mou H, Smits SL, Dekkers DHW, Muller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature* 2013 Mar 14;495(7440):251–4.
- [53] Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. *Emerg Microb Infect* 2020 Mar 17;9(1):601–4. <https://doi.org/10.1080/22221751.2020.1739565>.
- [54] Jackson EK, Dubinon JH, Mi Z. Effects of dipeptidyl peptidase iv inhibition on arterial blood pressure. *Clin Exp Pharmacol Physiol* 2008;35:29–34.
- [55] Marney A, Kunchakarra S, Byrne L, et al. Interactive hemodynamic effects of dipeptidyl peptidase-IV inhibition and angiotensin-converting enzyme inhibition in humans. *Hypertension* 2010;56:728–33.
- [56] Devin JK, Pretorius M, Nian H, et al. Substance P increases sympathetic activity during combined angiotensin converting enzyme and dipeptidyl peptidase-4 inhibition. *Hypertension* 2014;63:951–7.
- [57] Brown NJ, Byiers S Carr D, Maldonado M, Warner BA. DPP-4 inhibitors use associated with increased risk of ACE-inhibitors associated angioedema. *Hypertension* 2009 Sep;54(3):516–23.
- [58] Abouelkheir M, El-Metwally TH. Dipeptidyl peptidase-4 inhibitors can inhibit angiotensin converting enzyme. *Eur J Pharmacol* 2019 Nov 5;862:172638.
- [59] Iacobellis G. COVID-19 and Diabetes: can DPP4 inhibition play a role? *Diabetes Res Clin Pract* 2020 Mar 26;108125. <https://doi.org/10.1016/j.diabres.2020.108125>.
- [60] Yang JK, Feng Y, Yuan MY, Yuan SY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med* 2006 Jun;23(6):623–8.
- [61] Badawi A, Ryoo SG. Prevalence of diabetes in the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus: a systematic review and meta-analysis. *J Public Health Res* 2016;5(3):733. <https://doi.org/10.4081/jphr.2016.733>.
- [62] Razavi Z, Maher S, Fredmal J. Comparison of subcutaneous insulin aspart and intravenous regular insulin for the treatment of mild and moderate diabetic ketoacidosis in pediatric patients. *Endocrine* 2018;61(2):267–74. <https://doi.org/10.1007/s12020-018-1635-z>.
- [63] Tran KK, Kibert 2nd JL, Telford ED, Franck AJ. Intravenous insulin infusion protocol compared with subcutaneous insulin for the management of hyperglycemia in critically ill adults. *Ann Pharmacother* 2019;53(9):894–8. <https://doi.org/10.1177/1060028019841363>.
- [64] Bhurayanontachai R, Rattanaprat T, Kongkamol C. Comparison of glycemic control between continuous regular insulin infusion and single-dose subcutaneous insulin glargine injection in medical critically ill patients. *Indian J Crit Care Med* 2018;22(3):174–9. https://doi.org/10.4103/ijccm.IJCCM_273_17.
- [65] Lee SW, Im R, Magbual R. Current perspectives on the use of continuous subcutaneous insulin infusion in the acute care setting and overview of therapy. *Crit Care Nurs Q* 2004;27(2):172–84.
- [66] Leelarathna L, English SW, Thabit H, Caldwell K, et al. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. *Crit Care* 2013;17(4):R159. <https://doi.org/10.1186/cc12838>.
- [67] Basu A, Slama MQ, Nicholson WT, Langman L, Peyser T, Carter R, Basu R. Continuous glucose monitor interference with commonly prescribed medications: a pilot study. *J Diabetes Sci Technol* 2017;11(5):936–41. <https://doi.org/10.1177/1932296817697329>.
- [68] Schuster KM, Barre K, Inzucchi SE, Udelsman R, Davis KA. Continuous glucose monitoring in the surgical intensive care unit: concordance with capillary glucose. *J Trauma Acute Care Surg* 2014;76(3):798–803. <https://doi.org/10.1097/TA.000000000000127>.

- [69] Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. *Pharmacol Res* 2017;125:21–38.
- [70] Yang P, Gu H, Zhao Z, Wang W, Cao B, Lai C, Yang X, Zhang L, Duan Y, Zhang S, Chen W, Zhen W, Cai M, Penninger JM, Jiang C, Wang X. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Sci Rep* 2014;4:7027.
- [71] Henry C, Zaizafoun M, Stock E, Ghamande S, Arroliga AC, White HD. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. *SAVE Proc* 2018;31(4):419–23.
- [72] Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, He MA, Cheng LX, Huang K, Zeng QT. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. *Zhonghua Xinxueguanbing Zazhi* 2020 Mar 2;48. <https://doi.org/10.3760/cma.j.cn112148-20200220-00105> (0): E004.
- [73] Position statement of the ESC Council on hypertension on ACE-inhibitors and angiotensin receptor blockers. Mar 11 2020. [https://www.escardio.org/Councils/Council-on-Hypertension-\(CHT\)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang](https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang).
- [74] ESH statement on COVID-19. <https://www.eshonline.org/spotlights/esh-statement-on-covid-19/>; March 12, 2020.
- [75] HFSA/ACC/AHA statement addresses concerns Re: using RAAS antagonists in COVID-19. <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>.
- [76] Batais MA, Khan AR, Bin Abdulhak AA. The use of statins and risk of community-acquired pneumonia. *Curr Infect Dis Rep* 2017;19(8):26. <https://doi.org/10.1007/s11908-017-0581-x>.
- [77] Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. *mBio* 2020 Mar 20;11(2). <https://doi.org/10.1128/mBio.00398-20>. pii: e00398-20.
- [78] Yuan S. Statins may decrease the fatality rate of Middle East respiratory syndrome infection. *mBio* 2015 Aug 11;6(4):e01120. <https://doi.org/10.1128/mBio.01120-15>.
- [79] Zheng L, Hunter K, Gaughan J, Poddar S. Preadmission use of calcium channel blockers and outcomes after hospitalization with pneumonia: a retrospective propensity-matched cohort study. *Am J Therapeut* 2017 Jan/Feb;24(1):e30–8. <https://doi.org/10.1097/MJT.0000000000000312>.
- [80] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020. [https://doi.org/10.1016/S2213-2600\(20\)30116-8](https://doi.org/10.1016/S2213-2600(20)30116-8). published online March 11.
- [81] Hollander JE, Carr BG. Virtually perfect? Telemedicine for covid-19. *N Engl J Med* 2020 Mar 11. <https://doi.org/10.1056/NEJMp2003539>.
- [82] Rogers LC, Lavery LA, Joseph WS, Armstrong DG. All Feet on Deck-The Role of Podiatry during the COVID-19 Pandemic: preventing hospitalizations in an overburdened healthcare system, reducing amputation and death in people with diabetes. *J Am Podiatr Med Assoc* 2020 Mar 25. <https://doi.org/10.7547/20-051>.