Ref: Ro J Infect Dis. 2020;23(2)
DOI: 10.37897/RJID.2020.2.1

PATIENTS WITH DIABETES AT RISK IN COVID-19 PANDEMIC

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ABSTRACT

The new coronavirus infection (COVID-19) spread rapidly from the outbreak in Wuhan, China with a wide range of clinical manifestations, from asymptomatic to fatal. Individuals from the risk factor category, including those with diabetes mellitus (DM), have a proven higher risk of developing a severe form of the disease, as well as a higher risk of mortality. Through this summary we aim to briefly review the general characteristics of COVID-19 and a special situation, namely that of infection in patients with diabetes. We addressed the potential mechanisms that may increase the susceptibility of diabetic patients to COVID-19, but also the current recommendations in Romania for diabetics in the COVID-19 pandemic. Based on current limited evidence we cannot draw conclusions. Further research on this association between COVID-19 and DM is necessary and justified.

Keywords: SARS-CoV-2, infection, COVID-19, pandemic, comorbidity, diabetes mellitus

INTRODUCTION

In December 2019, a new coronavirus, now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the etiological factor of an outbreak of acute respiratory disease in Wuhan, a city in Hubei Province, China. In February 2020, the World Health Organization (WHO) announced COVID-19 as the disease name. The infection has spread, leading the WHO to declare a public health emergency on 30 January 2020 and characterize it as a pandemic on 11 March 2020. On 05 May 2020, were 3,517,345 confirmed cases reported from over 210 countrie,s with 243,401 deaths (1-2).

The purpose of this paper is to provide a brief summary of the general characteristics of COVID-19, as well as a detailed description of the association between this new infectious disease and diabetes.

METHOD

A literature review was performed by searching for English-language articles indexed in PubMed and Google Scholar databases until May 4, 2020. The following keywords were used: "SARS-CoV-2", "COVID-19", "infection", "clinical features", "comorbidity", "diabetes", "prognosis". We accessed the scientific recommendations and articles currently available on the websites of the WHO, the European and United States Centers for Disease Control and Prevention (ECDC, respectively CDC) and the National Institute of Public Health in Romania.

General features of COVID-19

Etiology. The coronavirus that causes COVID-19 is a beta-coronavirus of the same subgenus as Severe Acute Respiratory Syndrome (SARS) virus (as well

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as several bat coronaviruses), but in a distinct class. The structure of the gene region that binds to the receptor is very similar to that of the SARS coronavirus and it has been shown that the virus uses the same receptor, the angiotensin converting enzyme 2 (ACE2), to enter cells (3). The "Coronavirus Study Group" for virus taxonomy has proposed that this virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4).

Epidemiology - distribution, route of transmission. Cases are reported from all continents, except Antarctica and are constantly growing worldwide. Enlarged local transmission clusters can now be found in Western Europe, United States and Iran. The cumulative incidence varies by country and probably depends on a number of factors, such as demographics and population density, testing and reporting, prevention and control strategies.

At the beginning of the outbreak, the epidemiological survey from Wuhan identified an initial association with a seafood market selling live animals, where most patients worked or were visitors (5). However, as the outbreak progressed, person-to-person transmission became the main mode of transmission, but the exact mode is unclear. Transmission is thought to occur, as with other respiratory pathogens including influenza and rhinovirus, through respiratory drops from coughing and sneezing (6). The virus released from the respiratory secretions of an infected person can infect another person if it makes direct contact with the mucous membranes; infection can also occur if a person touches an infected surface and then touches their eyes, nose or mouth. The drops usually do not spread more than about two meters and do not persist in the air. It is controversial whether SARS-CoV-2 can be transmitted by air under natural conditions, but the direct relevance and clinical implications of these findings are unclear. Aerial precautions remain recommended when performing aerosol generating procedures (7-15). The duration of viral shedding varies significantly and possibly depends on the severity. SARS-CoV-2 can be transmitted before the onset of symptoms and during the disease (16-19). The risk of transmission from an individual with SARS-CoV-2 infection varies depending on the type and duration of exposure, the use of preventive measures, and probable individual factors (for exemple, the amount of virus in respiratory secretions). Most secondary infections have been described among household contacts, in care or healthcare facilities when personal protective equipment has not been used, and indoors (cruise ships). Social or labour gatherings are also at risk of transmission through restricted contact (20-23). The virus present on contaminated surfaces can be another source of infection. The frequency and relative importance of this type of transmission remains unclear. It may be more likely a potential source of infection in certain circumstances (for example, in the household of an infected person or in hospitals) (7,9,24-28).

Clinical features. Patients with COVID-19 have presented a wide range of clinical forms, from asymptomatic / mild symptoms to serious illness and death. Symptoms may appear 2-14 days after viral exposure, and are as follows: coughing, shortness of breath or respiratory failure, fever, chills, muscle pain, sore throat, new loss of taste or smell. Other uncommon symptoms have been reported, such as gastrointestinal symptoms (nausea, vomiting or diarrhea) (29). Children have similar symptoms to adults and generally have mild manifestations, although cases have been reported - children with severe forms of COVID-19 and two deaths (30-34). Severe disease occurs predominantly in older adults or in adults with underlying medical comorbidities.

An analysis based on data from within and outside of China shows that age is a strong gradient in the risk of death. Similarly, the hospitalization rate increased with age, with a rate of 1% for 20-29 year olds, 4% for 50-59 year olds and 18% for> 80 year olds (35). Older age is also associated with increased mortality. Case fatality rates have been reported in Italy from 12.8 to 20.2% among those aged 70-79 years and ≥ 80 years, respectively (36.37).

The established epidemiological risk factors are: age > 65 years, pre-existing lung disease, chronic kidney disease, DM, history of hypertension, history of cardiovascular disease (CVD), obesity (BMI ≥ 30). Possible risk factors include: use of biological substances (ex. TNF inhibitors, interleukin inhibitors, anti-B-cell agents), history of transplantation or other immunosuppressive conditions and HIV, CD4 cell count <200 cells/µl or unknown CD4 count. The CDC also includes liver disease as potential risk factors for severe disease (20,38). Males accounted for a higher number of deaths in cohorts in China, Italy, and the United States (36, 39-40). Poor prognosis was also associated with some particular laboratory characteris-

tics, such as: lymphopenia, elevated liver enzymes, elevated LDH, elevated acute phase reactants (for ex. C-reactive protein, ferritin), elevated D-dimer (> 1 μg/ml), increased prothrombin time, elevated troponin, elevated creatine phosphokinase, acute kidney damage (20).

Diagnosis of COVID-19 infection. Testing patients, which meets the criteria set by WHO and government, can be performed in state public health laboratories, hospitals and some commercial laboratories. Reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 virus is the standard method for initial diagnosing virus from respiratory samples (oropharyngeal and nasopharyngeal swabs) and lower respiratory tract samples (sputum), in patients with productive cough (41).

SARS-CoV-2 invades the respiratory tract and lungs, leading to a new type of viral pneumonia (42), in which severe cases can progress rapidly to respiratory distress syndrome, septic shock, and multiple organ dysfunction syndrome (43). We do not address case management and preventive measures in this study. Individuals from the risk factor category mentioned above have a higher demonstrated risk of developing a severe form of the disease as well as a higher risk of mortality (16,44-45).

Below we will summarize a special situation, that of SARS-CoV-2 infection in patients with DM, the impact between the two global pandemics, being a gloomy reality the fact that DM is the second most common comorbidity in COVID-19 disease (16).

ASSOCIATION BETWEEN COVID-19 AND DM

Rates of diabetes in patients infected with SARS-CoV-2. Rates of type 2 diabetes mellitus (T2D) in patients with COVID-19 vary with age, studied population, disease severity and test method. In a report from China, diabetes was present in about 15% of 1099 patients (children and adults) hospitalized with a laboratory-confirmed diagnosis (43). Analysis of a randomly selected subset of fatal cases of COVID-19 in Italy (mean age 79.5 years) revealed a 35% prevalence of diabetes (36). In a publication from 3 April 2020 in the United States with 7,162 confirmed cases of COVID-19 (between Feb. 12 and March 28, 2020), and listed by the CDC examining comorbidities, diabetes was ranked first in frequency (10.9%), of which 6% not hospitalized, 24% hospitalized in non-intensive care units, respectively 32% hospitalized in intensive care units (49). In Romania, on May 5, 2020, out of 803 deaths, 243 (30.3%) had diabetes as a comorbidity. We mention that the prevalence of DM in Romania according to the PREDATORR study is 11.6% (50).

Susceptibility to infections in patients with DM. It is widely accepted both in medicine and by the general public that diabetics have an increased tendency to develop infections. Although several epidemiological studies have shown that diabetics receive treatment for infections more often than non-diabetics (46), the extent of the effect of diabetes on the risk of COVID-19 infection remains an active research question. A study from Netherlands evaluated the number of patients with T2D cared for in a general practice over a two-year period. A total of 458 infections were present in 193 patients, with an average of 2.4 (± 1.9) infections per patient (47). Torres et al. summarize in their study that patients with diabetes have an increased risk of up to 1.4 (OR) for community-acquired pneumonia. The risk of hospitalization related with diabetes-associated pneumonia was also higher in those without other comorbidities and in those with a longer duration of diabetes and/or poor glycemic control (based on hemoglobin A1C levels) (48). Most, but not all, studies suggest that the risk of infection in diabetes is associated with hyperglycemia or lack of control of DM. For example, Critchley et al. demonstrate the strong association, but the report from the Netherlands mentioned above, with the limitations of the study, concludes that hyperglycemia is more likely to be a result than a cause of common infections (47,49).

Potential mechanisms that may increase the susceptibility of patients with diabetes to COVID-19 include: 1) higher affinity cellular binding and efficient virus entry, 2) decreased viral clearance, 3) diminished T cell function, 4) increased susceptibility to hyperinflammation and "cytokine storm" syndrome and 5) the presence of CVD (51).

SARS-CoV-2 uses ACE2 receptors for entry into target cells and increased ACE2 expression has been demonstrated in lungs, kidneys, heart and pancreas in rodent models with DM (3, 52-53). Insulin administration attenuates ACE2 expression, while hypoglycemic agents (e.g. glucagon-like peptide-1 receptor agonist, thiazolidinediones), ACE inhibitors and statins regulate ACE2 (51). Rao et al. explored diseases or traits that may be causally linked to increased ACE2

expression in the lung. They found that DM was causally associated with increased pulmonary ACE2 expression (54). Otherwise circulating levels of furin (cellular protease involving viral entry) are elevated in patients with DM (55).

Analyzing demographic, clinical and laboratory data of 106 patients hospitalized in a Wuhan hospital between 5 January and 25 February 2020 to identify factors influencing SARS-CoV-2 clearance negatively, Chen et al. found that advanced age, male gender and ACE2 associated factors (including hypertension, DM and CVD) adversely affected viral clearance (56).

Humans and mice with T2D exhibit a switch from predominately regulatory or anti-inflammatory macrophages and regulatory T cells in adipose tissue into predominately proinflammatory macrophages and Th1 cells (T helper type 1) and Th17 $CD4^+$T. Kulcsar et al. examined the effects of DM in a humanized mouse model infected with MERS-CoV on a high-fat diet. The disease was more severe and prolonged in diabetic and male mice, and was characterized by altered $CD4^+$T cell counts and abnormal cytokine responses (elevated IL17a values). This altered immune profile is thought to contribute to a variety of consequences associated with T2D, including increased susceptibility to infections (57). Epidemiological studies indicate that T2D was the main comorbidity associated with severe or fatal MERS-CoV infections (58). Regarding the current pandemic, COVID-19 DM is the second most common comorbidity (16).

Plasma levels of inflammatory biomarkers (interleukin-6, serum ferritin, C-reactive protein) and D-dimer are higher in patients with COVID-19 and DM compared to those without, suggesting that diabetics are more susceptible to the "cytokine storm", leading to rapid deterioration of the disease (59).

Considering increased prevalence of CVD, obesity and hypertension in diabetic patients, it is not known whether diabetes independently contributes to this increased risk of severe SARS-CoV-2 infection. However, plasma glucose levels and DM are independent predictors of mortality and morbidity in patients with SARS (60).

Challenges for clinicians and diabetics. In view of the current situation, the lack of solid scientific evidence and specific treatment, COVID-19 has become a global health problem. Currently quarantine, isolation, social distancing and strict restrictions on internal and international travel are the most effective preventive strategies, along with the practice of good hygiene. These measures are likely to have an impact on worsening glucose control: limiting the physical activity of people with diabetes; restricting food deliveries during quarantine would have forced diabetics to change their eating habits that were earlier associated with good glycemic control; the purchase of anti-diabetic drugs and blood glucose test strips would have been difficult due to restrictions, as was the possibility to visit doctors for routine follow-up (61). For such situations, it is very important to educate and support the self-management of diabetes. Clinicians, on the other hand, need to be proactive in responding to the needs of patients using telemedicine, including voice or video calls, if available. It is possible that regulating care through these technologically advanced means may have a lasting impact on how diabetics are treated and follow up in the long-term (62).

Specific recommendations for people with diabetes offered by the Romanian Federation of Diabetes, Nutrition and Metabolic Diseases are as follows: reducing the number of people they come in contact with; avoiding contact with people suspected of acute respiratory infections; travel reductions; cleaning hazardous surfaces with chlorine or alcohol based disinfectants; individual hygiene measures, avoiding to touch the face, eyes, nose and mouth; washing hands very often with soap and water (minimum 20 seconds) and necessarily before using the glucometer and injecting insulin or other injectable medication; use of protective masks; not using antiviral drugs and antibiotics, unless your doctor prescribes it; maintaining contact with the diabetologist and the family doctor for planning the visit / prescription of medication and establishing the method by which you get in possession of the prescription / medication; providing sufficient medication, including comorbidity medication (3 months) and sufficient blood glucose monitoring tests to avoid interruptions in administration; when there are problems in the supply of pharmacies with antidiabetic medication, contacting the diabetologist to replace the medication; glycemic control by following lifestyle and medication recommendations; compliance with dietary recommendations; 7-8 hours sleep per night; physical activity at home; ensuring that the control and treatment of hypoglycaemia (sugar at hand) is possible; ensuring the necessities in case of self-isolation / quarantine / illness; list of contacts

and telephone numbers (family members, family doctor, diabetologist), followed treatment and medication to be available in case of emergency or illness (63).

CONCLUSIONS

COVID-19 has spread rapidly from the outbreak in Wuhan, China and has a wide range of clinical manifestations. Isolation, early diagnosis and associated management bring better control of the disease.

DM, as a comorbidity, is shown to be a predictor of morbidity and mortality.

Social distancing, strict hygiene, good self-management of diabetes and communication with the diabetes specialist are very important in the COVID-19 pandemic.

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