Artur Furga[1]

COVID-19 AND DIABETES

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Abstract

Almost immediately after the emergence of the SARS-CoV-2 corona-virus, it was observed that people with chronic disease, including diabetes, presented an increased risk of hospitalisation and mortality. Diabetes can increase the risk of COVID-associated mortality by more than six times. The hypothesis of a bidirectional relationship between COVID-19 and diabetes assumes that diabetes is a risk factor for worse outcomes of COVID-19 treatment, and that coronavirus infection is a predisposing factor for newly diagnosed diabetes or hyperglycaemic emergencies. New diagnoses or exacerbations of existing diabetes are associated with direct damage to the pancreas or the body's response to chronic inflammation, and ACE receptors play a large role in this pathomechanism. The restrictions imposed in many countries resulted in the poorer control and underdiagnosis of diabetes. This review summarises the impact of acute COVID-19 on diabetics, discusses how presentation and epidemiology changed during the pandemic, and considers the broader impact of the pandemic on patients and healthcare delivery.

Keywords: diabetes mellitus, COVID-19, pandemic, mortality

[1] Artur Furga, Department of Oncological, Transplant and General Surgery, Invasive Medicine Centre, Medical University of Gdańsk, ul. Smoluchowskiego 17, e-mail: arturfurga@gumed.edu.pl, ORCID: 0000-0003-2370-6367.

1. Introduction

The first case of COVID-19 was identified and isolated in Wuhan, Hubei Province, China in late 2019[2]. In August 2020, the World Health Organisation (WHO) confirmed 25 million cases of the disease, including 800,000 deaths[3]. All age groups have been affected by the virus, especially the elderly, in particular those burdened with chronic conditions. Among the chronic diseases listed as risk factors, diabetes was found to be one of the main causes of a more severe course of SARS-CoV-2 infection, as well as a higher mortality rate[4]. This review discusses the current literature on the impact of COVID-19 infections on patients with diabetes, the epidemiology of new-onset diabetes during the pandemic and its influence on patients and healthcare delivery.

2. COVID infection in people with diabetes

Early reports from Wuhan, China, suggested an over-representation of individuals with diabetes among those dying from COVID-19[5]. Shortly thereafter, a population-based cohort study was conducted that included all people diagnosed with diabetes in the English population. The study confirmed that diabetics were more severely affected by SARS-CoV-2 infection[6]. Data concerning 263,830 (0.4%) people diagnosed with type 1 diabetes and 2,864,670 (4.7%) people diagnosed with type 2 diabetes, as well as 41,750 (0.1%) people with other types of diabetes and 58,244,220 (94.8%) non-diabetics were compared with 23,698 in-hospital deaths associated with COVID-19. When the results were adjusted for

[2] D.S. Hui, E.I. Azhar, T.A. Madani, et al., *The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – The latest 2019 novel coronavirus outbreak in Wuhan, China*. Int J Infect Dis. 2020 Feb;91.

[3] Coronavirus disease (COVID-19) Weekly Epidemiological Update Data as received by WHO from national authorities, as of 10 am CEST 30 August 2020 dostępne na: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200831-weekly-epi-update-3.pdf

[4] A.H. Abdelhafiz, D. Emmerton, A.J. Sinclair, *Diabetes in COVID-19 pandemic-prevalence, patient characteristics and adverse outcomes*, Int J Clin Pract. 2021;75.

[5] S. Di Gangi, B. Lüthi, L. Diaz Hernandez, et al., *Quality outcome of diabetes care during COVID-19 pandemic: a primary care cohort study*, Acta Diabetol. 2022; 59.

[6] E. Barron, C. Bakhai, P. Kar, et al. *Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study*, Lancet Diabetes Endocrinol 2020; 8.

age, sex, socioeconomic deprivation, ethnicity and geographic region, the risk of COVID-19-related in-hospital death was 3.5-fold higher in patients with type 1 diabetes and 2-fold higher in those with type 2 diabetes compared with those without diabetes[7]. The effect of diabetes on death was greater among those under the age of 70. Moreover, it was found that male sex, older age, non-Caucasian race, socioeconomic deprivation, history of previous stroke, heart failure and renal impairment (eGFR <60 ml/min per 1-73 m2) were associated with increased COVID-19-related mortality in both type 1 and type 2 diabetes[8]. Subsequent studies in Scotland[9] and Sweden[10] confirmed these results.

Despite the higher risk associated with COVID-19 in terms of hospitalisation, intensive care unit admission and mortality in people with diabetes, there is no evidence that diabetes predisposes to SARS-CoV-2 infection[11].

[7] *Ibidem*.

[8] N. Holman, P. Knighton, P. Kar, et al. *Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study*. Lancet Diabetes Endocrinol. 2020;8.

[9] S.J. McGurnaghan, A. Weir, J. Bishop, et al.*, Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland.* Lancet Diabetes Endocrinol. 2021;9.

[10] A. Rawshani, E.A. Kjolhede, A. Rawshani, et al.*, Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: a nationwide retrospective cohort study*. Lancet Reg Health Eur. 2021;4.

[11] J. Hartmann-Boyce, K. Rees, J.C. Perring, et al.*, Risks of and from SARS-CoV-2 infection and COVID-19 in people with diabetes: a systematic review of reviews*. Diabetes Care. 2021;44.

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3. New diabetes diagnoses in the pandemic

Immediately after the outbreak of the pandemic, there were reports of an increase in cases of newly diagnosed diabetes[12] and cases of ketoacidosis in people with previously diagnosed diabetes as well as newly diagnosed diabetes[13].

Many experts hypothesised a bidirectional relationship between COVID-19 and diabetes[14], whereby diabetes itself was a risk factor for worse COVID-19 outcomes. At the same time, however, the presence of COVID-19 was also a factor predisposing to newly diagnosed diabetes or sudden hyperglycaemic states.

Several studies have confirmed the increased prevalence of diabetes during the pandemic period[15]. A large cohort study, based on the US Department of Veterans Affairs' National Database, involving 181,280 COVID-19 positive participants,

[12] R. Unsworth, S. Wallace, N.S. Oliver, et al., *New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K.* Diabetes Care. 2020;43.; Y.J.Chee, S.J.H. Ng, E. Yeoh, *Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus.* Diabetes Res Clin Pract. 2020;164.; J. Li, X. Wang, J. Chen, et al., *COVID-19 infection may cause ketosis and ketoacidosis*. Diabetes Obes Metab. 2020;22.; H. Li, S. Tian, T. Chen, et al., *Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19.* Diabetes Obes Metab. 2020;22.

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[15] K. Khunti, S. Del Prato, C. Mathieu, et al., *COVID-19, hyperglycemia, and new-onset diabetes.* Diabetes Care. 2021;44.

revealed that over a median follow-up period of 352 days, COVID-positive individuals had a 1.4 times increased risk of diabetes compared to the control group[16].

During the first year of the pandemic, an increase in the number of new cases of type 1 diabetes, ketoacidosis and severe ketoacidosis was observed, with increases of 9.5%, 25% and 19.5%, respectively, compared with the pre-pandemic period. Median glucose and HbA1c values in newly diagnosed children with type 1 diabetes after the COVID-19 pandemic increased by 6.43% and 6.42%, respectively[17].

The pathogenesis of new-onset diabetes in COVID-19 infections remains unknown, and may include previously undiagnosed diabetes, stress-induced hyperglycaemia, steroid therapy-induced hyperglycaemia or direct or indirect effects of SARS-CoV-2 infection on pancreatic beta cells[18]. Among the SARS-CoV-2 infection survivors with newly diagnosed diabetes, 56.3% remained diabetic and 40.6% returned to normoglycaemia or pre-diabetes[19].

4. Post-COVID-19 syndrome

The spectrum of clinical manifestations of COVID-19 ranges from asymptomatic to severe disease. Recovery time from COVID-19 is highly variable and depends on the severity of the disease, age and previous comorbidities. People with mild infection may recover in a few days to two weeks, while those with severe disease may have a prolonged recovery period ranging from 2 to 3 months. If symptoms persist for more than four weeks after the onset of infection, the term long COVID is used, while persistence of symptoms for more than 12 weeks is

[16] Y. Xie, Z. Al-Aly, *Risks and burdens of incident diabetes in long COVID: a cohort study.* Lancet Diabetes Endocrinol 2022 May;10

[17] M. Rahmati, M. Keshvari, S. Mirnasuri, et al., *The global impact of COVID-19 pandemic on the incidence of pediatric new-onset type 1 diabetes and ketoacidosis: A systematic review and meta-analysis*. J Med Virol. 2022 Nov;94.

[18] H. Li, S. Tian, T. Chen, et al., *Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19.* Diabetes Obes Metab. 2020;22.

[19] A.E. Dixon, U. Peters, *The effect of obesity on lung function*. Expert Rev Respir Med. 2018;12.

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qualified as PCS (Post-COVID syndrome)[20]. Over 90% of patients with post-COVID syndrome needed 35 weeks or longer to fully recover[21]. The most common symptoms of PCS include extreme fatigue, tiredness, shortness of breath, brain fog, taste and smell changes, musculoskeletal pain and arthritis pain. It may resemble chronic fatigue syndrome, which seems to be the most common complaint and limits daily activities such as cooking, showering, grocery shopping or exercising[22]. Chronic low-grade inflammation is thought to persist in this phase, which can last for weeks or months[23]. Although much information has been obtained on the hyperglycaemia and diabetes associated with COVID, its pathomechanism and progression have not yet been fully explored.

5. Mechanisms of diabetes development in COVID patients

The pathophysiological changes following COVID onset that predispose to glucose intolerance have been actively investigated. Specifically, three possible pathophysiological mechanisms have been identified. They refer to an increased proinflammatory state, the role of angiotensin-converting enzyme type 2 (ACE2) and pancreatic beta-cell dysfunction[24].

5.1. Pro-inflammatory factors

The "International Study of Inflammation in COVID-19", a multicentre study involving 2044 patients hospitalised for COVID-19, examined the impact of diabetes on in-hospital outcomes, the contribution of inflammation and hyperglycaemia to the risk attributed to the disease. Using this comprehensive database, Vasbinder and colleagues measured levels of inflammatory biomarkers

[20] National Institute for Health and Care Excellence (2021) COVID-19 rapid guideline: managing COVID-19. Available from https://www.nice.org.uk/guidance/ng191. Accessed on 14th April 2022.

[21] H.E. Davis, G.S. Assaf, L. McCorkell, et al., *Characterizing long COVID in an international cohort: 7 months of symptoms and their impact.* EClinicalMedicine. 2021;38

[22] C. Fernandez-de-Las-Penas, C. Guijarro, J. Torres-Macho, et al., *Diabetes and the risk of long-term post-COVID symptoms.* Diabetes. 2021;70.

[23] A.A. Rizvi, A. Kathuria, W. Al Mahmeed, et al., *CArdiometabolic Panel of International experts on Syndemic COvid-19 (CAPISCO). Post-COVID syndrome, inflammation, and diabetes*. J Diabetes Complications. 2022;36(11).

[24] K. Khunti, J. Valabhji, S. Misra, *Diabetes and the COVID-19 pandemic*. Diabetologia. 2023;66.

at hospital admission and analysed glucose levels and insulin therapy data throughout hospitalisation[25]. Their findings suggest that the association between diabetes and poorer COVID-19 outcomes is largely driven by: "hyper-inflammatory" state, obesity, hyperglycaemia and age. In hospitalised patients with diabetes, the pro-inflammatory metabolic state resulting from the presence of the virus promotes severe insulin resistance, hyperglycaemia and a tendency to rapidly develop renal failure, low blood pressure that requires vasopressors and steroids and the need for nutritional support[26].

5.2. Role of ACE2 receptors

Two angiotensin-converting enzymes are distinguished – both play a significant role in the regulation of the body's fluid and electrolyte balance and the renin-angiotensin-aldosterone (RAA) system, which is largely responsible for controlling blood pressure. The enzyme of this system, angiotensin-converting enzyme type 2 (ACE2), is also a cell surface receptor which enables SARS-CoV-2 to enter host cells. ACE2 receptors play an important role in insulin resistance and the pathophysiological development of diabetes; they are highly expressed in the heart, kidneys and lungs and are excreted into plasma[27]. SARS-CoV-2 causes angiotensin-converting enzyme imbalance and RAAS activation, which contributes to the development of insulin resistance and leads to COVID-19 progression, particularly in patients with comorbidities such as hypertension, diabetes and cardiovascular disease[28]. The exact role that ACE2 receptors play in the pathomechanism of SARS-CoV-2 infection has not yet been fully elucidated[29].

[25] A. Vasbinder, et al., *On behalf of the ISIC Study Group. Inflammation, hyperglycemia, and adverse outcomes in individuals with diabetes mellitus hospitalized for COVID-19.* Diabetes Care. 2022;45.

[26] A.S. Shah, A.W. Wong, C.J. Hague, et al., *A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. Thorax.* 2021;76:402-404; A. Vasbinder, et al. *On behalf of the ISIC Study Group. Inflammation, hyperglycemia, and adverse outcomes in individuals with diabetes mellitus hospitalized for COVID-19*, Diabetes Care. 2022;45.

[27] W. Li, M.J. Moore, N. Vasilieva, et al., *Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus.* Nature. 2003;426.

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[29] W. El-Huneidi, M. Hamad, J. Taneera, *Expression of SARS-CoV-2 receptor „ACE2" in human pancreatic ß cells: to be or not to be! Islets.* 2021;13.

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However, research is underway using ACE2 as a therapeutic target for the treatment of COVID-19 infections. These strategies include: delivering a soluble form of ACE2 that would bind coronavirus, thereby reducing the viral load on host cells[30], and blocking the interaction between SARS-CoV-2 and the ACE2 receptor using monoclonal antibodies[31].

5.3. SARS-CoV-2 causes damage to pancreatic cells

There is evidence that the SARS-CoV-2 virus directly affects the pancreas, including *beta* cells, leading to damage to these cells and subsequent impairment of insulin secretion[32]. Although it may be observed in people without previously diagnosed diabetes, in patients with diabetes it is associated with poorer clinical outcomes due to the presence of comorbidities and inflammatory diseases[33]. SARS-CoV-2 affects the pancreas via angiotensin-converting enzyme 2 (ACE2), which becomes highly expressive in the pancreas compared to other organs, leading to damage of its cells[34].

6. Impact of the pandemic on access to healthcare

Two days prior to the confirmation of the first case of SARS-CoV-2 infection in Poland, the public authorities, in accordance with Article 68(4) of the Constitution of the Republic of Poland ("Public authorities are obliged to combat epidemic diseases and prevent the negative health effects of environmental degradation"), implemented a number of restrictions aimed at combating the pandemic and minimising its impact. The law of 2 March 2020 on special solutions related to preventing, counteracting and combating COVID-19, other

[30] D. Batlle, J. Wysocki, K. Satchell, *Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy?* Clinical Science. 2020;134.

[31] C. Yi, X. Sun, J. Ye, et al., *Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies.* Cellular & Molecular Immunology. 2020;17.

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[33] R. Unnikrishnan, A. Misra, *Diabetes and COVID19: a bidirectional relationship.* Nutr Diabetes. 2021;11; S. Shao, Q. Yang, R. Pan, et al., *Interaction of severe acute respiratory syndrome coronavirus 2 and diabetes*. Front Endocrinol. 2021;12.

[34] W. El-Huneidi, M. Hamad, J. Taneera, *Expression of SARS-CoV-2 receptor „ACE2" in human pancreatic β cells: to be or not to be! Islets.* 2021;13.

infectious diseases and emergencies caused thereby[35], pursuant to Article 31(3) of the Constitution of the Republic of Poland, imposed a number of restrictions on Polish citizens. To allocate as many medical resources as possible to the fight against the pandemic and to limit the spread of the virus as much as possible, non-acute health care services were severely restricted, including: accessibility to medical services, face-to-face consultations in both primary and specialist health care. The main emphasis was on the use of telemedicine with virtual consultations predominating, the major disadvantage thereof being the lack of direct access to the patient. Consequently, this imposed omitting the physical examination, taking body measurements, blood tests and annual blood glucose checks[36]. Very soon after the announcement of the pandemic outbreak, we learnt about the direct risks of SARS-CoV2 for diabetics. However, not until now are we learning about the negative impact of pandemic-related long-term neglect of diagnosis, including detection and treatment of chronic diseases, such as diabetes. It has been shown that during the pandemic, regular checks for people with type 2 diabetes decreased by 76-88% compared to 10-year trends[37]. A UK study assessed 25 million patients and estimated that around 60,000 people had missed or delayed diagnosis of type 2 diabetes[38]. It is highly probable that these patients are partly responsible for the disproportionate increase in terms of "newly diagnosed" diabetes compared to pre-pandemic data.

6. Conclusions

In this review of existing studies, we have shown that diabetics are at higher risk of hospitalisation, require intensive care and are also at risk of death due to infection. These findings highlight the need for special care for diabetic patients with SARS-CoV-2 infection and the need to implement prevention strategies in this population.

[35] Dz.U. z 2023 r. poz. 1327, ze zm.

[36] A.J. Sinclair, A.H. Abdelhafiz, L. Rodríguez-Mañas, *Frailty and sarcopenia - newly emerging and high impact complications of diabetes. J Diabetes Complication*. 2017;31; X. Yao, R.G. Hamilton, N.P. Weng, et al., *Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults. Vaccine*. 2011;29.

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[38] *Ibidem.*

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The impact of the pandemic on diabetes includes an increase in newly diagnosed cases of diabetes. This increase could be the result of both existing diabetes diagnosed due to both COVID-19 symptoms as well as newly developed cases of diabetes due to the impact of infection or metabolic stress.

We hypothesised a bidirectional relationship between COVID-19 and diabetes, claiming that diabetes is a risk factor for poorer COVID-19 treatment outcomes and that coronavirus infection is a predictor of newly diagnosed diabetes or sudden hyperglycaemic states.

Inflammation, the role of angiotensin-converting enzyme (ACE-2 receptor) and pancreatic damage represent theories explaining the pathomechanism of newly diagnosed diabetes secondary to COVID-19 infection. There is an emerging therapeutic strategy based on the activation of ACE2 receptor by using either a soluble form of ACE2 to bind virions or monoclonal antibodies to block the interaction between SARS-CoV2 and the ACE2 receptor.

The impact of the pandemic on access to healthcare for patients with diabetes is significant. Reduced access to traditional medical care, a focus on telemedicine and deferral of regular check-ups has led to a decline in diabetes detection and control, with potential long-term health consequences.

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