State of art paper

The COVID-19 pandemic and diabetes mellitus

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Submitted: 23 May 2020
Accepted: 28 May 2020

Arch Med Sci Atheroscler Dis 2020; 5: e200–e205
DOI: https://doi.org/10.5114/amsad.2020.97435

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Abstract

COVID-19, a disease caused by a novel coronavirus, SARS-CoV-2, has reached the proportion of a pandemic and presents with either mild and moderate symptoms or in severe cases with acute respiratory distress syndrome, multiple organ dysfunction syndrome and even death. Older age, hypertension, cardiovascular disease, diabetes mellitus and obesity significantly increase morbidity and mortality in COVID-19 patients. In the present review we summarize the existing, and daily growing, data on the impact of COVID-19 infection on patients with diabetes, their antidiabetic therapy as well as the extra precautions, apart from good glucose control, they have to take in order not to contract the virus. Social distancing and strict hand hygiene are of great importance in order to help the global goal of eradication of the disease.

Key words: COVID-19, SARS-CoV-2, diabetes, social distancing, angiotensin I-converting enzyme, dipeptidyl peptidase-4.

Introduction

In December 2019, a pneumonia of unknown origin with high fatality, mostly due to acute respiratory distress syndrome (ARDS), was observed in Wuhan, China. On February 11, 2020 the cause of the disease was discovered and named SARS-CoV-2 by the International Committee on Taxonomy of Viruses [1, 2]. SARS-CoV-2 belongs to the coronaviruses, like severe acute respiratory syndrome coronavirus (SARS-CoV) and middle-east respiratory syndrome coronavirus (MERS-CoV), which are named for the crown-like spikes on their surface. SARS-CoV-2 is more infectious, with over 80,000 cases in China and nearly 2,800,000 cases worldwide reported as of April 25, 2020, according to the Center for Systems Science and Engineering at John Hopkins University [3]. Most COVID-19 patients present with mild and moderate symptoms, but severe cases can present with ARDS, multiple organ dysfunction syndrome (MODS) and even death. It has been reported that the fatality rate of COVID-19 varies from 1.4% to 4.3% in different regions or hospitals [4, 5].

Diabetes, and its complications, is one of the leading causes of morbidity and mortality worldwide [6]. Patients with diabetes are at high risk of infections, especially influenza and pneumonia [7, 8]. Chronic hyperglycemia that characterizes patients with diabetes leads to impaired phagocytosis by neutrophils, macrophages and monocytes, impaired neutrophil chemotaxis and bactericidal activity, and impaired innate cell-mediated immunity [7, 8]. Therefore, in order to protect patients

with diabetes from influenza and pneumonia, pneumococcal and annual influenza vaccinations are recommended to all patients with diabetes aged above 2 years. In addition, uncontrolled glycemia is a significant risk factor of severity and death in patients with diabetes who are infected by different viruses [9–11]. During the last three pandemics, Influenza A 2009 (H1N1), SARS coronavirus and MERS-CoV, diabetes per se was an important risk factor for morbidity and mortality [9–11]. This is also confirmed in the present pandemic of COVID-19, as will be discussed in the next sections.

Therefore, the aim of the present review is to summarize the existing literature data on the epidemiology of COVID-19 in patients with diabetes, the possible pathogenetic mechanisms linking the two diseases, and the potential effects of antidiabetic agents on the infection.

Epidemiology of COVID-19 in patients with diabetes

It is very interesting that data on the prevalence of diabetes in patients with COVID-19 diabetes are growing day by day and are different depending on the studied population.

Three recent meta-analyses showed that the most prevalent comorbidities among patients with COVID-19 were hypertension and diabetes, followed by cardiovascular diseases and respiratory system disease [12–14]. The first one, including 8 studies with 46,248 infected patients, demonstrated a prevalence of diabetes of about 8 ±6% (95% confidence interval (CI): 6–11%) [12]. The second one was a comprehensive systematic search on articles published until 15 February 2020 and included data of 76,993 patients from 10 different studies [13]. According to this meta-analysis, the prevalence of diabetes in people infected with SARS-CoV-2 was estimated as 7.87% (95% CI: 6.57–9.28%). Another meta-analysis conducted to estimate the prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China included six studies with 1,527 patients [14]. The proportions of hypertension, cardio/cerebrovascular disease and diabetes in patients with COVID-19 were 17.1%, 16.4% and 9.7%, respectively. The incidences of hypertension, cardio/cerebrovascular diseases and diabetes were about twofold, threefold and twofold, respectively, higher in intensive care unit (ICU)/severe cases than in their non-ICU/severe counterparts.

Even higher prevalence of diabetes in people infected with SARS-CoV-2 was found in studies from Wuhan, the center of the disease. A study by Zhou *et al.* [15], in 191 patients with COVID-19, showed that almost half of them had a comorbidity, with hypertension being the most common (30% patients), followed by diabetes (19% patients) and coronary heart disease (8% patients). In another study in 85 patients, 68.2% had one or more comorbidities, with hypertension (37.6%), diabetes (22.4%) and coronary heart disease (11.8%) being the most common comorbidities [16]. In a study by Wan *et al.* [17], of 135 hospitalized patients with COVID-19 who were enrolled, 31.9% of patients had underlying disease, primarily hypertension (9.6%), diabetes (8.9%), cardiovascular disease (5.2%), and malignancy (3.0%). Guan *et al.* analyzed the data from 1,590 laboratory-confirmed hospitalized patients with COVID-19 from 575 hospitals in China between December 11th, 2019 and January 31st, 2020. According to their findings, the most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). Diabetes (hazard ratio (HR): 1.59, 95% CI: 1.03–2.45) was a risk factor of mortality [18].

A study by Yang *et al.* [19], in 32 non-survivors from a group of 52 ICU patients with COVID-19, found that the most common comorbidities were cerebrovascular diseases (22%) and diabetes (22%). Another study [20], which included 1,099 patients with COVID-19, showed that in 173 with severe disease the most common comorbidities were hypertension (23.7%), diabetes (16.2%), coronary heart (5.8%) and cerebrovascular disease (2.3%). In a third study [21], in 140 patients who were admitted to hospital with COVID-19, 30% had hypertension and 12% diabetes, while diabetes was not a risk factor for severe disease course.

Presence of diabetes in patients with COVID-19 was associated with the worst outcomes. Diabetes was present in 42.3% of 26 fatalities due to COVID-19 in Wuhan, China [22]. Wu *et al.* showed that in 201 patients with COVID-19 prevalence of diabetes among patients who developed ARDS, compared with those who did not, was 19.0% compared to 5.1%, respectively [23]. Another study that estimated clinical features of deaths in the novel COVID-19 epidemic in China found a significant difference in the proportion of diabetes between the deceased patients (26.2%) and the Hubei population (5.6%) [24]. The authors suggested that diabetes might be associated with increased risk of mortality.

Since March 19th 2020, when Italy was the country second most affected by COVID-19, new data on the prevalence of diabetes among patients in Europe have been added to the literature. At the University Hospital of Padova, among 146 hospitalized patients with confirmed COVID-19, 13 had pre-existing diabetes, yielding a prevalence of 8.9% (95% CI: 5.3–14.6) [25]. Even higher diabetes prevalence was recorded by another two studies. A study by the Istituto Superiore di Sanita reported that among 355 deceased patients with available information on comorbidities, diabetes

prevalence was 35.5% [26]. In 2018, diabetes prevalence among Italian citizens with the same age range and sex distribution was 20.3% [27]. Thus, the rate ratio of diabetes among patients who died with SARS-CoV-2 infection compared to the general population was 1.75.

An analysis on 122,653 U.S. COVID-19 cases reported to the Centers for Disease Control and Prevention as of March 28, 2020, showed that underlying health conditions, including, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, coronary artery disease, cerebrovascular disease, chronic renal disease, and smoking, are risk factors for severe disease or death from COVID-19 [20, 28]. Finally, a study in the U.S.A. in patients from 9 Seattle-area hospitals who were admitted to the ICU with confirmed infection with severe COVID-19 showed that 58% of patients had diabetes mellitus [29]. In 5,700 patients with COVID-19 admitted to 12 hospitals in New York the most common comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) [30]. Another publication analyzing data of COVID-19-associated hospitalization rates for patients admitted during March 2020, the first month of U.S. surveillance, showed that the most common underlying conditions were hypertension (49.7%), obesity (48.3%), chronic lung disease (34.6%), diabetes mellitus (28.3%), and cardiovascular disease (27.8%) [31].

In conclusion, diabetes is a risk factor for COVID-19 and, in addition, is associated with increased mortality, as has been confirmed by a recent metanalysis [32]. Among 1,382 patients, diabetes was the second more frequent comorbidity while diabetic patients had a significantly increased risk of ICU admission (OR = 2.79, 95% CI: 1.85–4.22) and a higher mortality risk (OR = 3.21, 95% CI: 1.82–5.64) [32]. Finally, in the current COVID-19 pandemic, reports from China, Italy and the U.S.A. showed that age is a significant risk factor for morbidity and mortality, in addition to diabetes per se, with older patients with diabetes being at higher risk for severe disease and mortality [20, 33, 34].

Pathogenetic mechanisms linking COVID-19 with diabetes: role of angiotensin-converting enzyme

It is known that diabetes, especially type 2 diabetes, is characterized by the presence of low-grade chronic inflammation induced by the excessive visceral adipose tissue. Chronic inflammation combined with hyperglycemia results in an abnormal and ineffective immune response, including decreased mobilization of polymorphonuclear leukocytes, chemotaxis, and phagocytic activity, lower secretion of cytokines such as interleukin-1 (IL-1) and IL-6, and glycation of immunoglobulin [35, 36]. IL-6, along with fibrinogen, C-reactive protein, and D-dimer, are found to be more elevated in COVID-19 cases with than in those without diabetes [35, 36].

Apart from impaired neutrophil chemotaxis and phagocytosis, there are several specific factors responsible for increased risk and severity of COVID-19 in diabetes. SARS-CoV-2, like SARS-CoV, utilizes angiotensin-converting enzyme (ACE)2 as a receptor for entry into the cell [37]. This enzyme is a homologue of ACE1, which converts angiotensin I to angiotensin II, and is therapeutically targeted in hypertension and heart failure. ACE2 is widely expressed, including in the lungs, cardiovascular system, gut, kidneys, central nervous system, and adipose tissue. The S-glycoprotein on the surface of SARS-CoV2 binds to ACE2 and causes a conformational change in the S-glycoprotein that induces proteolytic digestion by host cell proteases, leading to internalization of the virion [38]. Cellular entry of the virus triggers an inflammatory response leading to a 'cytokine storm' which could lead to organ damage and multi-organ failure seen in severe disease [38]. Diabetic mice have been found to have increased expression of ACE2 in the renal cortex, liver and pancreas, but not in the lungs [39]. Amongst others, pioglitazone and liraglutide have also been shown to be associated with ACE2 upregulation in animal studies [40, 41].

Furthermore, diabetes more often co-exists with hypertension, and treatment with either ACE inhibitors, or angiotensin-receptor blockers (ARBs) is very common. Therefore, one could assume that ACE inhibitors and/or ARBs might have deleterious effects in patients with diabetes and COVID-19. ACE inhibitors inhibit ACE, leading to decreased angiotensin I levels, causing a possible negative feedback loop that ultimately upregulates more ACE2 receptor to be able to interact with the decreased angiotensin I substrate available [42]. In addition, plasma levels of angiotensin II increase with ARB dosing [43]. Angiotensin II is a known substrate for ACE2 and might result in increasing the expression of the linked enzyme. This ACE2 receptor upregulation results in increased binding sites for SARS-CoV-2, leading to preferential COVID-19. On the other hand, treatment with ARBs has been proposed as a potential therapeutic strategy for COVID-19 [44], supported by observations that blocking the renin-angiotensin system in animal models attenuated the lung injury caused by SARS-CoV, which also utilizes ACE2 [45].

However, a study by Peng *et al.*, among 112 patients, showed that most deaths occurred secondarily to fulminant inflammation, lactic acidosis, and thrombotic states [46] while ACE inhibitor and ARB therapy was not associated with morbid-

ity or mortality [46]. Another study, in 1,178 hospitalized patients with COVID-19 infections at the Central Hospital of Wuhan, suggested that ACE inhibitors/ARBs are not associated with the severity or mortality of COVID-19 in such patients [47]. The percentage of patients with hypertension taking ACE inhibitors/ARBs did not differ between those with severe and non-severe infections (32.9% vs. 30.7%, $p = 0.645$); nor did it differ between non-survivors and survivors (27.3% vs. 33.0%, $p = 0.34$) [47]. A recent position statement from the European Society of Cardiology recommends that patients continue treatment with their usual anti-hypertensive treatment and that there is no clinical or scientific evidence to suggest that treatment with ACE inhibitors or ARBs should be discontinued because of COVID-19 [48].

Role of antidiabetic agents in COVID-19

There are no data on the differential effects of oral antidiabetic drugs on the disease course in COVID-19. In general, previous antidiabetic agents in patients with mild COVID-19 should be evaluated and followed as appropriate. For severe and critically ill patients, intravenous insulin therapy, including rapid-acting prandial/basal insulin, should be the preferred therapy option.

During the COVID-19 pandemic, the relationship of coronavirus to the cellular type II transmembrane protein dipeptidyl peptidase-4 (DPP-4) (CD26) has generated great interest since a lot of patients with diabetes are under DPP4 inhibitors therapy. It is known that DPP4 inhibitors target the enzymatic activity of DPP4, a type II transmembrane glycoprotein, expressed ubiquitously in many tissues, including immune cells [49]. Apart from breaking down circulating glucagon-like peptide-1 (GLP-1), DPP4 activates T-cells, and upregulates CD86 expression and the NF-κB pathway, thereby promoting inflammation. DPP4 serves as the receptor for MERS-CoV, in the same way as ACE2 is the receptor for SARS-CoV and SARS-CoV2 [50, 51], and, therefore, DPP-4 inhibitors might reduce the viral entry of MERS-CoV. However, an *in vitro* study, using sitagliptin, vildagliptin and saxagliptin, failed to stop coronavirus viral entry into the cells [52].

Regarding the newer antidiabetic agents, GLP-1 receptor analogues have shown significant anti-inflammatory and anti-adipogenic effects [53, 54], but no data exist regarding their effect on patients with COVID-19. Similar evidence on the effect on inflammation is also available for the sodium-glucose cotransporter-2 (SGLT-2) inhibitors [55]. However, SGLT-2 inhibitors should be used with caution in patients with COVID-19 since there is the fear of euglycemic diabetic ketoacidosis in case of dehydration. Finally, a new randomized, global trial, named DARE-19, will evaluate dapagliflozin's ability to reduce the risk of disease progression, clinical complications, and death from COVID-19 in patients with cardiovascular, metabolic or kidney risk factors [56].

Finally, the anti-malarial hydroxychloroquine has been used against COVID-19. The drug acts by raising intracellular pH, which inhibits enzymatic degradation of insulin, resulting in recirculation of a substantial proportion of insulin in the active form [57, 58]. It has been known for more than 30 years that hydroxychloroquine has hypoglycemic effects that might cause hypoglycemia. Therefore, in the case of co-administration of hydroxychloroquine together with other anti-diabetic drugs, the dosages of concomitant therapies may be reassessed, particularly in patients at higher hypoglycemic risk [57, 58].

Management of diabetes in the COVID-19 era

During the COVID-19 pandemic, diabetes management can be challenging. Some general recommendations regarding the management of diabetes per se and for patients with diabetes and COVID-19 have been published by the American Diabetes Association [59]. In general, patients with diabetes have to drink lots of water and fluids in order to avoid dehydration, have to maintain glycemic control, and have to monitor blood sugar levels more frequently in order to avoid hypoglycemic episodes and ketoacidosis. Furthermore, patients with diabetes have to establish and maintain strict personal hygiene, such as washing hands and cleaning the injection/infusion and finger-stick sites with soap and water or rubbing alcohol.

Finally, the optimization of physician–patient communication for diabetes management in the era of social distancing, isolation, and quarantine must be emphasized. As long as patients have access to technology, their communication with their health care providers can be maintained quite unobstructed, even if it is related to mild to moderate symptoms of COVID-19 infection that can be managed at home or it is related to their diabetes management [60]. More important, this can be done without the need for physical office visits.

Conclusions

Most of the available studies have shown that diabetes as a distinctive comorbidity is associated with more severe disease, acute respiratory distress syndrome and increased mortality. Hence, following current recommendations for the general population, social distancing, and strict hand and respiratory hygiene are of great importance in order to help the global goal of eradication of the disease. Finally, and always looking at the bright

side of things, the new era that already has started is giving us the opportunity of new ways of communication between patients with diabetes and health care providers that can be established and used also after the COVID-19 pandemic.

Conflict of interest

The authors declare no conflict of interest.

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