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

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14 (2020) 809–814

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

Metabolic syndrome and COVID-19: An update on the associated comorbidities and proposed therapies

Fernanda Farias Costa [a], Wilian Reis Rosário [a], Ana Cláudia Ribeiro Farias [a], Ramon Guimarães de Souza [b], Roberta Sabrine Duarte Gondim [c], Wermerson Assunção Barroso [a, *]

[a] Department of Biomedicine, CEUMA University (UNICEUMA), R. Barão do Rio Branco, 100, Entroncamento, Imperatriz, MA, 65903-093, Brazil
[b] Amorim II Basic Health Unit, Conjunto Consolata, s/n, Amorim, Zé Doca, MA, 65365-000, Brazil
[c] Department of Pharmacy, Graduate Program in Health Sciences, Federal University of Maranhão, Campus do Bacanga, Av. dos Portugueses, s/n, Bacanga, São Luís, MA, 65080-040, Brazil

ARTICLE INFO

Article history:
Received 18 May 2020
Received in revised form
2 June 2020
Accepted 8 June 2020

Keywords:
COVID-19
Metabolic syndrome
Obesity
Diabetes
Cardiovascular disease
Liver disease
Drugs

ABSTRACT

Background and aims: Many patients with coronavirus disease 2019 (COVID-19) have comorbidities related to metabolic syndrome (MS) during the disease course. Its presence in different ethnicities and continents places MS as an important risk factor for COVID-19. Adequate understanding of the interplay between MS, COVID-19 and proposed therapies is required for optimum management of these patients.
Methods: We systematically searched the PubMed and Google Scholar databases until June 1st, 2020 and accessed the full text on COVID-19 and MS to prepare a narrative review on this topic.
Results: Patients with metabolic disorders like obesity, diabetes, cardiovascular and liver disease may face a higher risk of infection of COVID-19, greatly affecting the development and prognosis of the disease, being associated with significantly worse outcome in these patients. The proposed drugs that are in clinical trial for COVID-19 treatment must be carefully considered for clinical use, especially in patients with MS.
Conclusion: MS is a risk factor influencing the progression and prognosis of COVID-2019. The drugs currently evaluated for the infection treatment are promising but need further studies to prove their efficacy and safety, due to the adverse effects may be exacerbated by combination therapy or due to viral infection. The development of a vaccine for immunization is still the best long-term solution.

1. Introduction

Named by the International Committee on Taxonomy of Viruses (ICTV) as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus, with origin associated with the city of Wuhan, Hubei province, China, spread rapidly worldwide causing thousands of deaths, characterizing the infection as a public health problem of global interest [1,2]. With a high infectivity rate, the coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, reached pandemic proportions [3].

According to the report published by World Health Organization (WHO) on June 1st, the number of confirmed cases reaches 6,057,853 distributed in 216 countries, with emphasis on the European and American continents, with more than two million cases each, together adding up around 82% of infected global number. COVID-19 has already killed more than 371,166 people worldwide, especially among elderly patients and individuals with comorbidities. Currently, the United States (U.S.) has already more than 1,734,040 confirmed cases, but, despite its large number of infected people, it is countries like Spain (29,045 deaths), Italy (33,415 deaths) and The United Kingdom (38,489 deaths) which presented the highest mortality rate, exceeding 10% [4].

The disease evolution and the symptoms vary from asymptomatic patients to severe cases of respiratory failure, which can lead to death [5]. Some risk factors may be associated with the evolution and disease severity. In a study conducted in the U.S., during March 2020, with 1482 patients hospitalized with COVID-19 in fourteen states, 12% of the total were history of comorbidities. Of this total, 49.7% were hypertensive, 48.3% were obese, patients with

* Corresponding author.
E-mail address: wermersonbarroso@yahoo.com (W.A. Barroso).

https://doi.org/10.1016/j.dsx.2020.06.016
1871-4021/

chronic liver diseases totaled 34.6%, diabetics represented 28.3% and people with cardiovascular diseases were 27.8% [6]. In another study conducted in Wuhan city, China, 191 patients with COVID-19 were followed up, of which 48% had comorbidities such as hypertension (30%), diabetes (19%) and coronary disease (8%) [7]. Until June 1st, 2020, Brazil had 347,398 confirmed cases of COVID-19 with 13,868 deaths associated with comorbidities. Heart disease was the most common comorbidity with total of 7318 deaths, followed by diabetes, kidney disease, neurological disease, pneumopathy, obesity, immunosuppression and asthma, with a total of 5627, 1218, 1159, 1061, 742, 740 and 397 deaths, respectively [8].

In this context, metabolic syndrome (MS) is inserted as a common denominator to these comorbidities, since it is defined as a set of metabolic disorders that include insulin resistance, dyslipidemia, central obesity and hypertension, which are risk factors for the development of type 2 diabetes and cardiovascular diseases [9,10]. In 2017, it was estimated that MS affected 20% of North American population, 25% of European population and approximately 15% of Chinese population [11,12]. In this scenario, the relationship between MS and its comorbidities that aggravate the COVID-19 prognosis cannot be ignored. Also, its presence in different ethnicities and continents places SM as an important risk factor for COVID-19. Thus, this review is aimed at providing overview of metabolic changes associated with MS and its relationship with development and worsening of SARS-CoV-2 infection, as well as to review the proposed drugs for the treatment of these patients. We collated and discussed the available evidences that have emerged so far on the presence of obesity, diabetes, cardiovascular and liver disease in the patients with COVID-19 and proposed therapies.

2. Search methodology

We systematically searched the PubMed and Google Scholar databases until June 1st, 2020 using the keywords COVID-19, metabolic syndrome, and following terms: obesity, diabetes, liver, NAFLD, hypertension, cardiovascular disease, chloroquine, hydroxychloroquine, antiretroviral drugs, and treatment of coronavirus. We also accessed the full text of the relevant cross references from the search results.

3. Obesity and COVID-19

The WHO points obesity as a global epidemic, estimating that in 2016 more than 650 million people over aged 18 years were obese worldwide [12]. Since obesity is a risk factor for several diseases, including infectious ones, these data become even more alarming [13]. The bodies of obese patients are in constant chronic inflammation, due to the high concentrations of chemokines, adipokines and pro-inflammatory cytokines. This chronic inflammation causes a delayed and inferior immune response, with decreased activation of macrophages in infection course. In addition, the immune memory of obese individuals is also impaired, both humoral and cellular, weakening both adaptive response of immune system to disease and immunization of these patients [13–15].

Obesity had previously been identified as a risk factor for viral infections due to its influence on immune response [15]. During the 2009 H1N1 outbreak, obese patients had more stringent complications and care needs [14]. In relation to COVID-19, research points to the high rate of obese patients with complications and need for hospitalization [16]. A study carried out in New York City (NYC), U.S., showed that among the 3615 patients who tested positive for COVID-19, 21% had obesity and 16% of total had a body mass index (BMI) > 35 kg/m^2 (severe obesity). Being much more likely to develop the most severe forms of the disease, these patients had a greater need for hospitalization and care in the intensive care unit (ICU) [17]. In another study also in NYC that followed 4103 patients with COVID-19, of which 1999 (48.9%) were hospitalized, it was observed that individuals with BMI > 40 kg/m^2 were six times more likely to be hospitalized [18]. In a retrospective study of 112 patients with COVID-19 conducted at a hospital in Wuhan city, the BMI of patients in critical group (BMI > 25 kg/m^2) was significantly higher than the non-critical group, and of 17 patients who died, 15 (88.2%) had a BMI > 25 kg/m^2 [19].

In view of alarming number of cases in countries like the U.S., where it is estimated that around 36% of population is obese [20], and in Europe, where, according to the most recent WHO estimates, obesity affects 10%–30% of the population [21], obesity represents a serious problem when related to COVID-19. These data reflect the current alarming situation faced by European countries, such as those already mentioned, The United Kingdom, Italy, Spain, and also the U.S. and Brazil, whose number of serious cases and deaths tops the global statistics, pointing to obesity as risk factor for COVID-19 mortality [4].

4. Diabetes patients and COVID-19

In 2016, diabetes was seventh most deadly disease worldwide, with approximately 1.6 million deaths directly [22]. It represents a risk factor for the development of other pathologies, standing out as a disease of great medical interest [23]. Its relationship with infectious diseases is not yet fully understood. However, in addition to suppressing the patient's immunity, it can cause metabolic dysfunction that directly affects homeostasis of the entire organism [24].

In a study about relationship between diabetes, morbidity and mortality rate among patients with SARS-CoV, it was observed that patients with a known history of diabetes who died were 21.5% versus 3.9% of diabetic survivors [25]. Diabetes patients have been reported to have up to four times more chance of hospitalization during the H1N1 pandemic [26]. Like SARS-CoV and H1N1, diabetes appears as a comorbidity with potential to aggravate and lead to death by the SARS-CoV-2 infection. In a meta-analysis that included more than 40,000 infected people from Wuhan, Hubei province, China, 8% of these were diabetic patients [27]. In another study conducted in Wuhan, 191 patients were followed up and 54 died, among non-survivors, 31% were diabetic [28]. The death rate reported by the Chinese Center for Disease Control for more than 70,000 cases was 2.3%, but this was increased to 7.3% when analyzed diabetics patients in the same group [29].

Diabetes has been identified as the second most common comorbidity among cases of COVID-19. Hypotheses have been raised that this high incidence rate in diabetic patients is directly linked to high gene expression of angiotensin-converting enzyme 2 (ACE2) in their cells, which are used by SARS-CoV-2 to enter human cells, due to treatment with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) [30]. This would not only increase the risk of these patients to infection but would also make it difficult to control comorbidity during treatment against COVID-19. This relationship is not yet fully understood and further studies are needed to confirm it, since the drug treatment protocols for diabetic patients remain the same for their metabolic dysfunction [31].

5. Cardiovascular (CV) disease and COVID-19

Hypertension has appeared in research in various countries and continents as the most common comorbidity among those infected with SARS-CoV-2 [5–7,27,28,30], as well as cardiovascular diseases (CVD) that appear as risk factors for severe complications of COVID-19. Arterial hypertension, heart failure and arrhythmia are some of diseases of the cardiovascular system that can generate several complications in SARS-CoV-2 infection course [32].

In an analysis of 99 patients with COVID-19, it was observed that 21% of patients had problems such as hypertension or coronary heart disease and of the 32 patients who developed severe forms of pneumonia caused by SARS-CoV-2, 17 individuals had some heart disease [33]. A meta-analysis involving more than 3000 patients with COVID-19 found that patients with CVD are up to five times more likely to develop the disease critical stage [34]. Data from the Chinese Center for Disease Control and Prevention pointed a 2.3% mortality rate in a group of 44,672 infected with COVID-19. However, this number was much higher among patients with hypertension and CVD, reaching 6% and 10.5%, respectively [32].

In addition to history of CVD being an aggravating factor in COVID-19 development, cardiovascular complications can also be result of the infection. Acute myocardial injury has been observed in 8% of confirmed cases of disease, with an elevation of high-sensitivity cardiac troponin I found in up to 12% of cases, while the troponin among patients with mild symptoms of infection was found in low concentration [32,35]. In the investigation, 187 patients with COVID-19 were evaluated, of the 36 patients who had a history of CVD and died, 25 had high troponin levels [35].

The high concentration of ACE2 in cardiac tissue can be pointed out as possible mechanism for the lesions, since this enzyme is used by SARS-CoV-2 to invade the cell, making the heart a favorable site for viral colonization. As in diabetes, many of drugs used to treat hypertension act as ACE inhibitors and ARBs, increasing ACE2 expression in the individual [30,32,36]. As a highly active tissue with a high demand for energy produced by mitochondria, hypoxia promoted by COVID-19 can cause damage in the myocardium and have severe consequences for the infected patient [32,35].

Currently, CVD are the main cause of death, being responsible for 31% of deaths in 2016. Much of this is reflection of eating habits and sedentary lifestyle that modern life has provided for the population. MS is a contributing factor to the development of CVD and, in the current pandemic scenario, this sedentary lifestyle takes its toll [37].

6. Liver and COVID-19

The liver is an important organ for the most diverse body metabolic functions. Damage caused to hepatic tissue by COVID-19 has been observed. In addition, pathologies that affect it are inserted as risk factors for complications and severe manifestations of pneumonia caused by the novel coronavirus [38]. Like other organs, liver cells, especially bile duct cells, have ACE2 enzyme on their surface, placing liver tissue as a possible infection site for the virus [39].

Previously, during the 2002 severe acute respiratory syndrome coronaviruses (SARS-CoV) outbreak, studies have shown direct action of virus on hepatocytes, causing apoptosis in cells and inducing injury. Elevated serum levels of pro-inflammatory cytokines have also been found in patients with liver damage. Like the 2012 epidemic by Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), liver damage caused by infection was observed in infected patients. However, unlike SARS-CoV and SARS-CoV-2, MERS-CoV uses another receptor to invade the cell, dipeptidyl-peptidase IV (DPP-4), which is widely expressed in hepatocytes. As with SARS-CoV infection, high serum levels of inflammatory cytokines have been described in these patients [40,41].

In the current pandemic caused by the novel coronavirus, some studies have already observed abnormal concentrations of liver function markers. In the study with 202 patients, it was observed that patients with NAFLD had a higher risk of COVID-19 progression, and of the 39 patients with progressive condition, 34 (87%) had NAFLD. Inflammation of liver tissue resulting from pro-inflammatory cytokines released by adipose tissue becomes even more aggravated by the pathogen presence, such as SARS-CoV-2, with complications not fully clarified, but potentially severe for infected patient [42]. It was observed that approximately 20%–30% of patients with COVID-19 had elevated transaminases, especially in those with metabolic disorders associated with obesity and non-alcoholic fatty liver disease (NAFLD) [42,43].

It is not yet clear whether liver damage is primary, caused directly by the virus and inflammatory reaction, or secondary, caused by drugs used in treatment and hypoxia caused by pneumonia. However, even if modest, the changes exist and certainly the history of pre-existing liver disease tends to worsen the infection prognosis [41,44].

In this context, NAFLD, which is considered the hepatic manifestation of MS, characterized by the deposit of fat in liver tissue, is inserted as a comorbidity, subject to detailed observation [45]. Its prevalence is estimated between 20% and 30% in the population of Western countries and between 5% and 18% among Asian countries, being significantly increased in obese and diabetic patients [46]. Researches on the relationship between NAFLD and COVID-19 are still scarce.

7. Proposed therapies and COVID-19

In the absence of any known effective therapy and due to the pandemic situation, recently many drugs in the treatment of COVID-19 have been tested. Drugs previously proposed for the treatment of viral diseases, including previous outbreaks by other coronavirus (SARS-CoV and MERS-CoV), began to be tested, with emphasis on chloroquine and its hydroxychloroquine analog, associated or not with azithromycin, corticosteroids and other antiviral medications in patients with COVID-19 [47,48]. The proposed pharmacological treatments are summarized in Table 1, which shows the mechanism of action and adverse effects of drugs.

Experimental studies have suggested that chloroquine (CQ) is a proven antimalarial drug that can inhibit the replication of various intracellular microorganisms, including coronavirus in vitro [49,50]. It is suggested a possible inhibition of SARS-CoV-2 replication by terminal glycosylation of ACE2, produced by pulmonary vessels, inhibiting the link between virus and receptor. Inhibition of viral infection by raising the endosomal pH is also reported, thus interfering with virus-cell fusion. In addition, it was observed that this medicine contributed to prevention of viral spread in cell cultures [47].

Hydroxychloroquine (HCQ) can also increase intracellular pH and inhibit lysosomal activity in antigen-presenting cells. This process reduces T cell activation, differentiation and expression of costimulatory proteins and production of cytokines. In the cytoplasm, it interferes with synthesis of viral nucleic acids, attenuating pro-inflammatory response. Both mechanisms strengthen the hypothesis that HCQ can suppress SARS-CoV-2 by inhibiting the hyperactivation of immune system triggered by the virus and, thus, reducing disease progression from mild to severe. However, still without clinical evidence [49,50].

Although HCQ and CQ have shown antiviral activity against SARS-CoV-2 in vitro, HCQ appears to have a more potent action. Furthermore, HCQ has a clinical safety superior to CQ with its long-term use, as it allows the use of higher doses and has few interactions with other drugs [51]. A non-randomized controlled trial showed that azithromycin associated with HCQ was significantly more efficient to eliminate virus, where 70% of patients had no detectable viral load after 6 days of treatment. However, these drugs must be used carefully. The azithromycin indiscriminate use, being an antimicrobial, can cause bacterial resistance. The use of CQ may cause an increase of QT interval, retinopathy and

Table 1
Proposed treatments for COVID-19: drugs, mechanisms of action and adverse effects.

Therapeutic options	Mechanism of action	Adverse effects	References
Chloroquine	Terminal glycosylation of ACE2 Elevation of endosomal pH	Increase of QT interval Retinopathy Cardiovascular disorders	[47,52]
Hydroxychloroquine	Increase intracellular pH and inhibit lysosomal activity in antigen-presenting cells	Serious skin reactions Liver failure Ventricular arrhythmia	[50,55]
Azithromycin	Antimicrobian activity	Bacterial resistance	[47]
Favipiravir	Inhibition of RNA polymerase activity	Increase of serum uric acid	[60]
Lopinavir/ritonavir	Inhibition of 3-chymotrypsin-like protease	Gastrointestinal discomfort Nausea Diarrhea Hepatotoxicity	[43,59]
Remdesivir	Specifically inhibits viral transcription and replication by blocking the RNA polymerase enzyme	Anemia Acute kidney injury Increased blood creatinine Increased total bilirubin Hyperglycemia Increased aminotransferase levels	[65–67]
Nitazoxanide	Inhibits the expression of viral nucleoprotein Suppresses pro-inflammatory cytokine production	Headache Diarrhea	[70]
Corticosteroids	Immunosuppression	Delayed viral clearance of the respiratory tract and blood Hyperglycemia Psychosis Avascular necrosis Increased risk of secondary infection	[71–73]
Convalescent plasma	Viral suppression Increased humoral activity	No serious adverse effects	[68]

cardiovascular disorders, which should certainly be of concern in hypertensive patients [52].

The research warns to the adverse effects and real effectiveness of medications. According to studies, widespread use of HCQ will expose patients to fatal consequences, including skin reactions, liver failure and ventricular arrhythmia, especially if prescribed in association with azithromycin. Furthermore, there is a risk that CQ phosphate can cause acute poisoning or even death [53–56]. Researchers analyzed 1376 patients with COVID-19 in New York City, where 58.9% (811) were treated with HCQ. Of the treated total, 346 developed respiratory failure, 180 were intubated and 166 died without intubation. According to the analysis, patients who took HCQ were more likely to develop respiratory failure than those who did not use it [54]. This makes randomized controlled trials with HCQ extremely necessary in patients with COVID-19, mainly associated with metabolic disorders.

Patients who have type 1 or type 2 diabetes and/or hypertension, who are treated with ACE inhibitors and/or ARBs, have a considerable increase in ECA2 receptors expression, which may facilitate the virus entry. The same authors report that patients using these drugs can develop severe and fatal COVID-19 [56]. As an appropriate alternative treatment, the use of calcium channel blockers as antihypertensive agents is suggested. A patient-centered approach should be used to guide the choice of pharmacological agents, considering age, severity of COVID-19, cardiovascular comorbidities and risk of hypoglycemia [56,57].

Another possibly promising drug is favipiravir, a drug with proven action against Ebola virus. The drug's efficiency in reducing SARS-CoV-2 infection is due to the inhibition of RNA polymerase activity [58,59]. A randomized clinical trial with 240 patients in China showed that favipiravir (71.43%) is more effective than arbidol (55.86%) in the treatment of COVID-19. Patients with hypertension and/or diabetes who used favipiravir experienced a reduction in fever and cough relief faster than patients who used arbidol. However, there was no difference in auxiliary oxygen therapy or non-invasive mechanical ventilation between patients [60].

Antiretroviral drugs lopinavir/ritonavir, an oral combination agent, approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV, demonstrated in vitro activity against other coronaviruses by inhibiting 3-chymotrypsin-like protease [61]. Adverse effects of lopinavir/ritonavir include gastrointestinal discomfort, such as nausea and diarrhea (up to 28%), and hepatotoxicity (2%–10%) [62]. In patients with COVID-19, these adverse effects may be exacerbated by combination therapy or due to viral infection [43].

Remdesivir (GS-5734), as adenosine nucleoside analogue prodrug, has a broad-antiviral spectrum against phyloviruses, paramyxoviruses, pneumoviruses and coronaviruses [63]. In vitro studies have shown the ability of remdesivir to inhibit coronaviruses replication in primary human lung cells [63,64]. Patients hospitalized with severe COVID-19 treated with compassionate-use remdesivir showed clinical improvement in 36 of 53 patients (68%) [65], well as showed shortened time to recovery and evidence of lower respiratory tract infection in the remdesivir group [66]. However, in another study, remdesivir in adults with severe COVID-19 was not associated with significant clinical benefits, but the patients who received remdesivir had a numerically faster time to clinical improvement than those receiving placebo, with symptom duration of 10 days or less [67]. In all studies, adverse events were reported during follow-up of patients (between 28% and 66%), such as anemia or decreased hemoglobin, thrombocytopenia, acute kidney injury, decreased estimated glomerular filtration rate, increased blood creatinine, increased total bilirubin, hyperglycemia and increased aminotransferase levels, which suggests clinical investigation in patients with complications associated with metabolic syndrome [65–67].

Another potential adjuvant therapy for COVID-19 is the use of convalescent plasma or hyperimmune immunoglobulins [68]. The justification for this treatment is that the antibodies of recovered patients can help in the immune response against the virus in individuals with COVID-19 or be a preventive measure of infection in cases of vulnerable individuals with diverse metabolic disorders.

Nitazoxanide, traditionally an anthelmintic agent, has broad antiviral activity and relatively favorable safety profile, demonstrated in vitro antiviral activity against MERS and SARS-CoV-2 [69,70]. In the lack of robust evidence, antiviral activity, immunomodulatory effects and safety profile of nitazoxanide justify further

study as a therapeutic option for COVID-19.

Current evidence demonstrates the use of corticosteroids to decrease inflammatory responses in the lungs. However, this benefit can be overcome by its adverse effects, including delayed viral clearance of the respiratory tract and blood and high rates of complications, including hyperglycemia, psychosis and avascular necrosis, as well as increased risk of secondary infection. Although the direct evidence for the use of corticosteroids in COVID-19 is limited, result revisions in other viral pneumonias are instructive. Observational studies in patients with SARS and MERS have not reported an association of corticosteroids with improved survival [71–73]. The risk of hyperglycemia in diabetic patients can be reduced, although not eliminated, by good glycemic control.

Although several therapeutic agents have been evaluated for the treatment of COVID-19, no therapy have yet been shown to be efficacious for patients.

8. Conclusion

Metabolic syndrome is a risk factor that influences COVID-19 progression and prognosis. The prevalence of obese, diabetic, hypertensive or liver damage patients with severe cases of COVID-19, in multiple countries, demonstrates the importance of the care with this risk group, in prophylaxis, monitoring and treatment. Similarly, the drugs currently evaluated for the infection treatment are promising but need further studies to prove their efficacy and safety, due to the adverse effects may be exacerbated by combination therapy or due to viral infection. The development of a vaccine for immunization is still the best long-term solution for the prevention of future outbreaks of SARS-CoV-2. In addition, people of any age who have pre-existing diseases, such as heart disease, diabetes, obesity, among others, also need to redouble their care in measures to prevent coronavirus.

References

[1] Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. J Adv Res 2020;24:91–8.

[2] Coronavirus disease (COVID-19) pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019. [Accessed 14 May 2020].

[3] WHO. Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at:-, https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020. [Accessed 14 May 2020].

[4] WHO. Coronavirus disease 2019 (COVID-19) situation report – 133. Available at:-, https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200601-covid-19-sitrep-133.pdf?sfvrsn=9a56f2ac_4. [Accessed 1 June 2020].

[5] Rothan HA1, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020 May;109:102433. Epub 2020 Feb 26, https://doi.org/10.1016/j.jaut.2020.102433.

[6] Garg S, Kim L, Whitaker M, Cummings C, Holstein R, Prill M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 — COVID-NET, 14 states, March 1–30, 2020. MMWR (Morb Mortal Wkly Rep) March 2020;69(15). https://www.cdc.gov/mmwr.

[7] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229):1054–62. Epub 2020 Mar 11, https://doi.org/10.1016/S0140-6736(20)30566-3.

[8] Ministério da Saúde (BR). Boletim epidemiológico especial COE-COVID-19: semana epidemiológica 21. Brasília (DF). 2020. Available at:-, https://www.saude.gov.br/images/pdf/2020/May/29/2020-05-25—BEE17—Boletim-do-COE.pdf. [Accessed 31 May 2020].

[9] Neto JCGL, Oliveira JFSF, Souza MA, Araújo FM, Damasceno MMC, Freitas RWJF. Prevalência da síndrome metabólica e de seus componentes em pessoas com diabetes mellitus tipo 2. Texto Contexto Enferm 2018;27(3):e3900016.

[10] Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis 2017 Aug 11;(8):215-225. https://doi.org/10.1177/1753944717711379.

[11] Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep 2018 Feb 26;20(2):12. https://doi.org/10.1007/s11906-018-0812-z.

[12] World Health Organization. Obesity and overweight Fact sheet n°311. Available at:-, http://www.who.int/mediacentre/factsheets/fs311/en/. [Accessed 10 April 2020].

[13] Luzi L, Radaelli M. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. Acta Diabetol 2020 Jun;57(6):759–64. https://doi.org/10.1007/s00592-020-01522-8 Epub 2020 Apr 5.

[14] Honce R, Cherry SS. Impact of obesity on influenza A virus pathogenesis, immune response, and evolution. Front Immunol 2019;10:1071. 2019 May 10, https://doi.org/10.3389/fimmu.2019.01071.

[15] Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. Int J Obes (Lond) 2013 Mar;37(3):333–40. https://doi.org/10.1038/ijo.2012.62. Epub 2012 1 de maio.

[16] Dietz W, Burgoa SC. Obesity and its implications for COVID-19 mortality. Obesity J 2020. v0, n0.

[17] Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa415.

[18] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell LF, Chernyak Y, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. medRxiv: the preprint server for Health Sciences. 2020. https://doi.org/10.1101/2020.04.08.20057794.

[19] Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. Zhonghua Xinxueguanbing Zazhi 2020 Mar 2;48:E004. 0, https://doi.org/10.3760/cma.j.cn112148-20200220-00105.

[20] Global Health Observatory (GHO). data: overweight and obesity. Available at:-, https://www.who.int/gho/ncd/risk_factors/overweight/en/. [Accessed 1 May 2020].

[21] WHO, EUROPE. Obesity: data and statistics. Available at:-, http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics. [Accessed 1 May 2020].

[22] WHO. Diabetes key facts. Available at:-, https://www.who.int/news-room/fact-sheets/detail/diabetes. [Accessed 3 May 2020].

[23] Knapp S. Diabetes and infection: is there a link? - a mini-review. Gerontology 2013;59(2):99–104. Epub 2012 Nov 24, https://doi.org/10.1159/000345107.

[24] Singh A, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr 2020 Apr 9;14(4):303–10. https://doi.org/10.1016/j.dsx.2020.04.004.

[25] Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med 2006 Jun;23(6):623–8.

[26] Allard R1, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care 2010 Jul;33(7):1491–3. https://doi.org/10.2337/dc09-2215.

[27] Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020 Mar 12;94:91–5. https://doi.org/10.1016/j.ijid.2020.03.017.

[28] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229):1054–62. Epub 2020 Mar 11, https://doi.org/10.1016/S0140-6736(20)30566-3.

[29] Hill M, Mantzoros C, Sowers J. Commentary: COVID-19 in patients with diabetes. Metabolism 2020 Mar 24;107:154217. https://doi.org/10.1016/j.metabol.2020.154217.

[30] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet 2020 March 11. https://doi.org/10.1016/S2213-2600(20)30116-8.

[31] Stoian A, Banerjee Y, Rizvi A, Rizzo M. Diabetes and the COVID-19 pandemic: how insights from recent experience might guide future management. Metab Syndr Relat Disord 2020;18(4):173–5. https://doi.org/10.1089/met.2020.0037.

[32] Bansal M. Cardiovascular disease and COVID-19. Diabetes Metab Syndr 2020;14(3):247–50. https://doi.org/10.1016/j.dsx.2020.03.013.

[33] Zheng Y, Xu H, Yang M, Zeng Y, Chen H, Liu R, et al. Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu. J Clin Virol 2020;127:104366. https://doi.org/10.1016/j.jcv.2020.104366.

[34] Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical and deadly cases of COVID-19: a systematic review of the literature and meta-analysis. J Infect 2020;S0163–4453(20):30234–6. https://doi.org/10.1016/j.jinf.2020.04.021.

[35] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 March 27. https://doi.org/10.1001/jamacardio.2020.1017.

[36] Lippi G, Wong J, Henry BM. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. Pol Arch Intern Med 2020 Apr 30;130(4):304–9. Epub 2020 Mar 31, https://doi.org/10.20452/pamw.15272.

[37] Cardiovascular diseases (CVDs) Key facts. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). [Accessed 3 May 2020].

[38] Feng G, Zheng K, Yan Q, Rios R, Targher G, Byrne C, et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol 2020 Mar 28;8(1):18–24.

[39] Feng G, Zheng KI, Yan QQ, et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol 2020 Mar 28;8(1):18–24. https://doi.org/10.14218/jcth.2020.00018.
[40] Guo Y, Korteweg C, McNutt MA, Gu J. Pathogenetic mechanisms of severe acute respiratory syndrome. Virus Res 2008 Apr;133(1):4–12. Epub 2007 Sep. 7, https://doi.org/10.1016/j.virusres.2007.01.022.
[41] Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020 May;40(5):998–1004. Epub 2020 Mar 30, https://doi.org/10.1111/liv.14435.
[42] Ji D, Qin E, Xu J, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. Letter to the Editor 2020 April 08. https://doi.org/10.1016/j.jhep.2020.03.044.
[43] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020;14(1):58–60. https://doi.org/10.5582/ddt.2020.01012.
[44] Li J, Fan JG. Characteristics and mechanism of liver injury in 2019 coronavirus disease. J Clin Transl Hepatol 2020 Mar 28;8(1):13–7. https://doi.org/10.14218/JCTH.2020.00019.
[45] Petta S, Valenti L, Bugianesi E, Targher G, Bellentani S, Bonino F. A "systems medicine" approach to the study of non-alcoholic fatty liver disease. Dig Liver Dis 2016 Mar;48(3):333–42. Epub 2015 Nov 14, https://doi.org/10.1016/j.dld.2015.10.027.
[46] Satapathy SK, Sanyal AJ. Epidemiology and natural history of nonalcoholic fatty liver disease. Semin Liver Dis 2015 Aug;35(3):221–35. Epub 2015 Sep. 17, https://doi.org/10.1055/s-0035-1562943.
[47] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an openlabel non-randomized clinical trial. Int J Antimicrob Agents 2020. 105949, https://doi.org/10.1016/j.ijantimicag.2020.105949.
[48] Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005 August;(22):2–69. https://doi.org/10.1186/1743-422X-2-69.
[49] Geamănu Pancă A, Popa-Cherecheanu A, Marinescu B, Geamănu CD, Voinea LM. Retinal toxicity associated with chronic exposure to hydroxychloroquine and its ocular screening. Review. J Med Life 2014;7(3):322–6. PubMed PMID: 25408748.
[50] Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother 2020 Mar 20. https://doi.org/10.1093/jac/dkaa114.
[51] Biot C, Daher W, Chavain N, Fandeur T, Khalife J, Dive D, et al. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. J Med Chem 2006;49(9):2845–9.
[52] Touret F, Lamballerie X. Of chloroquine and COVID-19. Antivir Res 2020;177:104762. https://doi.org/10.1016/j.antiviral.2020.104762.
[53] Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in patients hospitalized with Covid-19. N Engl J Med 2020 May 7. https://doi.org/10.1056/NEJMoa2012410.
[54] Ferner RE, Aronson JK. Chloroquine and hydroxychloroquine in covid-19. BMJ 2020 April 8;369:m1432. https://doi.org/10.1136/bmj.m1432.
[55] Barbosa J, Kaitis D, Freedman R, Le K, Lin X. Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomized comparative study. N Engl J Med [Internet] 2020 Apr 4 [Accessed 04 May 2020], https://www.sefq.es/_pdfs/NEJM_Hydroxychlorquine.pdf.
[56] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020 March 11. https://doi.org/10.1016/s2213-2600(20)30116-8.
[57] Wang W, Lu J, Gu W, Zhang Y, Liu J, Ning G. Care for diabetes with COVID-19: advice from China. J Diabetes 2020 April 13. https://doi.org/10.1111/1753-0407.13036.
[58] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (SARS-CoV-2) in vitro. Cell Res 2020;30(3):269–71. 2020 February 04.
[59] Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020;14(1):58–60. https://doi.org/10.5582/ddt.2020.01012.
[60] Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv 2020 April 15. https://doi.org/10.1101/2020.03.17.20037432.
[61] Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004 Mar;59(3):252–6. https://doi.org/10.1136/thorax.2003.012658.
[62] Lopinavir/ritonavir [database online]. Hudson (OH): Lexicomp Inc; 2016. http://online.lexi.com. [Accessed 17 April 2020].
[63] Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci Rep 2017 Mar;7:43395. https://doi.org/10.1038/srep43395.
[64] Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017 Jun;9(396):eaal3653. https://doi.org/10.1126/scitranslmed.aal3653.
[65] Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe covid-19. N Engl J Med 2020. NEJMoa2007016, https://doi.org/10.1056/NEJMoa2007016.
[66] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19—preliminary report. N Engl J Med 2020. https://doi.org/10.1056/netjmoa2007764.
[67] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo controlled, multicentre trial. Lancet 2020;395:1569–78. https://doi.org/10.1016/S0140-6736(20)31022-9.
[68] Chen L, Xiong J, Bao L, Shi Y. Plasma convalescente como terapia potential para COVID-19. Lancet Infect Dis 2020;20(4):398–400. https://doi.org/10.1016/s1473-3099(20)30141-9.
[69] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (SARS-CoV-2) in vitro. Cell Res 2020;30(3):269–71. 2020 February 04, https://doi.org/10.1038/s41422-020-0282-0.
[70] Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health 2016 May-Jun;9(3):227–30. Epub 2016 Apr 16, https://doi.org/10.1016/j.jiph.2016.04.001.
[71] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(10223):473–5. https://doi.org/10.1016/S0140-6736(20)30317-2.
[72] Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3(9):e343. https://doi.org/10.1371/journal.pmed.0030343.
[73] Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med 2018 Mar 15;197(6):757–67. https://doi.org/10.1164/rccm.201706-1172OC.