REVIEW ARTICLE

Association between cardiometabolic risk factors and COVID-19 susceptibility, severity and mortality: a review

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Abstract

The novel coronavirus, which began spreading from China Wuhan and gradually spreaded to most countries, led to the announcement by the World Health Organization on March 11, 2020, as a new pandemic. The most important point presented by the World Health Organization about this disease is to better understand the risk factors that exacerbate the course of the disease and worsen its prognosis. Due to the high majority of cardio metabolic risk factors like obesity, hypertension, diabetes, and dyslipidemia among the population over 60 years old and higher, these cardio metabolic risk factors along with the age of these people could worsen the prognosis of the coronavirus disease of 2019 (COVID-19) and its mortality. In this study, we aimed to review the articles from the beginning of the pandemic on the impression of cardio metabolic risk factors on COVID-19 and the effectiveness of COVID-19 on how to manage these diseases. All the factors studied in this article, including hypertension, diabetes mellitus, dyslipidemia, and obesity exacerbate the course of Covid-19 disease by different mechanisms, and the inflammatory process caused by coronavirus can also create a vicious cycle in controlling these diseases for patients.

Keywords COVID-19 · Cardio Metabolic Risk Factors · Dyslipidemia · Diabetes mellitus · Hypertension · Obesity

Introduction

The latest pandemic of the coronavirus has affected all components of the human lifestyles and has unfolded the sickness rapidly at some stage in the world. The coronavirus disease of 2019 (COVID-19) has been recognized as 2019-nCOV. This novel virus motives COVID-19 ailment that has comparable signs and symptoms as severe acute respiratory syndrome coronavirus 2 (SARS-COV2) [1]. Since April 10, 2021, a total number of 135 Million cases of COVID-19 occurring in at least 170 countries and territories were reported with relatively 3–4% of fatality rate. [2]. Although not all factors affecting mortality and severity of COVID-19 disorder have now been identified, studies have

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shown that the majority of mortality were amongst patients of > 60 [2].According to previous studies, the prevalence of cardio metabolic risk factors like obesity, diabetes mellitus, hypertension and dyslipidemia in people over 60 years old are significantly higher [3]. Hypertension (HTN) is one of the main cardiovascular comorbidities, but it is still unclear whether the association between HTN and COVID-19 is independent from advanced age or not [4]. SARS COV2 gains entrance to cells through the angiotensin converting enzyme 2(ACE2) [5]. On the same basis, there are many concerns about taking Angiotensin converting enzyme inhibitors (ACEI)/Angiotensin Receptor Blocker (ARB) drugs and making the patient more susceptible to viral host cell entry and propagation [6–9]. Diabetes mellitus (DM) is another cardio metabolic risk factor that seems to be an important factor that changes the severity of the COVID-19 disease [10–13]. Infections especially pneumonia and influenza Hemagglutinin Type 1 and Neuraminidase Type 1 (H1N1), are more common and more severe in patients with type2 diabetes [13–15]. There are several studies on the effects of SARSCOV2 which trigger higher stress conditions leading to hyperglycemia in diabetic patients [16]. Therefore the effects of inflammatory status and changes in the immune system as well as the effect of SARSCOV2 virus on insulin secretion in diabetic patients are still unknown [15]. Reviewing studies will help better control diabetes during the coronavirus pandemic. Dyslipidemia is a critical risk factor of the current approach to cardiovascular disease (CVD) risk management [17, 18]. Among different levels of dyslipidemia which include elevated low-density lipoprotein (LDL), cholesterol levels, or low levels of high-density lipoprotein (HDL) [19], low HDL _C is a strong predictor of CVD progression [18]. Based on the multiple roles of HDL_C in modulating the immune system, antithrombotic, and antioxidants, the use of drugs effective in increasing HDL_C levels can suppress the coagulation cascade as well as platelets over activity, which play a role in the exacerbation of COVID-19 disease and its morbid complications [20]. Obesity is the last cardio metabolic risk factor addressed in the present research. Obesity is commonly defined by body mass index (BMI) [21], and importantly this epidemic disease of the last century has been associated with other cardiovascular diseases, insulin resistance, type 2 diabetes and several cancers [22, 23]. In addition to the role of obesity in reducing the immune responses, causing chronic inflammation, metabolic dysfunction, it is associated with a large number of comorbidities, and the mesenchymal dysfunction in obese patients can exacerbate the cytokine storm caused by COVID-19 disease and promoting pulmonary fibrosis leads to severe form of the disease [24]. Due to the high incidence of cardio metabolic risk factors in the world population and other roles in changing the course of many diseases, in this study, which is a narrative review

article [3], we decided to review the role of COVID-19 and recent pandemic in altering these risk factors such as HTN, DM, dyslipidemia and obesity along with the impact of these metabolic comorbidities in the course of COVID-19 disease in infected people.

Cardio metabolic risk factors and *COVID-19* fatality

The recent crisis that has gripped the world is the outbreak of the novel COVID-19 disease and its rapid worldwide spread. The novel virus is thought to belong to the same family as the Middle East respiratory syndrome (MERS) coronavirus and severe acute respiratory syndrome (SARS) coronavirus, but it is unique in its way [25]. As the main concern of all researchers around the world is several risk factors that cause the severity of COVID-19. The World Health Organization (WHO) indicated that elderly patients, as well as those with underlying medical conditions, are at higher risk of developing severe COVID-19 disease [26]. As of today 10 April, 2021, over 135 million cases are infected by the virus and more than 2.9 million people have lost their lives. Most of the death and severe cases of the disease are believed to be associated with the underlying comorbidities [27].

Introduction to *COVID-19* and hypertension

The coronavirus caused a pandemic worldwide with the severe acute respiratory syndrome and a very high rate of transmission. Comorbidities associated with this infectious disease play an important role in the severity of the disease and its mortality in the affected individuals. High blood pressure (hypertension) is one of the most common comorbidities in severe COVID-19 patients [28]. There are different studies on the association between the severity of COVID-19 disease in people with hypertension and also the higher incidence of this virus in these people. The association between HTN and developing pneumonia was assessed in the UK biobank data of 107,310 patients with high blood pressure with 3% of them developing pneumonia afterward. The data analysis of this study revealed that the risk of respiratory disease is remarkably higher among patients with HTN. These patients were also considered to be at a greater risk of acute and chronic respiratory disease, independent of age, sex, smoking status and BMI. Generalizing these results to COVID-19 is rational and led to many studies that focus on hypertension as a strong indicator of COVID-19 severity[29]. Guan et al. reported data from 1099 confirmed COVID-19 patients, of which the single highest risk factor of infection was HTN in 15% of patients. Among patients with severe form of the disease (173 cases) the

most frequent co-morbidity was HTN(23.7%), and 35.8% of patients demanding intensive care unit(ICU) admission, and mechanical ventilation or those who expired also had HTN as an underlying condition [30].

- *Pathophysiological link between hypertension and COVID-19*

High pressure level (also stated as HBP or hypertension) is when your pressure, the force of blood flowing through your blood vessels, is consistently too high.

Hypertension is a controllable and common risk factor for cardiovascular diseases. The reported prevalence of hypertension varies around the world, with rock bottom prevalence in rural India (3.4% in men and 6.8% in women) and accordingly the highest prevalence in Poland(68.9% in men and 72.5% in women) [31]. Its estimated that 1.13 billion people worldwide are suffering hypertension, most (two-thirds) living in low- and middle-income countries [32]. In Iran the estimated prevalence of hypertension in 30 – 55 and > 55-year-old population are around 23% and 50%, respectively. The prevalence in men was 1.3% less than that in women [33]. One of the most commonly used treatments for hypertensive patients is angiotensin converting enzyme inhibitors (ACEI) or Angiotensin Receptor Blocker(ARB), with 50% of the hypertensive population in the United States using these drugs to control their blood pressure [34]. Preliminary reports from the Wuhan and New York Centers showed that there was a high prevalence of hypertension among people with severe illness as well as hospitalized patients [35, 36]. The predominance of hypertension in studies conducted in several countries, including the United States, China and Italy, showed similar prevalence among COVID-19 infected patients, as 56%, 50% and 49%, respectively. This implies that about 50% of COVID-19 infected patients have a history of hypertension [35, 37, 38]. Despite these observations, the association between hypertension and COVID-19 still remains unclear. While overrepresentation of high blood pressure is seen in patients admitted to hospitals COVID-19, it is uncertain whether this connection is due to the older age of these patients and the presence of other comorbidities including obesity, diabetes mellitus, and chronic kidney disease, or this is just a simple random association. The reason behind the association between HTN and severe form of COVID-19 was evaluated in the study of Kulkarni et al. in which this association was attributed to prevalence of hypertension in older individuals. According to CDC reports about 63% of people over 60 years old are hypertensive [39]. However an alternative explanation is end organ damage in hypertensive patients. Two common complications of

HTN are left ventricular hypertrophy and fibrosis which may make the hypertensive heart considerably vulnerable to SARS-COV2 [40]. The theory of virus (SARS-COV2) entry into host cells via angiotensin converting enzyme 2(ACE2) raised doubts about continuing treatment with ACEI or ARB or discontinuing them in patients with underlying hypertension [41]. Human angiotensin converting enzyme2 (ACE2) is an endothelium bound carboxymonopeptidase with single active site catalytic region whose expression is restricted mainly to endothelial cells of the arteries, arterioles and venules in different organs such as the heart, lungs and kidneys [42]. Figure1 shows the RAAS[1] cascade.

- *COVID-19 and Interaction with Renin-Angiotensin Aldosterone System Inhibitors*

ACE2 plays an important role in several cardiovascular and immune pathways. The binding affinity of the novel coronavirus with ACE2 appears to be stronger than SARS virus which could explain the considerably higher global influence of COVID-19 than the initial SARS [43]. The research of Chen et al. recently identified that human cardiac pericytes have high expression of ACE2 which could also be the target cells of SARS-COV2. Patients with heart failure showed elevated ACE2 expression at both mRNA and protein levels, which further raises the risk of heart attack and the critically ill conditions in patients infected by SARS-COV2 [44].

- *Impact of Renin-Angiotensin Aldosterone System Inhibitors on COVID-19 outcome*

The usage of ACEI (angiotensin converting enzyme inhibitors) and ARB (angiotensin 2 receptor blocker) in the setting of SARS-COV2 infection is a hypothesis which is supported by these findings: 1.replication of a prominent effect in multiple animal studies and models 2. It is revealed that tissues with low expression of ACE2 following the treatment with ACEI/ARB show a considerable increase in their expression of ACE2. 3. Sufficient data is available that the increase in ACE2 expression in response to ACEI/ARB treatment enhances the ability of SARS-COV2 to infect cells 4.epidemiological data have shown that patients with COVID-19 administrated ACEI/ARB have increased morbidity and mortality. But these findings have not been supported by sufficient evidence and reports in further studies [36, 45–49]. The findings of the research of Sriram et al. as a literature review of studies in experimental animals and human

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[1] renin–angiotensin–aldosterone system.
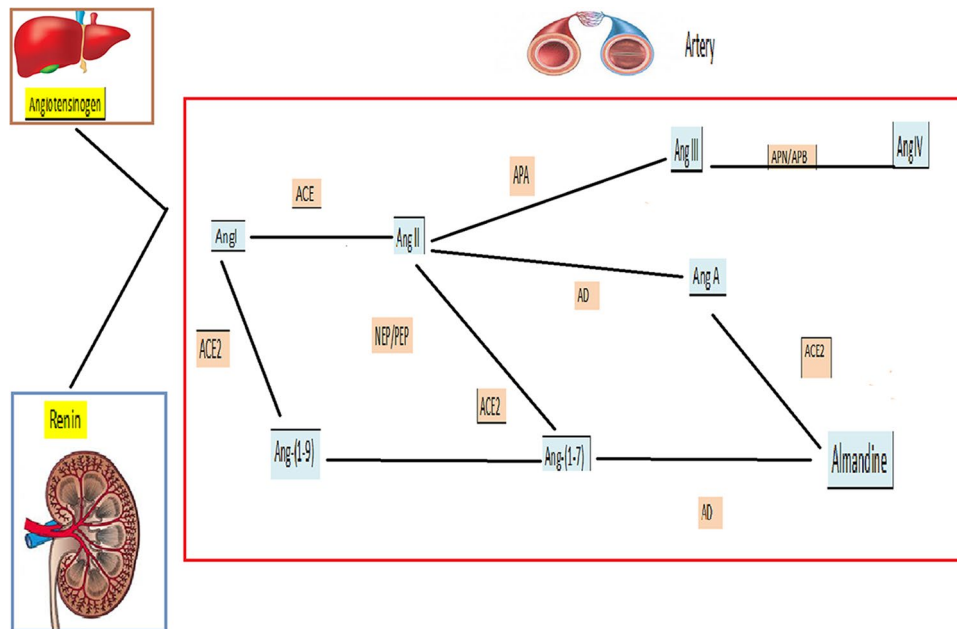
Fig. 1 The Renin angiotensin system cascade: first the liver produces angiotensinogen (AGT) which is secreted in sinusoidal capillaries. Renin is an enzyme produced by juxtaglomerular apparatus of the kidney which is also secreted in the circulation. In the blood stream, angiotensinogen is cleaved by Renin into Ang1, which can also split by ACE2, producing Ang-1–9 by NEP(neutral-endopeptidase) or PEP, producing Ang (1–7) and bye ACE and synthesize Ang-(1–7) or it can be cleaved by APA(aminopeptidase) producing Ang III. Ang II can still have its first amino acid replaced, forming Ang A, which can be cleaved by ACE2 into almandine. This heptapeptide almandine can also be formed by Ang-(1–7) due to the replacement of one amino acid. Ang III can be cleaved by APN (aminopeptidaseN) and form AngIV

objects (n = 12) and evaluating the evidence regarding the impact of administration of ACEI/ARB on ACE2 expression revealed inconsistent effects of RAAS inhibitors on ACE2 levels. Also the hypothesis that use of these drugs would increase SARS-COV2 virus infectivity and/or severity of COVID-19 is therefore not approved by current information recommending the continuation of using ACEI/ARB [50]. On the other hand, many cases of myocardial infarction, myocarditis and cardiomyopathy have been reported in COVID-19 patients and discontinuation of cardio protective drugs, including RAAS inhibitors can lead to clinical heart decompensation [51].

The remarkable point is that a study that investigated COVID-19 patients with HTN treated with ACEI/ARB confirmed that patients receiving ACEI/ARB therapy had a lower risk of the severe form of COVID-19 and also decreased level of IL-6 in their peripheral blood. Moreover, it showed that ACEI/ARB therapy increased the level of CD3 and CD8 T-cells in peripheral blood and reduced the peak viral load compared to other antihypertensive drugs. These findings were the first evidence that supports the benefit of ACEI/ARB in COVID-19 patients. The authors assumed that RAAS inhibitors did not directly inhibit the viral replication but had an indirect antiviral role by regulating the immune system and inhibiting of the inflammatory response [52].

In a retrospective cohort study conducted in 17 referred hospitals affiliated to Iran University of Medical science (IUMS) between February 20th and April 4th 2553 patients with COVID-19 were recruited among which 1569 (61.5%) patients had a history of an underlying diseases. There were 710 patients with history of HTN (45.3%) and among all patients 83(3.3%) received ACEI, 444(17.4%) received ARB. According to the findings of this study administration of ACEI/ARB in COVID-19 patients with concurrent HTN will lead to improvement of clinical outcomes and these medications can be potential therapeutic options and increases the survival probability in these cases [53].

In a retrospective multicenter study by Zhang et al. 1128 adult patients with HTN diagnosed with COVID-19, among which 188 were taking ACEI/ARB and 940 without using them admitted to 9 hospitals in Hubei province, china from December 31 2019 to February 20 2020 were recruited. After adjusting confounding components such as age, gender, comorbidities, and in-hospital drugs, the detected hazard for all-cause mortality was lower within the ACEI/ARB group versus the non-ACEI/ARB group. The results of the study also demonstrated lower risk of COVID-19 mortality in patients who received ACEI/ARB [54].

In a systematic review and met analysis which consisted of 18 studies comparing the occurrence of severe COVID-19 in infected hypertensive patients who received ACEI/ARB vs no treatment or other antihypertensive drugs with 17,311 patients revealed that the use of RAS inhibitors was associated with a significant 16%decreased risk of the combined outcome (death, admission to ICU, mechanical ventilation requirement or progression to severe or critical pneumonia) RR = 0.84(95% Cl: 0.73–0.95). P = 0.007, I^2 = 65% [55].

Another systematic review evaluating the association between different underlying disease and COVID-19 severity and fatality showed that like diabetes, hypertension has been proven to be linked to a significantly higher chance of respiratory infection, making it a substantial indicator of COVID-19 severity.[56]Furthermore this study demonstrated that hypertension is a common comorbidity in COVID-19 death cases as well as higher rate of ICU admission. According to this review similar to other studies mentioned earlier, hypertension treatment should be continued to lower the risk of severity [25].

- *Hypertension and COVID-19 in brief*

To give an abstract of what have been reviewed in this research, HTN is one of the most common comorbidities in COVID-19 patients confirmed by several studies and this condition also plays an important role in exacerbating the infection with SARS-COV2 and leads to higher rate of mortality, ICU admission and the requirement of mechanical ventilation. The theory of ACE receptors which facilitate the entry of SARS-COV2 in their target cells also has been studied abundantly and the effect of RAAS inhibitor drugs like ACEI/ARB on severity and fatality of COVID-19 patients with hypertension are continuously evaluated. Reviewing these studies showed that administration of ACEI/ARB decreases the severity and fatality of COVID-19 significantly and there seems to be a general agreement with most health organizations, who suggested HTN treatments such as ACEI/ARB should be continued in patients with SARS-COV2 infection. In "Table 1" we reviewed several articles investigating the consequences of antihypertensive medications and also the incidence of COVID-19 in these patients. There is still a controversy about the use of these drugs (ACEI/ARB) as a prevention of severe form of COVID-19.

Introduction to *COVID-19* and diabetes

Since the outbreak of novel COVID-19 disease and the problems caused by this pandemic, researchers turned their attention to the factors that contribute to the exacerbation or mortality of the disease. Among these comorbidities, diabetes has been reported as one of the most important risk factors for the adverse outcomes of COVID-19 [65, 66]. Studies have shown that diabetics are at higher risk for respiratory infections [67] and have higher mortality rates than non-diabetics [68]. But other studies suggest that despite the increased risk of severe complications following diabetes, including Adult Respiratory Distress Syndrome (ARDS) and multi-organ dysfunction in COVID-19 disease, diabetes alone is not associated with an increased risk of respiratory infections [69]. There are some theories can reveal diabetic patients are susceptible for COVID-19. According to a Mendelian randomization analysis which showed the diseases, traits and blood proteins that may causally affect ACE2 expression in the lung, diabetes mellitus has the most causal effect on the ACE2 expression. The probable hypothesis is that, diabetes not only can increase the chance of worst outcome in patients, but also can empower the risk of COVID-19 infection [70]. Chen et al. [71] stated that diabetes has adverse effect on viral clearance as a gold standard of the recovery of COVID-19 patients. Therefore, diabetic patients will have poor prognosis during infection.

- *Pathophysiological link between diabetes and COVID-19*

Since the initial outbreak of COVID-19 in China, due to the poor prognosis of this respiratory disease in diabetic patients, much attention has been focused on diabetics. Diabetes is one of the most common diseases in the world with an increasing number of patients in recent decades [72]. The global prevalence of diabetes is currently over 382 million people and it estimated to rise to 592 million by 2035 [73, 74]. Diabetes is one of the foremost important risk factors for cardiovascular disorder [75].

Among the comorbidities associated with COVID-19 patients, the prevalence of diabetes was 17.4 [76]. Due to the global prevalence of diabetes, and its extensive effects on mortality and morbidity, special considerations needs to be made for COVID-19 infection in diabetic patients during the COVID-19 pandemic which affects all dimensions of health care. Reasons for a poor prognosis of COVID-19 infection in diabetic patients are multifactorial.

ACE2 is expressed widely in various organs, including the endocrine part of pancreas [77]. Inflammatory stress and cytokine storm during COVID-19 disease, upregulate ACE2 expression in both mRNA and protein in pancreatic beta cells [78]. SARS-CoV-2 could destroy pancreas islet cells by binding ACE2 receptor [79]. Affecting islet cells by SARS-CoV-2 leads to deteriorating the control of blood glucose level. High blood glucose in patients may decrease immune response to SARS-CoV-2 and inhibit neutrophil chemotaxis, phagocytosis, and intracellular killing, resulting

Table 1 Hypertensive Treatment and COVID-19 Patient Outcomes: various articles on the effect of different hypertensive drugs on the outcome of COVID-19 are shown

Author (publication date)	country	N (HTN)[a]	Type of study	Drugs for HTN	Outcome	Endpoints
Yang et al. [56] March 2 2020(56)	China	112(92)	Retrospective cohort	ACEI/ARB	Neutral	No effect on morbidity mortality
Zhang et al. [57] April 10 2020(57)	China	476(113)	Retrospective cohort	ACEI/ARB	positive	Increased use of ACEI/ARB in moderate vs severe covid19 patients
Zhang et al. [57] April 17 2020(54)	China	1128(1128)	Retrospective cohort	ACEI/ARB	positive	Decreased all-cause mortality
Tadic et al. [58] May 1 2020(58)	Italy	6272(3632)	Population case control study	ACEI/ARB	Neutral	No association between number of patients and severity or mortality rate
Caldeira et al. [59] May 14 2020(59)	Spain	1139(617)	Population case control study	ACEI/ARB	Neutral	No increase in ICU admission or fatal or hospitalize cases
Solaimanzadeh [60] May 12 2020(60)	USA	65(22)	Retrospective cohort	CCB	positive	associated with significantly improved mortality and a decreased risk for intubation and mechanical ventilation in elderly patients hospitalized
Chao Gao et al. [61] June 4 2020(61)	China	2877(850)	retrospective observational study	No drugs/RAAS/non RAAS drugs	Neutral	those without antihypertensive treatment had a significantly higher rate of mortality compared with those with antihypertensive/no difference between RAAS and non RAAS groups
Sardu et al. [62] July 1, 2020(62)	Italy	297(152)	Prospective Cohort Study	ACEI/ARB/CCB	Neutral	Anti-hypertensive drugs didnt affect the prognosis in patients with COVID-19
Khawaja et al. [63] (2020)(63)	UK	406,793(135,604)	Prospective Cohort Study	ACEI, ARB, CCB, b-blockers, diuretics	NEGATIVE	Hospitalization with COVID-19 INCREASE SIGNIFICANTLY with number of antihypertensive drug used
Liabeuf et al. [64] 2020(64)	France	268(152)	Cohort Study	ACEI, ARB, diuretics	NEGATIVE	ICU admission, death increase with use of RASI compared with other antihypertensive drugs and no drugs

in more severe and prolonged disease [80, 81]. Also, Yang et al. study showed that the binding of SARS-CoV to its receptor on endocrine part of pancreas leads to an acute insulin dependent diabetes mellitus [79]. Another reason for hyperglycemia in COVID-19 patients is insulin resistance due to activated immune system [82]. Thus both impaired insulin secretion and insulin resistance together cause diabetic ketoacidosis (DKA) [83].

- *Vicious cycle between COVID-19 and diabetes*

Because of the chronic state of low grade inflammation due to the activation of pro inflammatory mediators and the excessive visceral adipose tissue, diabetic patients have a delay in the activation of Th1 cell-mediated immunity and a late hyperinflammatory response [84]. In a clinical study, which analyzed diabetes in a mouse model of

MERS-CoV infection, Kulcsar et al. [85] detected that level of inflammatory monocyte/macrophages,CD4 + T cells, TNFa, IL6, IL12b and Arg1 expression are lower in diabetic mice but they have higher levels of IL17a expression. Thus, they believed this dysregulated immune response could be the result of more severe and prolonged lung injury.

Based on Chen et al. meta-analysis patients with severe COVID-19 disease had higher blood glucose level than mild group but HbA1c did not differ significantly between groups [71].

Zhang et al. in a retrospective cohort study concluded that the fatality of COVID-19 in diabetic patients is associated with the fasting blood glucose [54]; on the other side, new studies on SARS-CoV-2 patients revealed that the inflammatory storm, also known as cytokine release syndrome (CRS), in diabetic patients, leads to rapid deterioration of COVID-19. In the first published biochemical features of patients with diabetes, Guo et al. [68] found that serum levels of inflammation-related biomarkers such as IL-6, C-reactive protein, serum ferritin and coagulation index, D-dimer, were significantly higher in diabetic patients compared to those without diabetes.

- **Impact of COVID-19 on diabetes management**

Lifestyle changes such as staying at home, social distance and reduction of outdoor activities through the COVID-19 pandemic may result in developing diabetes in susceptible population [86]. Also, these sedentary behaviors may potentially increase the risk of poorer health outcomes in known diabetic patients. Based on World Health Organization (WHO) study on 155 countries, 49% of diabetic patients disrupted their follow-up care for treatment or their specific complications [87]. In a study on diabetic patients hospitalized for COVID-19 in 53 French centers, authors revealed that BMI, microvascular (including severe diabetic retinopathy, diabetic kidney disease and history of diabetic foot ulcer) and macrovascular complications (including ischemic heart disease, cerebrovascular disease and peripheral artery disease) were associated with the risk of tracheal intubation for mechanical ventilation and/or death within 7 days of admission [88].

Another complication of COVID-19 infection in diabetic patients is thrombotic microangiopathy [89]. Diabetic patients based on their glycemic control, duration of disease and other metabolic conditions have different degrees of endothelial dysfunction [90, 91]. Also, COVID-19 infection itself promote the process of endotheliitis in multiple organs as a direct consequence of viral involvement [92]. Super imposed thrombotic microangiopathy to their endothelial dysfunction and SARS-CoV-2 induced endotheliitis cause

serious disease, including renal and neurological disease [89, 93].

Because of hyperglycemia effect on Covid-19 patient's treatment and prognosis, managing hyperglycemia is one of the most important steps in patients care. For critically ill patients insulin is a first choice. The benefits of insulin including toll-like receptors (TLRs) suppression, reduction of proinflammatory nuclear transcription factor kB (NF-kB) activation and modulation of inflammatory mediators could improve the prognosis of COVID-19 patients [94–96]. Among different cytokines which increase in CRS, IL6 may play a major role in COVID-19 patients and IL6 blockade could be beneficial to manage COVID-19-induced CRS in some diabetic patients [97, 98]. Studies have shown that pioglitazone a drug from the family of thiazolidinediones,a common treatment for insulin resistance, has anti-inflammatory effects and significantly can reduce IL6 and TNF-a [99, 100]. The efficacy of Tocilizumab as a treatment for moderate to severe COVID-19, which binds to the IL-6 receptor, could be affected in diabetic patients with hyperglycemia [101, 102]. Patients should follow the instructions to drink adequate amount of fluids and do aerobic activities while staying in quarantine. It is also important to take enough proteins in their diet and avoid smoking because it could exacerbate the corona virus infection. Patients with diabetes also tend to reduce their meetings with their doctor to avoid exposure to COVID-19 but this could lead to the mismanagement of their disease and uncontrolled hyper or hypoglycemia so the health care system need to develop new policies for telehealth services to provide support and care to diabetic patients during this pandemic safely [103].

- **Impact of Diabetes treatment on COVID-19 outcome**

Pharmacological treatment of diabetic patients with COVID-19 disease is associated with considerations. Pharmacological treatments may need to be changed based on the severity of the disease and the likelihood of complications. On the other hand, studies show that some of these classes of antidiabetic drugs may affect the severity or course of COVID-19 disease. In the Fig. 2 we summarized effect of some antidiabetic drugs like Metformin and DPP4 inhibitors on COVID-19 disease which their role is also elaborated in details in the article.

- **Metformin:**

In recent studies some mechanisms of action of metformin on COVID-19 was challengingly discussed. The main mechanism of metformin to effect on glucose is the phosphorylation of AMP-activated protein kinase (AMPK) in hepatocytes [104]. AMP activation cause
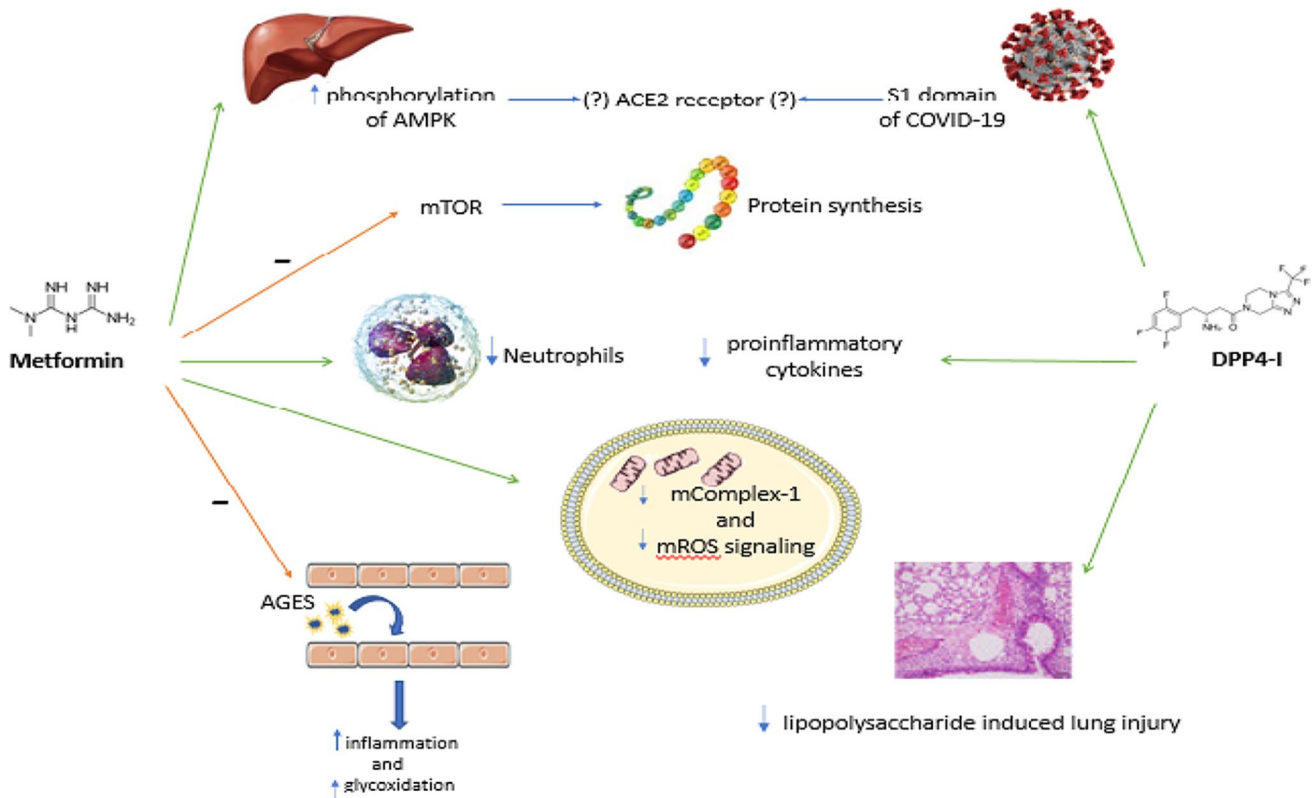
Fig. 2 The relation between antidiabetic drugs such as DDP-4 (Dipeptidyl peptidase 4 Inhibitor) and metformin and COVID-19 infection in a quick review.ACE2 = Angiotensin-converting enzyme 2, AMPK = adenosine monophosphate-activated protein kinase, mTOR = a kinase that in humans is encoded by the MTOR gene, AGES = Advanced glycation end products

the phosphorylation of ACE2 and this, theoretically can change ACE2 receptor and can potentially reduce the risk of COVID-19 [105, 106]. On the other hand, some authors have suggested that metformin increases ACE2 expression and availability in respiratory tract [107].

Among this conflicting data Pal et al. [108] states there is no interaction between ACE2 and metformin and there is no concern to continue metformin.

Metformin is a medication that is commonly prescribed for all type 2 diabetic patients except those with contraindications. It is especially used in obese patients with diabetes mellitus type 2 because the prevalence of obesity and overweight is high in type 2 diabetic patients and obesity itself is a risk factor of poor prognosis in COVID-19 patients [109, 110].

Based on Luo et al. retrospective analysis, patients with diabetes who receiving metformin showed decreased mortality rate compared to diabetics not receiving metformin [111]. Beside antidiabetic features of metformin, it has various effects including cardiorenal protection, anti-inflammatory effects, cell protection and cancer prevention [112–114]. Also metformin was used as an anti-flu drug to treat influenza [115].

One mechanism of the anti-inflammatory effect induced by metformin is the inhibition of advanced glycation end products (AGEs) formation, which enhance inflammation and glycoxidation [116].

Metformin also subside hyperactivation of immune system in many ways including the inhibition of mTOR pathway [117], reduction in neutrophils [118], inhibition of mitochondrial complex1 and suppression of mitochondrial reactive oxygen species (ROS) signalling [119]. Therefore metformin could reduce insulin resistance. Also, Bramante et al. claimed that metformin has protective effect through the reduction of tumor necrosis factor (TNF) alpha more in female than male. Based on their study, mortality reduction of metformin was significantly observed only in female [120].

Another mechanism of metformin is the damage of viral endocytic cycle by affecting the endosomal Na^+/H^+ exchanger, thereby increasing cellular pH [121].

On the other hand, metformin has some side effects such as lactic acidosis and some contraindications including chronic kidney disease and liver failure which raised concerns about using this beneficial drug for hospitalized patients. Actually, metformin alone is not the reason of lactic acidosis. Patient condition such as organ failure,

tissue hypoxia, liver and kidney disease facilitate anaerobic glycolysis process [122, 123].

Gastrointestinal side effects of metformin including nausea, vomiting, diarrhea, flatulence indigestion, abdominal discomfort and dyspepsia which usually resolve after some days of starting treatment [124]. But it should be distinguished from gastrointestinal symptoms of COVID-19.

- **Dipeptidyl peptidase 4 Inhibitor (DPP4 inhibitors)**

Human dipeptidyl peptidase 4 (DPP4 inhibitors), a serine ectopeptidase that is commonly known as cluster of differentiation (CD26) is a functional receptor for MERS-Co-V spike protein [125, 126]. DPP4 inhibitors also has a soluble form (DPP4 inhibitors) in the circulation [127]. DPP4 inhibitors enzyme beside its effects on glucose and insulin metabolism by inactivating and cleavage incretins such as glucagon like peptide1 (GLP-1), has an important role in activation and proliferation of T cells [128, 129]. DPP4 inhibitors cleavage proline- or alanine-containing peptides including growth factors, chemokines, cytokines, neuropeptides, hormones and vasoactive peptides in many organs including lung, kidney, liver and gastrointestinal tract [130, 131]. Most DPP4 inhibitors such as sitagliptin and linagliptin are competitive with substrate, while vildagliptin and saxagliptin act as pseudo-substrates [132, 133]. Between DPP4 inhibitors, sitagliptin has the shorter distance from one of predicted binding site of SARS-CoV-2 [134, 135]. A meta-analysis found that DPP4 inhibitors which block the enzymatic activity of DPP4 inhibitors do not increase the overall risk of respiratory tract infections [136].

Iacobellis claimed that DPP4 inhibitors, might decrease the risk of severity and complications COVID-19 patients with diabetes [128]. Kawasaki et al. studied sitagliptin effects on lipopolysaccharide induced lung injury in mice [137]. They found sitagliptin by inhibiting proinflammatory cytokines including IL-1β, TNFα, and IL-6 could alleviated histological findings of lung injury.

Recent study of Vankadari et al. showed that DPP4 inhibitors may interact with the S1 domain of the viral spike glycoprotein [134]. But based on Tai et al. study, receptor-binding domain (RBD) of Covid-19 binds to human ACE2-expressing 293 T cells not to human DPP4 inhibitors-expressing 293 T cells [138]. By Pitocco et al. opinion, because of not exclusive role of DPP4 inhibitors binding in tropism of the Coronavirus family, DPP4 inhibitors inhibition is not acceptable treatment for Covid-19[139].

- **Glucagon-like peptide-1 (GLP-1) receptor agonists**

GLP-1 receptor agonists such as liraglutide are anti diabetic drug which have anti-inflammatory effects and improve endothelial dysfunction [140, 141]. Reduction of cytokine concentration and pulmonary inflammation in respiratory disease by GLP-1 receptor agonists, could be promising that these agents are beneficial for COVID-19 patients [142–144].

- **Thiazolidinediones**

Thiazolidinediones such as pioglitazone are other anti diabetic agent which decrease insulin resistance in peripheral tissues due to their agonistic effect on peroxisome proliferator-activated receptor g1 (PPARg1) and PPARg2 [145]. Other pioglitazone benefits including reduce monocyte gene and protein expression of cytokines, reduction of lung inflammation by controlling adipose inflammation and the reduction of pulmonary fibrosis brings the idea of adding this class of anti-diabetic agents to the list of COVID-19 drugs [146–148].

- **Sodium–glucose cotransporter type-2 (SGLT2) inhibitors**

Studies showed that sodium–glucose cotransporter type-2 (SGLT2) inhibitors such as dapagliflozin has anti-inflammatory effects on the kidney, cardiovascular system and pancreas and it supposed to be helpful for pulmonary involvement of COVID-19 patients [149, 150]. Although a study on diabetic mice showed that dapagliflozin could reduce respiratory infection, because of the risk of euglycaemic ketoacidosis UK guidelines not recommended to use SGLT2 inhibitors [151, 152].

- **Diabetes and COVID-19 in brief**

To summarize the available data, diabetes is one of the most important and common comorbidities of Covid-19 disease. COVID-19 is a great health issue which the entire world encountered with it and have an effect on everyday lives of people worldwide. Cardio metabolic disease such as diabetes could be affected by this matter and also could change the process of dealing with this infection and got more serious form of it.

In this article we reviewed different studies evaluate the effect of COVID-19 on diabetes and also the effect of diabetes on severity and management of COVID-19 infection and acute respiratory infection caused by it.Diabetes could alter immune system and weakened the immune response against COVID-19 like other infections such as influenza and pneumonia [67].

And according to various studies, the prevalence and mortality of this contagious infection is higher in diabetic patients. SARS-CoV-2 binding to the endocrine part of pancreas, as an expression site of ACE2, and insulin resistance due to hyper activated immune system cause poor control of glucose level in diabetic patients. Immune system responses

such as phagocytosis, and intracellular killing diminished during hyperglycemic state. Thus, diabetic patients are more suspicious for poorer prognosis between patients with COVID-19 [77, 78, 84, 85]. The antidiabetic drugs are the other subjects which have been studied repeatedly nowadays and most studies suggest to continue the use of oral agents during this pandemic and also after infection with coronavirus but in critical patients similar to other diseases it has been suggested to use insulin to have better control over the blood sugar of these patients and also to improve their nutritional status and also the overall outcome of the disease [83, 153].

The last matter addressed in the present research is the management of diabetes during this pandemic. Studies suggest that diabetic patients should follow their antidiabetic drugs as prescribed, have routine aerobic activities, control their glycemic indexes in their diet and check their blood sugar to make sure their diabetes is under control and should stay in touch with their physicians by telephone or over the internet to help them be safe and healthy during the pandemic [103].

- **Introduction to COVID-19 and Dyslipidemia**

Dyslipidemia characterized as elevated low-density lipoprotein (LDL) cholesterol levels, or low levels of high-density lipoprotein (HDL) cholesterol, could be the main risk factor for coronary heart disease (CHD) and stroke. [154] Dyslipidemia is a common disease and according to the US national health and nutrition examination survey conducted from 1999 to 2000, 25% of adults had total cholesterol greater than 239.4 mg per dL or were taking lipid lowering medication [155].

We believe that hyperlipidemia is a potential risk factor for deteriorating COVID-19 patients because obesity and underlying medical conditions such as coronary heart disease and metabolic syndrome are closely related to patients with poor prognosis [36, 156, 157]. Based on a meta-analysis by Hariyanto et al. dyslipidemia is an exacerbation factor in the outcome of COVID-19 patients [158].

Cholesterol is the major neutral lipid of pulmonary surfactant [159]. Thus hypercholesterolemia can dysregulate the protective features of surfactant in alveolar spaces [160]. In other hand, cholesterol is a major structural component of immune cell membranes, elevated level of cholesterol can affect pulmonary immune responses; therefore it can enhance pulmonary inflammation response [161, 162].

- ***Pathophysiological link between Dyslipidemia and COVID-19***
- ***Low-density lipoprotein (LDL)***

SARS-CoV needs oligomeric status of N-terminal fusion peptide to enter into host cells and recent studies showed

cholesterol can facilitate this process [163]. Patients with dyslipidemia have high levels of low-density lipoprotein (LDL). LDL accumulation in macrophages in atherosclerotic plaques and other immune cells, promotes inflammatory responses including augmentation of Toll-like receptor (TLR) signaling, inflammasome activation and the secretion of the pro-inflammatory cytokines such as IL-1B and IL-18 [162]. Cytokine storm in COVID-19 which means the presence of high levels of pro-inflammatory cytokines is associated with severe outcomes [164]. On the other hand, studies have shown that plasma level LDL may be associated with the prognosis of COVID-19 patients. Based on a large retrospective analysis in Wuhan, patients with mild symptoms had hypolipidemia and patients with severe symptoms had more reduced level of LDL and TC [165]. HDL only reduced in critically ill patients but not in mildly infected patients with COVID-19 [165]. Multiple reasons including liver damage and increased metabolism of cholesterol due to hyper inflammation and cytokine storm could explain reduction of LDL level in COVID-19 patients [165, 166]. Due to liver function damage, synthesis of LDL could be reduced and serum liver enzymes include ALT, AST and ALKP will increase. But fewer than 50% of patients had moderate increase of liver enzymes that this show minor effect of virus on patients' liver [165, 167]. Also SARS-CoV-2 could inhibit the activity of many proteins involved in cholesterol metabolism [168, 169]. Also increased vascular permeability through hyper inflammation state can cause LDL leakage. In another theory, exudative fluid in patients' lung due to increased vascular permeability has high level of LDL [170, 171]. Also the degeneration of LDL are increased in COVID-19 patients because of enhanced free radicals from infected host cells [41].

In patients with dyslipidemia, lipotoxicity through accumulation of LDL will cause endothelial dysfunction which activates prothrombotic cascade and eventually leads to vascular thrombosis and cardiovascular complications [172, 173]. Changes in lipid metabolism are an early step in atherogenesis and can cause vessel injury through coagulopathy and endothelial dysfunction [174, 175]. Thus vasculopathy, the independent risk factor promoting disease severity, is related to cholesterol changes in COVID-19 patients [176]. Also in COVID-19 patients, this endothelial dysfunction has other important role because of ACE2 receptor expression, the receptor for SARS-CoV-2, occur in endothelial cells [177].

- ***High-density lipoprotein (HDL)***

Patients with dyslipidemia have low levels of high-density lipoprotein (HDL). HDL-c has potential protective properties in variety of diseases such as cardiovascular disease and viral pneumonia [178]. HDL has ant oxidative,

anti-inflammatory, ant apoptotic, antithrombotic, anti-infective, and vasoprotective effects [179]. A case-controlled study by Deniz et al. found that serum HDL-c levels are lower in patients with community-acquired pneumonia (CAP) and serum total cholesterol/HDL-c ratios might increase proportionally with radiological extent of the disease in CAP patients [180]. HDL plays a major role in the regulation of innate immune response which working on the first lines of body defense mechanism against COVID-19 infection [181].

In a cross-sectional study on 143 patients with confirmed COVID-19, meaningful decrease of HDL-c was found in severe/critical patients contrast mild/moderate patients [182]. HDL negatively regulates T-cell activation and the expression of inflammatory mediators in macrophages by interaction with ABCA1 or ABCG1 [183, 184]. In another retrospective study conducted on 114 COVID-19 patients and 80 healthy controls, patients had significantly decreased serum total cholesterol, HDL-c and LDL-c but there was no difference in serum level of triglyceride between two groups. And between these lipid changes, only HDL-c is associated with the severity of COVID-19 infection between patients [36]. Decreased serum HDL level could be explained by affinity of SARS-CoV-2 spike protein to attach HDL; thus antagonists of HDL receptor could be used as a potential anti-viral treatment [185]. In another theory, massive suppression of metabolism in COVID-19 patients causes dysregulation of apolipoproteins (Apo) like Apo A1 and Apo E [186]. Also, decreased serum level of lecithin cholesterol acyltransferase (LCAT) due to inflammation could change HDL functions [187]. Another mechanism for HDL dysfunction is the inactivation of paraoxinase1 (PON1), an antioxidant enzyme of HDL, in inflammatory condition [188]. Through such mechanism, the reduced level of HDL could be explained.

Furthermore studies have shown that HDL-c concentration is associated with other markers meaningfully. Hu et al. [36] found HDL was negatively correlated with CRP (r = 0.396, P < 0.001) and positively correlated with lymphocytes(r = 0.396, P < 0.001). Studies on death cases in Wuhan showed that elevated CRP as well as declined lymphocytes can be used as indicators for disease deterioration [189].

- *Apolipoproteins (APOs):*

ApoB, the major apolipoprotein of LDL, are oxidized during inflammation. Also anti-inflammatory effects of HDL are diminished during inflammation by decrease of HDL associated Apos and increase of serum amyloid protein A (SAA) [190]. In fact, inflammation may change hepatic gene expression of apolipoproteins and increase binding of SAA which apoa1 levels [191]. In this case, recent studies

declared serum level of SAA as a factor for prognosis of COVID-19 patients [57]. HDL associated lipoproteins such as ApoA1 and ApoM have potential effect on lipid rafts that are enriched in Immune cell receptors such as toll like receptor and T cell receptors [192, 193].

Furthermore ApoE function, as a component of HDL lipoproteins which expressed in lung macrophages and alveolar epithelial cells, could be affected during SARS-CoV-2 infection [194]. As we know IL6 is a major cytokine elevated during the cytokine storm of COVID-19 [195]. In vivo study on mice showed that ApoE-/- animals are more susceptible to acute lung injury during the elevated level of oxLDL due to IL6 induced mechanisms [196]. ApoE4 genotype also was reported as a factor to predict COVID-19 severity. Based on analysis, ApoE4/E4 homozygotes are more suspicious for positive COVID-19 test [194].

Although hypocholesterolemia including decreased level of LDL, HDL and TC have been reported in many advanced diseases, but it can be understood from studies that LDL and HDL level act as markers which could predict poor outcomes in COVID-19 patients [197, 198].

- ***Impact of lipid-lowering drugs on COVID-19outcome***

Actually until now there is no strong evidence on the use of statins in COVID-19 patients. Statins are known for their lipid-lowering, anti-thrombotic, antioxidant and anti-inflammatory benefits; hence, they were suggested to be used in COVID-19 patients [199, 200]. It have been mentioned that COVID-19 disease in patients already using statins, is milder among home care setting [201]. Also Choi et al. in an umbrella review showed that the mortality rate of COVID-19 patients within 28 days was 5.2% and 9.4% in the statin and non-statin groups [202]. Statins lessen cholesterol synthesis by restricting the activity of HMG-CoA reductase.[203]Statins improve endothelial function which plays a major role in pathogenesis of COVID-19 [204–206]. Statins also inhibit the synthesis of other biologically active sterols, oxysterols that have multiple immunomodulatory roles, key isoprenoid intermediates and 25-hydroxycholesterol that involved in the type I interferon antiviral response [207–209].

Based on Zhang et al. study on 13,981 COVID-19 patients, statin therapy significantly reduced the severity and mortality of COVID-19 [210]. Similar to HCV, SARS-CoV-2 is a lipid rich enveloped, positive-strand RNA virus. Based on previous studies on hepatitis C virus (HCV) which showed HCV replication is related with lipid metabolism, fluvastatin administration for chronic HCV patients may reduce virus reproduction rate and increase virus clearance from the blood [211–213]. SARS-CoV-2 has four main structural proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins [214]. The virus

attach to ACE2 receptor which expressed on lipid rafts of lower respiratory tract cells by S protein [215]. It has been proved that atorvastatin upregulate the expression of ACE2 and high level of ACE2 could facilitate possibility of SARS-CoV-2 infection [216, 217]. Also, Lipid rafts play an important role for some certain viruses include SARS-CoV-2 to enter host cells by interaction between S protein and ACE2 receptor [218, 219]. Lipid rafts are discrete lipid domains of the plasma membrane that enriched with cholesterol, glycosphingolipids, and glycosyl-phosphatidylinositol which contain ACE2 receptor [220, 221]. The location of ACE2 on lipid rafts is not clearly understood. Also cholesterol control post-binding processes of virus infection by impressing viral mRNA synthesis in host cells [218]. An important cause of COVID-19 patients' deterioration is ARDS. Statin treatment recommendations for patients with sepsis-associated ARDS and ventilator associated pneumonia (VAP) are conflicting. An observational cohort study showed that statin therapy in patients with sepsis-associated ARDS will improve their outcomes and reduce their mortality rate [222]. Another study stated that pravastatin administration may significantly increase probability of being free from ventilator and reduce patients' mortality rate [223]. On the other hand, some other randomized clinical trials showed that there is no difference between statin therapy and placebo in VAP and sepsis-associated ARDS outcomes [224, 225]. One reason for this conflicting data is subgroup of ARDS and differential response to statin. A randomized controlled trial analysis showed that Simvastatin treatment will significantly improve 28-day survival of hyper inflammatory sub phenotypes rather than hypo inflammatory sub phenotypes; but by rosuvastatin treatment, there was no difference between hyper inflammatory and placebo groups [226, 227]. A recent molecular study in silico showed that statins could block virus entry into cells by inhibition of the main proteinase of SARS-CoV-2 [228]. In this study which compared binding energy of several statins, showed that rosuvastatin, lovastatin, fluvastatin and especially pitavastatin could inhibit main protease (Mpro) of SARS-CoV-2 [228]. However Zho et al. failed to report this interaction [229].

Cellular proliferation require cholesterol, an essential component of cell membranes and the responsible biosynthetic pathway for new cholesterol synthesis is also the source of isoprenoid intermediates used for the prenylation of a large number of intracellular signaling proteins [208]. Statins inhibit protein prenylation by the reduction of isoprenoid intermediates [230]. By this way they could inhibit SARS-CoV-2 infectivity.

By reduce synthesis of 25-hydroxycholesterol, statins could limit the switching of human CD4$^+$T cells from production of the antiviral/pro-inflammatory cytokine IFN-gamma to the immunoregulatory IL-10 [231]. Thus statins could enhance the antiviral capability of CD4$^+$ T cells [232].

Other mechanisms of statins to combat pathology of SARS-CoV-2 include endothelial dysfunction and endotheliitis in several organs, stabilizing the endothelial leakage, limiting leukocyte transmigration and increasing local nitric oxide [208, 233]. Another reason for use of statin in COVID-19 patients is drugs induced hyperlipidemia that caused by protease inhibitor-based antiretroviral and immunosuppressive drugs are used to treat patients [234, 235]. Finally, in statin treatment for COVID-19 patients, we should notice drug interactions, side effects and contraindications. For instance statins have interaction with some antiretroviral drugs and macrolides [236]. On the other hand myalgia in patients could be one of the COVID-19 symptoms or a side effect of statin. Another lipid-lowering drug is fibrates, which its potential antiviral effects for influenza have been proved [237]. In vitro study on mice infected with influenza virus, Alleva et al. showed that fibrates could increase survival of infected mice [237]. Takano et al. claimed that U18666A, cholesterol synthesis and transport inhibitor, shows antiviral effect against type I feline CoV, but not type II FCoV [238]. Furthermore, an in-depth multi-organ proteomic analysis of COVID-19 patient autopsy samples showed that Niemann-Pick C1 (NPC1) was significantly upregulated in most organs, including the lung, spleen, and heart which might be a potential drug target for COVID-19 treatment [239]. A recent in vitro studies showed scavenger receptor class B type 1 (SR-B1), which facilitate the uptake of cholesteryl esters from HDL in the liver, might be a potential target for COVID-19 drugs and blockade of SR-BI inhibited SARS-CoV-2 infectivity in an in vitro study [240, 241].

Cepharanthine, a Japanese natural drug, was announced by FDA as a potent inhibitor of virus–cell attachment [242]. This drug that approved for managing radiation-induced leukopenia [243], alopecia areata [244], alopecia pityrodes [245], idiopathic thrombocytopenic purpura [246], has anti-inflammatory, ant oxidative, immunomodulating, antiparasitic, and antiviral effects.

Cepharanthine effects several aspects of cell metabolism including cholesterol trafficking [244].

- ### *Dyslipidemia and COVID-19 in brief*

Dyslipidemia as an effective factor in the occurrence of myocardial infarction as well as stroke is known as a cardio metabolic risk factors affecting human's health.

In this article we reviewed different studies which evaluated dyslipidemia as a prognostic risk factor in this pandemic of COVID-19 and its role in the course of this acute respiratory infectious disease. Dyslipidemia affects the COVID-19 disease in different due to its different roles, including increasing LDL and lowering HDL, as well as altering in Apo protein levels. Accumulation of LDL in

dyslipidemia causes vasculopathy which is an independent risk factor in increasing the severity of COVID-19 disease. Also this vasculopathy leads to endothelial damage and the expression of ACE2 receptor in endothelial cells as an entry way for SARSCOV2 into cells [176, 177].

Low level of HDL is a prognostic risk factor of COVID-19 disease severity by multiple mechanisms which has been explained in details before. There is controversy of using statins in COVID-19 patients but most studies have supported the use of it in these patients [160, 206, 228, 230, 231], although a number of studies in conflict with this theory have also been reviewed [224, 225, 247]. Recent studies have shown that scavenger receptor classB type1 (SR_B1) which facilitate the uptake of cholesteryl esters from HDL in liver, might be a potential target for COVID-19 drugs but these are still invitro studies [240, 241].

Introduction to *COVID-19* and Obesity

Corona virus, as the latest pandemic in the world, causes severe and acute infections of the respiratory system, but it affects all organs of the body [248]. Obesity as an epidemic of the last century also has different effects on the body systems, especially the immune system, so the impact of obesity on COVID-19 disease seems to be possible. Obesity has reached epidemic levels in the United States and most of the western world. About three fourths of adults older than 20 years old in the US meet the criteria for being diagnosed as overweight or obese (BMI = weight in kilograms divided by the height in meters squared ≥ 30 kg/m^2). More than 9% of the US adults are morbid or severe obese (BMI ≥ 40). Other countries have also reported an increasing prevalence of obesity [249, 250]. Obesity mainly affects most of the physiological process and interfere the functions of the system including immune system [251]. As an evidence of this claim, reference is made to the H1N1 influenza A occurred in 2009, in which a significant number of the hospitalized patients and mortality cases were related to obese individuals, and an estimated 151,700–575,400 total death was reported [252, 253]. Due to this, the higher mortality rate in obese patients with novel COVID-19 infection is predictable. To review the major cause of higher mortality rate in obese patients, we can acknowledge metabolic syndrome and other comorbidities such as HTN and DM which themselves increase the mortality rate significantly and the major role of obesity in impairing the immune system in various way [30, 37, 254–256]. This will be discussed in details in the following.

- *Pathophysiological link between obesity and COVID-19*
- *Definition of obesity*

Obesity can lead to more advanced and severe disease in COVID-19 patients by increasing insulin resistance and over

activity of the RAAS system as well as creating an inflammatory background [156]. Body mass index (BMI), which is weight in kilograms split up by height in meters squared, is used to recognize obesity. For adults, a BMI of 25.0 to 29.9 kg/m2 is defined as overweight and a BMI of 30 kg/m2 or higher is defined as obese [257]. For every 5-unit increase in BMI above 25 kg/m2, overall mortality increases by 29%, vascular mortality by 41%, and diabetes-related mortality by 210% [258]. Patients with obesity are at higher risk of morbidity from dyslipidemia, T2D, hypertension, coronary heart disease, stroke, gallbladder disease, respiratory problems, sleep apnea, osteoarthritis, and some cancers [257]. Obesity prevalence is higher in older adults compared to the young, and its complications, such as hypertension, diabetes and cardiovascular disease, increase with increasing obesity severity and duration [259]. Importantly, a report on 4103 patients with COVID-19 disease in New York City found that the most important clinical features leading to hospital admission were age > 65 years and obesity itself, more than hypertension, diabetes or cardiovascular disease [260].

- *Mechanism of effect of obesity on COVID-19*
- *Respiratory system*

As previous studies showed, obesity is related with higher risk of many respiratory system diseases like asthma and obstructive sleep apnea syndrome [261]. Compliance of respiration system and expiratory reserve volume are commonly reduced in obese individuals due to their altered respiratory mechanism and chest wall physiology. Deposits of mediastinal and abdominal adipose tissue lead to some changes in their respiration physiology such as reduction in chest wall elastance, limitation in truncal expansion, lowering of respiratory muscles strength and increased airway resistance [262–264]. Overall, these functional and physiological changes predisposed them to hypoventilation- associated pneumonia, pulmonary hypertension, and cardiac stress [265]. Moreover, obese individuals consume more oxygen to retrieve lower P02 due to poor-ventilation of lower zones of lungs and ventilation-perfusion mismatch [266–269]. These could explain why respiratory system of obese patients is vulnerable to viral infection like COVID-19.

- *Immune system*

There are multiple mechanisms that make obese individuals' immune system vulnerable to defeat the SARS-CoV 2 infection. Excess adipose tissue is responsible for over secration of adipocytes and proinflammatory cytokines and put obese individuals in a proinflammatory state. This state upset the balance between cytokines and leads to an impaired immune response. Tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) are some

of these oversecrated cytokines [270, 271]. Moreover, IL-6 oversecration is an COVID-19 severity independent factor [256]. Also, high levels of IL-6 may be associated with the overreaction of complement system in obese patients [272, 273]. This state and especially, IL-6 predispose immune system to an impaired response like cytokine storm and further multiorgan failure which were seen in severe cases of COVID-19 [271, 274, 275].

The proinflammatory state also could lead to a decrease in macrophage activation [276, 277]. Also, obesity associated with the disruption of lymphoid tissue integrity and leukocyte activity impairment [278]. This could result in memory T-cell decrease and malfunction that could contribute to more tissue damage during COVID-19 immune challenge [279] and weak antibody response as reported by influenza's vaccination studies [276].

High levels of Leptin and DPP4 inhibitors (Dipeptidyl peptidase-4) in obese patients are two other potential mechanisms that impair immune system. DPP4 inhibition is one mechanism that could suppress proinflammatory cytokines secretion [280], and also leptin plays a crucial role in B cells' cycle [281], both mechanisms are impaired in obese individuals.

- **Other comorbidities in obese patients**

In addition to the association obesity and independent risk factors of COVID-19 severity, such as T2DM and HTN, metabolic disorders related to obesity could increase the risk of cardiovascular events [265]. It is very important to note that in most studies the reason of higher mortality rates in obese people was not only attributable to obesity, but the associations of obesity and hypertension, diabetes mellitus and cardiovascular disorders play a great role in higher death rates in these individuals [282–284]. Vitamin D deficiency is another possible risk factor for developing severe COVID-19 [285]. Vitamin D as an immunomodulator plays an essential role in decreasing the production of proinflammatory cytokines. About 40–80% of the obese population is vitamin D deficient [286]. Also, obese patients admitted to ICU with malnutrition had a worse prognosis than obese patients without malnutrition [287].

- **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Receptors in obese patients**

Also, one of the potential mechanisms that could explain why obesity should be considered as a risk factor for COVID-19 is the high levels expression of ACE-2 (Angiotensin-Converting Enzyme 2) receptors known as the main SARS-CoV2 binding receptors in adipose tissue [288, 289]. Epicardial and ectopic fat tissues could eases spreading the virus to lung, heart and other organs [279].

- **Endothelial dysfunction**

There is evidence of endothelial dysfunction in obesity. Obesity related endothelial dysfunction is caused by several mechanisms like low grade inflammation produced by either perivascular adipose tissue or the vasculature itself. This endothelial dysfunction may lead to subsequent damages to some vital organs which also affects the severity of COVID-19 infection in obese patients [290, 291].

- *Management of hospitalized obese patients*

Moreover, there are some challenges in managing obese patients: requiring more ICU beds, lack of bariatric beds, difficulty in transportation and positioning, weight limits of CT-scan machines, difficult catheterization and intubation due to fat tissue in larynx [278, 292–294].

- *Role of visceral and abdominal adipose tissue*

Abdominal fat, composed from 2 adipose layers: visceral and subcutaneous. Subcutaneous layer links to decreased expiratory reserve volume by reducing excursion of diaphragm excursion [295]. However, visceral abdominal fat is associated with metabolic syndrome [296], and type 2 diabetes mellitus and hypertension as parts of metabolic syndrome are independent risk factors of COVID-19 severity [265]. Moreover, the proinflammatory state in obese individuals could be induced by either abdominal or non-abdominal Visceral adipose tissue [294].

- *Studies on the association between obesity and COVID-19 severity*

In a meta-analysis which studied reporting mortality with COVID-19 in patients with/without obesity, they reviewed 14 studies on this subject. The data has shown that body mass index (BMI) to be significantly associated with the mortality. Patients with BMI ≥ 25 are extremely more likely demand advance respiratory support and also BMI ≥ 30 is a considerable factor for critical illness during COVID-19 [297]. Another study were performed in China on 383 patients reveals that obese patients compared to normal weight patients even after adjusting for potential confounders had a 2.42 fold higher risk of developing severe pneumonia [298]. There are several studies on the need for mechanical ventilation in obese patients including A study of 124 COVID-19 patients admitted in the intensive care unit in a university hospital in Lille, France, which reported a 7.36-fold need for intubation in patients with BMI > 35 (85.7% of them) compared to those with BMI < 25 kg/m2, independent of other comorbidities. Obesity (BMI ≥ 30) and severe obesity (BMI ≥ 35) were found in 47.6% and 28.2%

of cases [299, 300]. Also, another study on 92 patients with COVID-19-associated pneumonia in Italy demonstrated that obesity is linked to a higher requirement of assisted ventilation (mechanical or non-invasive ventilation) and ICU admission, as two important indicators of disease severity, after adjusting for other variables. This study reported intensive or semi-intensive respiratory unit admission and mortality in 41.3% and 47.4% of obese patients. However, in this study, obese patients did not show significantly higher mortality rates [301].

- *Recommendations on weight control in COVID-19 era*

According to obesity effects on COVID-19, weight gain prevention is highly recommended during the pandemic. Changing lifestyle plays the most critical role in this prevention. Increase physical activity and exercise at home or outdoor with social distancing are critical ways to prevent weight gain in normal-weight people and also lose weight in overweight or obese individuals. Exercise also could improve the metabolic and immunologic functions of the
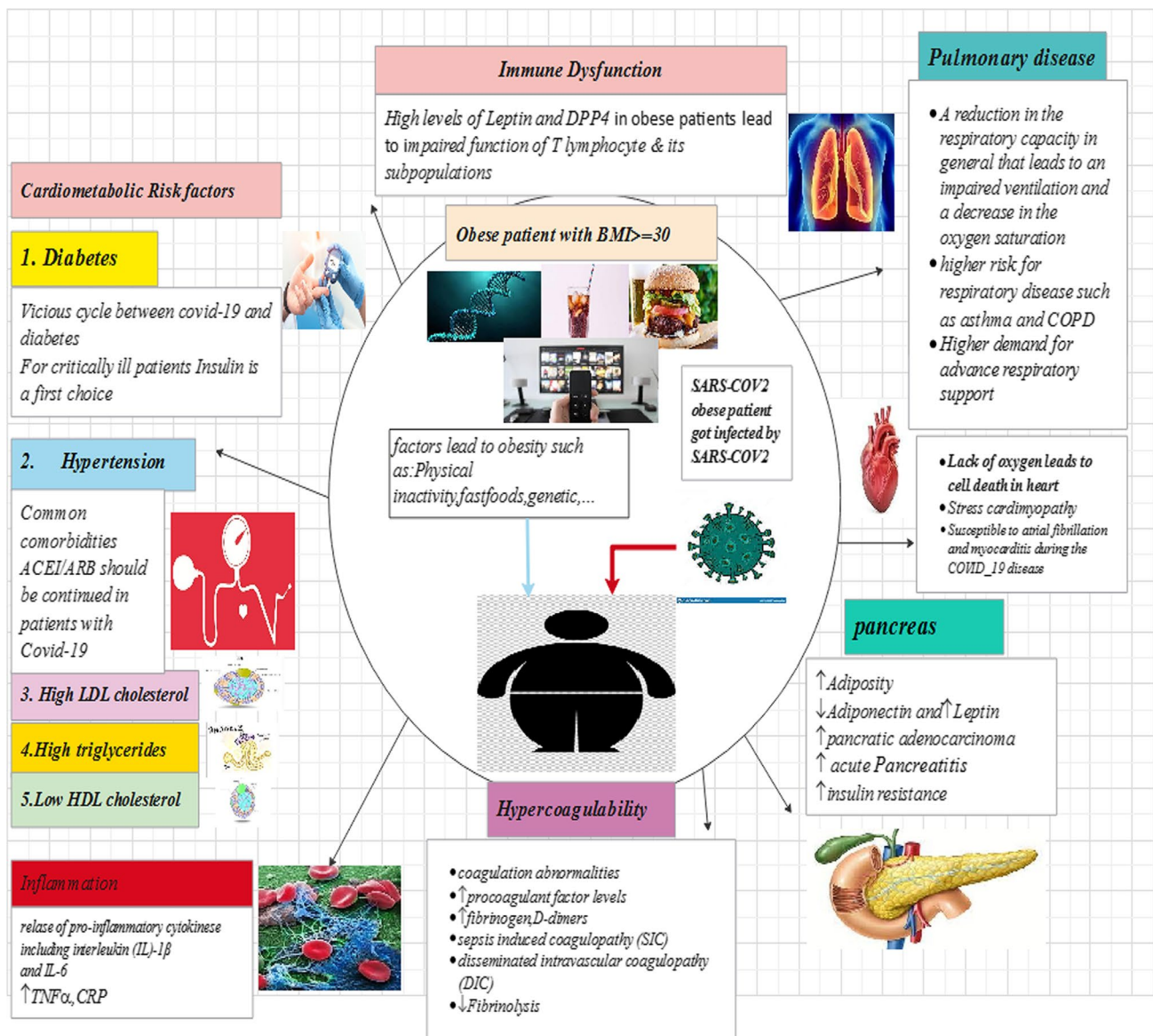
Fig. 3 possible obesity implications and mechanisms in COVID-19 disease. AF=atrial fibrillation, COPD=Chronic obstructive pulmonary disease, HDL=high density lipoprotein, HFpEF=heart failure with preserved ejection fraction, IL-6=interleukin 6, LDL=low-density lipoprotein, DPP4=Dipeptidyl peptidase-4, SARS-CoV-2=severe acute respiratory syndrome Coronavirus 2, TNF-a=tumor necrosis factor a.CRP=C-reactive protein, ACE=angiotensin- converting enzyme, ARB=angiotensin receptor blocker, BMI=Body mass index, COVID-19=Coronavirus Disease 2019

body [302]. Creative methods to do exercise more at home and also, high activity games with children may help to more activity despite limitations. Reduced high-caloric food consumption is another feasible way to lose weight. Increase fresh foods and decrease canned and junk food consumption are notable points that should not be ignored in this era. Moreover, psychological support and treatment or medical interventions to control stress and avoiding emotional eating, and also, sleep regulation could be so useful to reach this purpose.

In addition to these recommendations, obese patients should consider a steady low- caloric diet and approved weight loss drugs (synthetic or herbal drugs under physician observation) to lose weight due to their increased risk of disease [303, 304]. Similarly, obese patients who have diabetes should tightly monitor their glycemic status and adapt their drugs and calorie consumption to these new conditions [300]. As a result, telemedicine could play a crucial role in the close monitoring of obese patients in the COVID-19 era.

- *Obesity and COVID-19 in brief*

In conclusion obesity as an epidemic of the last century in conjunction with the coronavirus pandemic can play an important role in changing the course of this infectious disease. As cited acknowledged in the article, obesity can reduce ERV (expiratory reserve volume) and FC (functional capacity) which leads to impaired ventilation [295]. Obesity weakens the immune system by multiple mechanisms. Metabolic syndrome and other comorbidities like DM and HTN will complicate the situation for obese patients tremendously. The ACE2 expression in adipose tissue is higher than that in the lungs, a major target organ by COVID-19 suggesting that adipose tissue May be more susceptible to COVID-19 infection. The obese populations have more adipose tissue and accordingly higher ACE levels. This potential mechanism can increase COVID-19 infection in obese individuals [288]. To sum up, obesity will affect infected patients with COVID-19 in several ways so all the physicians worldwide encourege obese people to better control their diet, their weight and other diseases associated with obesity such as diabetes and HTN during this pandemic era. Figure 3 depicts briefly the mechanisms involved in the potential association between obesity and COVID-19 disease.

Conclusion

Due to the predominance of individuals with cardio metabolic illnesses, in this pandemic, we decided to review articles on the impact of cardio metabolic risk factors on coronavirus disease 2019 and the viability of coronavirus within the course of cardio metabolic diseases. Various studies revealed the association between the severities of COVID-19 infection in individuals with hypertension besides the higher frequency of this infection in these people. Most of the articles looked into in this paper concurred on continuing treatment with ACEI or ARB (as the foremost common antihypertensive drugs) during this pandemic and after getting COVID-19 disease. Diabetes is another cardio metabolic risk factor that in this article is perceived as one of the factors that exacerbated COVID-19 infection, but autonomously was not a factor in increasing the chance of developing the disease. Dyslipidemia is a viable factor within the occurrence of myocardial infarction as well as stroke, and is known as a cardio metabolic risk factor impacting human wellbeing. Dyslipidemia affects the COVID-19 infection in several ways, including the level of HDL as a prognostic risk factor of COVID-19 disease severity by multiple components which has been clarified in detail before. There's a controversy over using statins in COVID-19 infected patients but a plenty of research have supported the usage of these drugs in these patients. Obesity is an epidemic of the last century that in conjunction with the coronavirus pandemic can play an important role in changing the course of this infectious disease. The ACE2 expression in adipose tissue is higher than that in the lungs as a major target organ by COVID-19 implying that adipose tissue may be more vulnerable to COVID-19 infection. In general, due to the high prevalence of cardiometabolic diseases, especially in the population over 60 years old, it seems that these diseases have contributed to the worsening of COVID-19 disease in a recent pandemic, and monitoring these cardiometabolic risk factors can improve the course of COVID-19 infections and could be beneficial generally.

Declarations

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