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Editorial

Covid-19 and Diabetes – A Bidirectional Relationship?

Maria Mota [1], Adela-Gabriela Stefan [2]

[1] University of Medicine and Pharmacy of Craiova, Craiova, Romania
[2] Department of Diabetes, Nutrition and Metabolic Diseases, Calafat Municipal Hospital, Calafat, Romania

*Corresponding Author: Dr. Maria Mota, Professor, 4 Brandusa Street, Craiova, Romania. E-mail: mmota53@yahoo.com

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Diabetes and Covid-19 are two devastating pandemics, which have been frequently associated in recent months. They have very different characteristics: Covid-19 is an acute and communicable illness, while diabetes is a chronic and non-communicable disease. Nevertheless, there is a close connection between them.

COVID-19 is a new pathology caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an outbreak with a new coronavirus that was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Coronavirus is a family of viruses that includes SARS and MERS (Middle-East Respiratory Syndrome). There is increasing evidence of human to human transmission [1].

The first infection cases (a new form of atypical pneumonia) emerged in Wuhan, Hubei region, China, in December 2019. More specifically, it seems that the starting point was the section of live animals of the Huanan Wholesale Market [1, 2].

The epidemiological status is continuously changing. A global and national overview updated on April 20, 2020, stated that "Globally, a number of 2,408,359 patients were diagnosed with Covid-19, of whom 26.12% recovered, 6.85% died and 67.01% are currently infected, while 54,216 were in a severe and critical state (2.25% of the total)". On the same date, there were 8,746 diagnosed cases in Romania, of which 21.63% recovered, 5.15% died, and 73.21% are currently infected, 256 (2.92%) being in a severe and critical condition[3].

The data regarding the association of diabetes with Covid-19 are controversial. There is a perception that the risk for both infection and severe disease is higher in patients with diabetes; it seems that diabetes increases the hospitalization and mortality rate of patients with Covid-19.

It is possible that adequate glycemic control may reduce the risk, but not completely eliminate it [4-7]. This finding is consistent with the association between diabetes and excess mortality caused by any acute and chronic conditions, including infections [8]. There are some risk factors that increase Covid-19 morbidity and mortality: people aged 65 and older or people of any age who have serious underlying medical conditions such as severe obesity (body mass index(BMI) ≥ 40kg/m2), diabetes, chronic lung disease including asthma, people in nursing homes or long-term care facilities, severe heart conditions, hypertension, immunodepression, chronic kidney disease, liver disease, and others [5, 9-11].

The Chinese Center for Disease Control and Prevention analyzed mortality among 44,672 confirmed cases and found the following: total mortality was 2.3%, increasing with age, reaching 8% in people aged 70-79, and 14.8% in people over 80 years old, while skyrocketing to 49.0% in critical cases. Mortality was higher among patients with preexisting comorbid conditions: 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer [12].

More relevant, recent data coming from Italy showed that more than two-thirds of COVID-19 patients who died by severe acute respiratory syndrome had diabetes [13, 14]. 16% of the patients with severe forms of COVID-19 had diabetes, in contrast to only 5.7% of those with mild forms of the disease [6].

The possibility of involving several mechanisms that may increase the susceptibility for COVID-19

in patients with diabetes is being discussed: the existence of an increased affinity of the virus towards the cellular receptors and their intracellular entry facilities; cellular receptors are represented by angiotensin-converting enzyme 2 (ACE2), expressed in the upper respiratory system, type I and II alveolar epithelial cells in the lungs, the heart, endothelial cells, kidney tubular epithelium, enterocytes, pancreas, liver, gut, partially explaining multiorgan insufficiency in severe forms of infection; increased ACE2 expression at these levels may favor increased cellular binding of SARS-CoV-2 [15-17].

The increase of ACE 2 expression in lungs, kidneys, heart, and pancreas has been demonstrated on animal models with diabetes, data which has been confirmed in humans as well. On the other hand, some drugs frequently used by patients with diabetes, like glucagon-like peptide-1 (GLP-1) receptor agonists, thiazolidinediones, antihypertensives such as ACE inhibitors, and statins, up-regulate ACE2. On the contrary, insulin treatment attenuates ACE2 expression, having a possible positive role in patients with diabetes, lowering the risk of infection [17-19].

Increased values of a cellular protease called furin have also been described in diabetes, which fa¬cilitates the entry of the virus into the cell, acting on the spike protein [20]. Decreased viral clearance, de¬creased T cell function, increased susceptibility to hy¬perinflammation and cytokine storm syndrome were described in diabetic patients. Chen X et al. reported in their study that clearance of SARS-CoV-2 was delayed in patients with diabetes. However, it is necessary for their results to be confirmed in more extensive studies [21].

In diabetes, a number of immune defense disorders occur: it inhibits neutrophil chemotaxis, phagocytosis, and intracellular killing of microbes. In these patients, an initial delay in the activation of Th1 cell-mediated immunity and a late hyper-inflammatory response is often observed [17, 21].

The presence of cardiovascular disease (CVD), besides hypertension, and severe obesity (BMI ≥ 40kg/m2) increases morbidity and mortality in patients with diabetes and COVID-19 [17].

How does SARS-CoV-2 infection influence diabetes? If diabetes can influence Covid-19 morbidity and mortality, greater attention should be paid to how SARS-CoV-2 infection can affect diabetes's evolution. Hepatic and pancreatic β-cells ACE2 receptors for SARS-CoV-2 may facilitate insulin resistance and β-cells destruction, worsening hyperglycemia, at least during the acute infection and increasing the number of people with diabetes. In the long term, however, autoimmune destruction of the pancreatic β-cells may occur, in predisposed subjects, as described for other viruses, which may induce insulin-dependent diabetes [22].

Conflict of Interest

The authors declare no conflict of interest.

References

1. Guja C. SARS-CoV-2 epidemics and Diabetes. Rom J Diabetes Nutr Metab Dis 27: 1-3, 2020.
2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 395: 470-473, 2020.
3. COVID-19 Coronavirus Pandemic. Accessed at: https://www.worldometers.info/coronavirus/ on April 20th, 2020, 07:09 GMT.
4. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020 Mar 28.doi: 10.1007/s40618-020-01236-2 [Epub ahead of print].
5. Kaiser UB, Mirmira RG, Stewart PM. Our Response to COVID-19 as Endocrinologists and Diabetologists. J Clin Endocrinol Metab 2020 May 1; 105(5). pii: dgaa148. doi: 10.1210/clinem/dgaa148.
6. Ma RCW, Holt RIG. COVID-19 and diabetes. Diabet Med. 2020 Apr 3. doi: 10.1111/dme.14300 [Epub ahead of print].
7. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes Metab Syndr 14: 211-212, 2020.
8. Zoppini G, Fedeli U, Schievano E, et al. Mortality from infectious diseases in diabetes. Nutr Metab Cardiovasc Dis.28: 444-450, 2018.
9. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19). Groups at Higher Risk for Severe Illness. Accessed at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html# on April 17th, 2020.
10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 Feb 24. pii: S2213-2600(20)30079-5. doi: 10.1016/S2213-2600(20)30079-5 [Epub ahead of print].
11. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Feb 28. doi: 10.1056/NEJMoa2002032 [Epub ahead of print].
12. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Feb 24. doi: 10.1001/jama.2020.2648 [Epub ahead of print].
13. Remuzzi A, Remuzzi, G. COVID-19 and Italy: what next? Lancet 395: 1225-1228, 2020.
14. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020 Mar 26; 162: 108125. doi: 10.1016/j.diabres.2020.108125 [Epub ahead of print].

 https://doi.org/10.46389/rjd-2020-1013

15. Liu F, Long X, Zou W, et al. Highly ACE2 Expression in Pancreas May Cause Pancreas Damage After SARS-CoV-2 Infection. medRxiv, 2020. doi: 10.1101/2020.02.28.20029181.
16. Lukassen S, Chua RL, Trefzer T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are predominantly expressed in a transient secretory cell type in subsegmental bronchial branches. bioRxiv, 2020. doi: https://doi.org/10.1101/2020.03.13.991455.
17. Muniyappa R, Gubbi S. COVID-19 Pandemic, Corona Viruses, and Diabetes Mellitus. Am J Physiol Endocrinol Metab. 2020 Mar 31. doi: 10.1152/ajpendo.00124.2020 [Epub ahead of print].
18. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 111: 2605-2610, 2005.
19. Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, et al. Activation of the GLP-1 Receptor by Liraglutide Increases ACE2 Expression, Reversing Right Ventricle Hypertrophy, and Improving the Production of SP-A and SP-B in the Lungs of Type 1 Diabetes Rats. Endocrinology 156: 3559-3569, 2015.
20. Fernandez C, Rysa J, Almgren P, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. J Intern Med 284: 377-387, 2018.
21. Chen X, Hu W, Ling J, et al. Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. medRxiv, 2020. doi: 10.1101/2020.03.22.20040774.
22. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020 Mar 31: e33213321. doi: 10.1002/dmrr.3321[Epub ahead of print].

