Clinical Epidemiology and Global Health 16 (2022) 101110

Contents lists available at ScienceDirect

Clinical Epidemiology and Global Health

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

Review article

Historical aspects and current understanding of the connections and implications of viruses and diabetes: A narrative review

Dr Jayakrishnan B

Department of Medicine, Educare Institute of Dental Sciences, Malappuram, Kerala, SafeCare Clinics, Tirur, Kerala, India

ARTICLE INFO

Keywords:
Hyperglycemia
Viruses
Diabetes
COVID-19
Immune dysfunction

ABSTRACT

The continued increase in diabetes indicates it to be a significant global challenge to the health and wellbeing of people. Hyperglycemia is linked to chronic inflammatory processes and diabetes-related vulnerability to infection. There is historic evidence linking viruses and microbes with diabetes and in some instances considered the causative agent. The viral infection causes inflammation and autoimmune destruction of beta cells, which, in turn, give rise to hyperglycemia, finally leading to diabetes. This review considers the historic aspects of viruses and diabetes, immune dysfunction with hyperglycemia, bidirectional relations between COVID-19 virus and diabetes, and new-onset diabetes in COVID-19.

1. Introduction

Diabetes is a growing global concern as its incidence is increasing at a rapid rate. Approximately 537 million a dults are living with diabetes as of 2021, and the numbers are projected to rise to 783 million by the year 2045.[1] In India, the number of people with diabetes is estimated to roughly double from 77 million in the year 2019 to 134 million by the year 2045. One in 10 people worldwide are currently living with diabetes and every sixth person with diabetes in the world is an Indian.[1] The microbes and viruses have been observed to play a key role as infectious agents linked to diabetic status and also as factors responsible for causing diabetes mellitus.[2]

1.1. History of viruses and diabetes

In the mid-nineteenth century, Stang mentioned the possibility of a relationship between mumps and diabetes. In 1899, Harris talked about the association of viruses with diabetes in detail. He mentioned a case of glycosuria followed by the onset of a mumps attack. However, it took almost 3 years for that person to develop full-blown diabetes with ketosis. In 1924, Patrick reported an association between mumps and diabetes in sporadic cases. Finally, in 1927, Gundersen published a paper with the title, "Is diabetes of infectious origin?" He suggested that mumps produced pancreatic disease, which resulted in diabetes in young after 3 years of initial infection. Since then, many studies have reported on the connection between mumps and diabetes.[3]

In the United States, approximately 9.4% of people have diabetes and 1.4% of them carry hepatitis C virus (HCV). The risk of type 2 diabetes mellitus (T2DM) is nearly four times greater in HCV-positive individuals than HCV-negative individuals. The association between HCV and diabetes gives a fair idea of the benefits of *anti*-HCV treatment in T2DM management. *Anti*-HCV treatment in diabetes has been shown to significantly improve glycemic control and has also been observed to reduce the need for insulin in persons with T2DM. As per the latest *in vitro* study, the infection of pancreatic islet cells by HCV may alter the cytokine expression, which, in turn, may contribute to insulin deficiency.[4]

The same trends that ushered severe acute respiratory syndrome (SARS) into the human population are prevalent in the current pandemic situation and there are many lessons to draw from the SARS experience:[5]

- History of diabetes and ambient hyperglycemia was found to be independent factors of death and mortality in people with SARS.
- Hyperglycemia had devastating effects on organ function in people with SARS.
- Intensive monitoring and optimal metabolic control have been reported to improve the prognosis of people with SARS.

2. Hyperglycemia and immune dysfunction

Hyperglycemia is linked to chronic inflammatory processes and diabetes mellitus-related vulnerability to infection. People with diabetes are prone to develop periodontal disease, tuberculosis, lung infection by legionella bacteria, and mucormycosis by the Mucoraceae family of

E-mail address: jaykdr@gmail.com.

https://doi.org/10.1016/j.cegh.2022.101110
Received 24 March 2022; Received in revised form 9 June 2022; Accepted 6 July 2022
Available online 11 July 2022

fungi. Impaired functioning of macrophages, dendritic cells, natural killer T cells, and B and T lymphocytes causes defects of the innate response.[6]

2.1. Immune defects associated with hyperglycemia

Hyperglycemia is responsible for impeding the production of interleukin-22 (IL-22) and type1 interferon, which, in turn, diminishes the protective effects offered by both the cytokines. Type 1 interferon possesses antiviral activity. IL-22 decreases chronic inflammation and improves antimicrobial immunity and insulin sensitivity.[6] Hyperglycemia downregulates the expression of cathelicidins in macrophages which further decreased antimicrobial properties and chemotaxis, impaired antibacterial activity, neutrophil degranulation in response to bacterial lipopolysaccharide[6] Hyperglycemia causes nonenzymatic glycation of multiple proteins, including those of the complement system involved in the opsonization of pathogens. Glycation stops complement activation through the mannan-binding lectin pathway as well as functions of the CD59 inhibitor of the membrane attack complex.[6]

2.2. Mechanisms of beta-cell destruction associated with viral infections

The direct effects of viral infections on beta cells include different cytolytic effects in pancreatic beta cells. The viral infection causes inflammation and autoimmune destruction of beta cells, which, in turn, give rise to hyperglycemia, finally leading to diabetes.[7]

The various indirect effects of viral infections on beta cells include the following: Viral antigens expressed in beta cells cause infection; the release of substances toxic to beta cells destroys surrounding tissues; altered expression of major histocompatibility complex and costimulatory molecules; bystander activation of autoreactive lymphocytes by cytokines, antigen-presenting cells, and beta cells; virally encoded antigens activate and expand autoreactive T cells; molecular mimicry of viral antigens with beta-cell antigens; altered immune regulation; and altered repertoire of memory T cells.[7]

2.3. Viral infections implicated in diabetes

Multiple varieties of viruses have a possible role as a major environmental factor in inducing diabetes.[7] Viruses for which there is extensive evidence for association with diabetes are Enterovirus including Coxsackie B strains,[8] and Rubella.[9] Viruses less commonly associated with diabetes are Cytomegalovirus,[10] Epstein-Barr virus,[11] Mumps,[12] Rota virus[13] and Retro virus.[8]

Multiple viruses including RNA and DNA viruses implicated in diabetes[7] is shown in Fig. 1.

3. Bidirectional relationship between COVID-19 and diabetes

Diabetes has been reported to be one of the common comorbidities in persons infected with coronavirus disease 2019 (COVID-19). This has generated interest in exploring the two-way relationship between diabetes and COVID-19.[14]

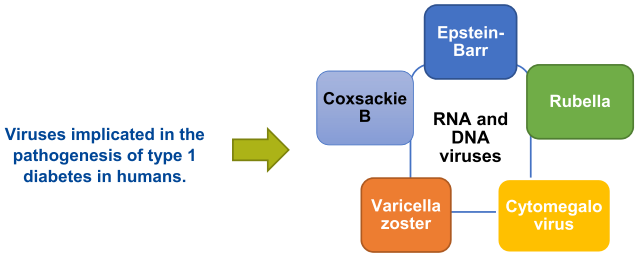

Fig. 1. Viruses causing type 1 diabetes.

- Newer emerging evidence suggests that the coronavirus might trigger diabetes. Increased risk of development of new-onset hyperglycemia in infected individuals[15,16]
- Moreover, COVID-19 infection in people with diabetes causes virus exploitation in multiple organs due to multiple mechanisms, such as altered angiotensin-converting enzyme 2 (ACE2) activity,[17] breakdown of Ca^{2+} homeostasis, activation of the renin-angiotensin–aldosterone system (RAAS),[18] pre-existing diabetes-related organ damage, impairment of sympathetic nervous system, and raised oxidative stress.[19,20]
- Several studies have also reported that COVID-19 may induce diabetes by causing beta-cell destruction, hepatic manifestations, increased stress, and changes in the pancreas–liver–gut-brain axis in people without diabetes.[14–16]

Yang et al. evaluated whether the multiorgan damage (mainly in the pancreas) was related to the expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor, ACE2 (Fig. 2). As per the study findings, the organ expression of SARS was linked to the organ expression of ACE2. The localization of ACE2 expression in the part of the pancreas confirmed that SARS-CoV-2 binds to the ACE2 receptor and damages the islet cells in the pancreas, further resulting in acute diabetes.[21] ACE2 is a functional receptor for SARS-CoV-2. The basic mechanism of engagement of RAAS with SARS-CoV-2 is given below.[22]

- SARS-CoV-2 binds to ACE2 and thus promotes the internalization of the viral receptor.
- ACE2-mediated production of angiotensin (1–7) gets disturbed and production of angiotensin II (1–8) increases.
- The alteration in the levels of angiotensin further changes the target receptor activity in selected tissues.

3.1. Angiotensin-converting enzyme-2: double-edged sword for people with diabetes

There has been an ongoing debate regarding the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in people with COVID-19. It is important to understand how ACE2 acts as a double-edged sword for people with diabetes.

- ACE2, an extracellular transmembrane enzyme, is responsible for converting angiotensin II into the angiotensin (1–7) heptapeptide.[22]
- ACE2 is the main receptor for binding and uptake of SARS-CoV-2 into the cell.[22]
- Viral binding causes internalization and enzymatic degradation of ACE2, hence resulting in hypertensive effects due to enhanced angiotensin II levels.[23]
- ACEIs and ARBs lead to overexpression of ACE2 and thus persons treated with ACEIs and ARBs could be at risk of developing COVID-19.[23]

3.2. Diabetes: a strong risk factor for COVID-19 severity

Research has indicated a higher risk of severe COVID-19 in individuals with comorbidities:

- Pre-existing T2DM has been reported to be independently associated with poor outcomes in people with SARS.[24]
- As per the study by Algahtani et al., T2DM was found to be the primary comorbidity linked to severe or lethal Middle East respiratory syndrome-related coronavirus infections.[25]
- Diabetes status has been associated with an increase in the requirement of medical interventions during COVID-19 and also escalated mortality risk of people with COVID-19.[26]

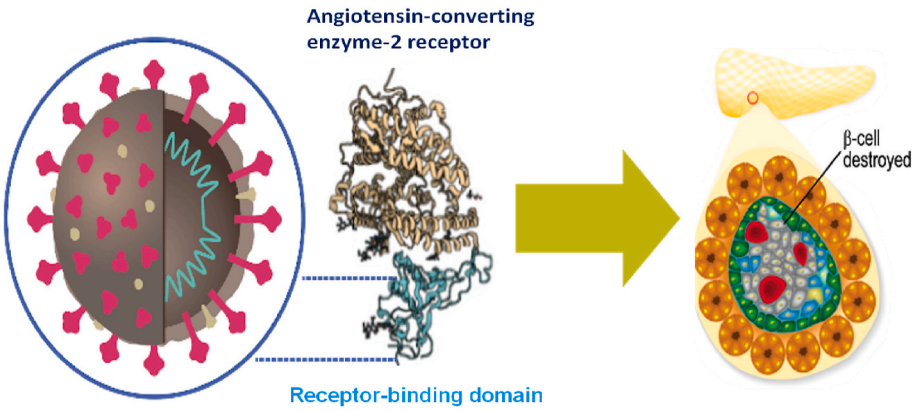

Fig. 2. The binding of SARS-CoV-2 to ACE2 receptor damages islet cells in the pancreas and causes acute diabetes
SARS-Cov: Severe acute respiratory syndrome coronavirus, ACE: Angiotensin-converting enzyme.

Several mechanisms explain that diabetes could be a strong risk factor for COVID-19. The major mechanisms are those linked directly to hyperglycemia and the associated imbalances in pathways involved in virus entry into the cell as well as in the immune and inflammatory response. Also, the diabetes-related comorbidities/complications with poor prognosis mediate certain effects of diabetes in people with COVID-19.[27]

3.3. New-onset diabetes in COVID-19

Clinical evidence is being accumulated regarding new-onset diabetes in COVID-19:

- A bidirectional relationship between COVID-19 and diabetes has emerged.[14]
- Recent evidence shows that coronavirus may trigger diabetes.[28]
- Many studies have reported new-onset diabetes and severe complications of pre-existing diabetes, such as diabetic ketoacidosis and hyperosmolarity in people with COVID-19.[29–31]
- People with COVID-19 with increased blood sugar and no prior history of diabetes should be tested for new-onset diabetes mellitus and diabetic ketoacidosis.[7]

SARS-CoV-2 after binding to ACE2 may lead to pleiotropic changes in glucose metabolism. This, in turn, complicates the pathophysiology of already existing diabetes or results in new mechanisms of disease.[32] Previous research has also indicated high incidences of fasting glycemia and acute-onset diabetes in people infected with SARS coronavirus 1 pneumonia.[33]

3.4. COVID-19 and thrombotic microangiopathy

Recent evidence suggests that signs and symptoms of COVID-19 infection resemble more the pathophysiology and phenotype of complement-mediated thrombotic microangiopathies (TMA). Thrombotic microangiopathies are characterized by microvascular thrombosis with thrombocytopenia, hemolytic anemia, and red blood cell fragmentation:[34]

- Pre-existing TMA and its markers (poor glycemic control and duration of diabetes) are risk factors for the severity of the disease.[35]
- Thrombotic microangiopathies have been reported to be a common event in people with COVID-19 and possibly involve endothelium-mediated complement activation.[36]
- Due to overexpression of ACEs in endothelial cells and podocytes, endothelium-mediated complement activation could be considered as a single mechanism of viral action in susceptible organs.[37]
- As per the latest clinical observations, SARS-CoV-2 infection causes induction of endothelins in several organs.[38]
- Endotheliitis may result in life-threatening complications and even multiple organ failure.[39]
- Increased Inflammatory response could be the reason for COVID-19–associated coagulopathy.[40]

3.5. Time to rethink diabetes management in COVID-19

The clinical management of diabetes is extremely challenging in the current COVID-19 times as the pathophysiology of COVID-19–related diabetes is complex. People with diabetes carry an increased risk of severe COVID-19. In people with COVID-19, high doses of insulin are needed for new-onset diabetes and related complications.[41,42]

SARS-CoV-2 is related to multiorgan damage with the most affected organs being kidneys, lungs, and heart. The severity of COVID-19 is directly related to old age, thrombocytopenia, and hyperglycemia. As SARS-CoV-2 causes ACE2-dependent damage to pancreatic cells, hyperglycemia could be the final consequence. Hyperglycemia, if left untreated, could result in various complications, such as limb amputations, kidney failure, blindness, and cardiovascular disease.[3] Therefore, it is important to regulate blood glucose levels.[43,44]

4. Conclusion

Viral infections are a major environmental factor in the etiology of diabetes mellitus. Recent evidence indicates the bidirectional relationship between COVID-19 and diabetes. People infected with COVID-19 with elevated blood sugar levels and no history of diabetes should be evaluated for the possibility of new-onset diabetes mellitus. Complement-mediated thrombotic microangiopathies should be watched in persons with COVID-19. A multidisciplinary approach should be looked into while managing diabetes in persons with COVID-19.

Source funding

The author received no financial support from any institution for the research, authorship, and/or publication of this article.

Ethical approval

Not required.

Declaration of competing interest

None declared.

Acknowledgment

The author would like to thank BioQuest Solutions for their editorial assistance and Dr. S Amarnath for editorial and scientific support.

References

1 International diabetes foundation atlas. Available at: https://www.idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html. Accessed March , 2022.
2 Toniolo A, Cassani G, Puggioni A, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. *Rev Med Microbiol*. 2019;30(1):1–17.
3 Taylor KW. Historical background: earlier studies on the connexion between viruses and diabetes. *Diabetes and Viruses*. 2012:3–6.
4 Toniolo A, Cassani G, Puggioni A, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. *Rev Med Microbiol*. 2019;30(1):1–17.
5 Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med*. 2006;23(6):623–628.
6 Toniolo A, Cassani G, Puggioni A, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. *Rev Med Microbiol*. 2019;30(1):1–17.
7 Jaeckel E, Manns M, Von Herrath M. Viruses and diabetes. *Ann N Y Acad Sci*. 2002;958:7–25.
8 Hyöty H, Taylor KW. The role of viruses in human diabetes. *Diabetologia*. 2002 Oct;45(10):1353–1361.
9 Forrest JM, Menser MA, Burgess JA. High frequency of diabetes mellitus in young adults with congenital rubella. *Lancet*. 1971 Aug 14;2(7720):332–334.
10 Pak CY, Eun HM, McArthur RG, Yoon JW. Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet*. 1988 Jul 2;2(8601):1–4.
11 Jun HS, Yoon JW. A new look at viruses in type 1 diabetes. *ILAR J*. 2003;45(3):349–374.
12 Hyöty H, Leinikki P, Reunanen A, et al. Mumps infections in the etiology of type 1 (insulin-dependent) diabetes. *Diabetes Res*. 1988 Nov;9(3):111–116.
13 Honeyman MC, Coulson BS, Stone NL, et al. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes*. 2000;49:1319–1324.
14 Balasubramanyam M. Does COVID-19 warn us to revisit virus-induced diabetes? *Exploratory Research and Hypothesis in Medicine*. 2020;5(4):129–133.
15 Mallapaty S. Mounting clues suggest the coronavirus might trigger diabetes. *Nature*. 2020;583(7814):16–17. https://doi.org/10.1038/d41586-020-01891-8.
16 Unnikrishnan R, Misra A. Diabetes and COVID19: a bidirectional relationship. *Nutr Diabetes*. 2021 Jun 23;11(1):21.
17 Ni W, Yang X, Yang D, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Crit Care*. 2020;24:422.
18 Dean RG, Burrell LM. ACE2 and diabetic complications. *Curr Pharmaceut Des*. 2007;13(26):2730–2735.
19 Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. *Diabetes Metabol Syndr*. 2020;14(6):2211–2217.
20 Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab*. 2021;3(2):149–165.
21 Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47(3):193–199.
22 Onweni CL, Zhang YS, Caulfield T, et al. ACEI/ARB therapy in COVID-19: the double-edged sword of ACE2 and SARS-CoV-2 viral docking. *Crit Care*. 2020;24:475.
23 Cristelo C, Azevedo C, Marques JM, et al. SARS-CoV-2 and diabetes: new challenges for the disease. *Diabetes Res Clin Pract*. 2020;164, 108228.
24 Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabet Med*. 2006;23:623–628.
25 Alqahtani FY, Aleanizy FS, Ali El Hadi Mohamed R, et al. Prevalence of comorbidities in cases of Middle East respiratory syndrome coronavirus: a retrospective study. *Epidemiol Infect*. 2018;147:1–5.
26 Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metabol*. 2020;31:1068–1077. e3.
27 Pugliese G, Vitale M, Resi V, et al. Is diabetes mellitus a risk factor for coronavirus disease 19 (COVID-19)? *Acta Diabetol*. 2020;57(11):1275–1285.
28 Mallapaty S. Mounting clues suggest the coronavirus might trigger diabetes. *Nature*. 2020;583:16–17.
29 Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract*. 2020;164, 10816.
30 Li J, Wang X, Chen J, et al. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metabol*. 2020. https://doi.org/10.1111/dom.
31 Heaney AI, Griffin GD, Simon EL. Newly diagnosed diabetes and diabetic ketoacidosis precipitated by COVID-19 infection. *Am J Emerg Med*. 2020 Nov;38(11):2491. e3-2491.e4.
32 Rubino F, Amiel SA, Zimmet P, et al. New-onset diabetes in covid-19. *N Engl J Med*. 2020;383(8):789–790.
33 Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damage islets and causes acute diabetes. *Acta Diabetol*. 2010;47:193–199.
34 Benz K, Amann K. Thrombotic microangiopathy: new insights. *Curr Opin Nephrol Hypertens*. 2010;19:242–247.
35 Sharma S, Schaper D, Rayman G. Microangiopathy: is it relevant to wound healing in diabetic foot disease? *Diabetes Metab Res Rev*. 2020;36(1), e3244.
36 Gavriilaki E, Brodsky RA. Severe COVID-19 infection and thrombotic microangiopathy: success does not come easily. *Br J Haematol*. 2020 Jun;189(6):e227–e230.
37 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliins in COVID-19. *Lancet*. 2020;395:1417–1418.
38 Kahwash Rami Campbell Courtney M. Will complement inhibition be the new target in treating COVID-19–related systemic thrombosis? *Circulation*. 2020;141:1739–1741.
39 Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. *Intensive Care Med*. 2020;46:1105–1108.
40 Becker RC. COVID-19 update: covid-19-associated coagulopathy. *J Thromb Thrombolysis*. 2020;50:54–67.
41 Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract*. 2020;164, 108166.
42 Ren H, Yang Y, Wang F, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. *Cardiovasc Diabetol*. 2020;19, 58–58.
43 Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol*. 2010;47:193–199.
44 Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2014;364(9):829–841.