Primary Care Diabetes 17 (2023) 113–118

Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: www.journals.elsevier.com/primary-care-diabetes

Review

Diabetes mellitus: Lessons from COVID-19 for monkeypox infection

JA Ruiz-Pacheco [a,*], LA Castillo-Díaz [b], R. Arreola-Torres [c], S. Fonseca-Coronado [d], B. Gómez-Navarro [e]

[a] Investigador por México-CONACYT, Centro de Investigaciones Biomédicas de Occidente, IMSS, Guadalajara, Jalisco, México
[b] Departamento de Medicina y Ciencias de la Salud, División de Ciencias Biológicas y de la Salud, Universidad de Sonora, Hermosillo, México
[c] Servicio de Cardiología, Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, México
[d] Unidad de Investigación Multidisciplinaria, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, Estado de México, México
[e] Servicio de Nefrología, Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco, México

ARTICLE INFO

Keywords:
Diabetes mellitus
Type 2 diabetes
Monkeypox
Immune dysfunction
Antidiabetic treatment

ABSTRACT

Background and aims: Type 2 Diabetes Mellitus is known to be linked to malfunctioning antiviral defense; however, its association with the severity of monkeypox is poorly understood. In this review, we discuss key immunological mechanisms in the antiviral response affected by poor glucose control that could impact the susceptibility and severity of monkeypox infection, leading to a heightened emphasis on the use of the available antidiabetic drugs.
Methods: We searched PubMed and Google scholar for articles published from January 1985 to August 2022. No criteria for publication data were set, and all articles in English were included.
Results: Currently, there are no studies about the risk or consequences of monkeypox infection in the diabetic population. A high incidence of diabetes is reported in countries such as China, India, Pakistan, EUA, Indonesia, Brazil, Mexico, Bangladesh, Japan, and Egypt, where unfortunately imported cases of monkeypox have been reported and the infection continues to spread.
Conclusions: High incidence of diabetes together with the cessation of smallpox vaccination has left large numbers of the human population unprotected against monkeypox. The best option for the population remains confined to the prevention of infection as well as the use of hypoglycemic agents that have also been shown to improve immune mechanisms associated with viral protection.

1. Introduction

Currently, the world is experiencing an outbreak of monkeypox infection (MPI) in various countries around the world. Approximately, 100 countries have been affected, with a total of 71,096 confirmed cases of MPI of which 70,377 are reported in countries with no previous history of the infection [1]. MPI is caused by a DNA virus whose symptomatology is similar to that caused by the smallpox virus infection but with a lower mortality rate. Unfortunately, there is no specific treatment to prevent MPI, and only two vaccines might be used against monkeypox: JYNNEOS, and ACAM2000 [2]. The rise in monkeypox cases follows the discontinuation of mass smallpox vaccination worldwide since 1980.

Diabetes mellitus (DM) has been a very important health problem with millions of cases worldwide. DM courses with chronic hyperglycemia, impaired secretion, and/or insulin action, and is directly related to genetics and lifestyle factors [3]. Diabetics are more susceptible to viral infections than non-diabetics. High glucose levels affect DNA sensors such as toll-like receptor 9 (TLR9), cyclic GMP-AMP synthase (cGAS), absent in melanoma 2 (AIM2), and DNA-dependent protein kinase (DNA-PK) [4]. This suggests that diabetic patients might be a population highly susceptible to infection with the monkeypox virus, a DNA virus. However, the use of an antidiabetic drug during viral infections, significantly reduced the risk of complications and death in COVID-19 patients [5]. Therefore, it is highly likely that controlling hyperglycemia would decrease the risk of MPI and subsequently the mortality of infected patients.

* Correspondence to: Laboratorio de Investigación Quirúrgica, Centro de Investigación Biomédica de Occidente, Instituto Mexicano del Seguro Social, Sierra Mojada 800, Independencia Oriente, 44340 Guadalajara, Jalisco, Mexico.
E-mail address: rpj_cell@yahoo.com.mx (J. Ruiz-Pacheco).

https://doi.org/10.1016/j.pcd.2023.01.008
Received 17 October 2022; Accepted 18 January 2023
Available online 30 January 2023

2. Monkeypox infection

In 1980, the World Health Assembly declared smallpox eradicated, leading to the end of smallpox vaccination and raising the risk of monkeypox infection. Virions measure 200–250 nanometers, and the linear double-stranded DNA surrounds and comprises an extended conserved core region with the genes necessary for its replication [6]. According with some studies, monkeypox has no potential for large-scale spread [7]; however, a current analysis showed an epidemic potential [8]. In humans, the virus may be transmitted human-to-human through saliva, lesion exudate, crust material, feces, and sexual contact [9]. Although MPI is similar to smallpox, the fatality rate of monkeypox is around 10% [10]. Unfortunately, there is no treatment for MPI; nonetheless, some vaccines to prevent smallpox, JYNNEOS, and ACAM2000, may be useful in conferring protection [2]. However, thinking about instituting a large-scale vaccination program is somewhat complicated due to the small number of vaccines available. For now, infected patients are managed only with supportive care [11], and isolation.

The first reported MPI in humans was observed in 1970 in the Democratic Republic of the Congo in a 9-month-old child [12]. From 1970–2021, other cases have been reported in Europe, and America [10, 13]. Recently, the European Centre for Disease Prevention and Control (ECDC) reported monkeypox outbreaks in different countries [14]. According to data published on 01 August 2022 by the Center for Disease Control and Prevention (CDC), there are 73,288 cases of MPI in 109 countries worldwide, while only seven countries had previously reported the disease [15].

3. Pathophysiology of Monkeypox infection

The mechanism of poxvirus infection is unknown; however, reports in nonhuman primates (NHPs) reveal that tissues such as lungs, lymph nodes, sternal bone marrow, testes, uterus, tongue, ovaries, kidney, and spinal cord are susceptible to infection [16]. Subsequent there is a usual incubation period of 7–14 days but which can range from 5 − 21 days where patients might experience fever, sore throat, pharyngitis, fatigue, headache, muscle aches, exhaustion, and unlike smallpox patients, monkeypox patients develop maxillary, cervical or inguinal lymphadenopathy. At around day 1–3, some subjects develop a rash mainly on the face, spreading to various areas, including the oral cavity [17]. Serious complications such as pulmonary distress or bronchopneumonia, vomiting, diarrhea, encephalitis, and eye infections with permanent vision loss have also been reported [18]. The mortality rate of monkeypox is estimated at 10% compared with variola major, a smallpox causal agent, at 30% [10].

4. Immunopathogenesis related to Monkeypox infection

A study in NHPs revealed high production of interleukin 1ra (IL-1ra), IL-2, IL-6, IL-8, interferon-γ (IFN-gamma), monocyte chemoattractant protein-1 (MCP-1), regulated upon activation, normal T cell expressed and presumably secreted (RANTES), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CS), and sCD40L. Additionally, monocytes were found to be increased during days 4 and 7 of infection, CD8 T cells showed a return to normality at day 9 in surviving NHPs, and CD4 T cells were decreased on day 13 of infection [16]. In another study, NHPs received intravenous inoculation of the monkeypox virus ($>1–2 \times 10^7$ PFU) to subsequently analyze the whole blood. The results showed that mainly neutrophils and monocytes were positively infected. However, B cells, CD4, CD8, and NK cells showed less monkeypox antigen staining [19]. An aerosol model of lethal MPI in Cynomolgus monkeys revealed that the lower airway epithelium is the main target for infection. Likewise, tonsils, mediastinal and mandibular lymph nodes, gastrointestinal tract, oral mucosa, spleen, thymus, skin, and reproductive system can become infected. In this case, virus antigen was detected in epithelial cells, macrophages, dendritic cells, and fibroblasts of affected tissues [20]. It also has been shown that rhesus macaques infected had an increase in the absolute number of circulating and resident NK cells. Though NK cells are capable of proliferating, their ability to produce C-X-C Motif Chemokine Receptor 3 (CXCR3), C-C Motif Chemokine Receptor 7 (CCR7), CCR6, IFN-γ, tumor necrosis factor (TNF-α), and degranulation was impaired [21]. In humans, monkeypox is capable of inducing the production of IL-1, IL-1RA, IL-2R, IL-4, IL-5, IL-6, IL-8, IL-13, IL-15, IL-17, MCP-1, and RANTES [22]. However, human T cells are unable of responding to monkeypox-virus-infected cells and produce inflammatory cytokines in a major histocompatibility complex (MHC)-independent mechanism [23].

5. Immune mechanisms associated to protect from Poxvirus protection

Monkeypox virus being a DNA virus makes DNA sensors responsible for inducing protection against this pathogen. The best-known DNA sensor is probably TLR-9, an endosomal protein activated by unmethylated cytidine-phosphate-guanosine (CpG) dinucleotides. During poxvirus infection, TLR-9 deficient mice showed a higher risk of severity and death derived from ectromelia virus (ECTV) infection [24]. Similar results have been observed in TLR3 and TLR4 deficient mice infected with the vaccinia virus (VACV) [25,26].

VACV protein C16 has the capacity to antagonize the function of DNA-PK, a nuclear serine/threonine kinase activated by DNA [27], suggesting a key role of DNA-PK during poxvirus infection. Melanoma differentiation-associated gene 5 (MDA5) is an RNA sensor whose activation promotes the IFN-I response [28]. Importantly, type II alveolar epithelial cells produce IFN-β in response to VACV in an MDA5-dependent manner [29]. Karem et al. analyzed a total of 92 subjects during the 2003 US monkeypox outbreak to assess pre-existing and acquired immunity. In this study, patients were categorized into 4 groups: vaccinated cases, unvaccinated cases, vaccinated contacts, and unvaccinated contacts. The results showed that, regardless of vaccination status, the production of specific IgM, IgG, CD4, CD8, and B cell responses were linked with protection [30].

6. T2D and infections

It is estimated that there will be > 590 million T2D-diagnosed patients worldwide by 2035 [31]. According to the International Diabetes Federation (IDF), the top 10 countries with a high number of adults (20–79 years) with diabetes in 2021 are China (140.9 million), India (74.2 million), Pakistan (33 million), USA (32.2 million), Indonesia (19.5 million), Brazil (15,7 million), Mexico (14.1 million), Bangladesh (13.1 million), Japan (11 million), and Egypt (10.9 million) [32].

Generally, the symptoms of such as type 2 diabetes (T2D) are known to be thirst, excessive urination, lethargy, fatigue, and short life expectancy. However, T2D poses a high risk for developing chronic-degenerative pathologies, including cardiovascular disease, neuropathy, amputation, and nephropathy, etc. [33]. Additionally, the T2D population is also known to be immunosuppressed with high susceptibility to infections. For example, a landmark prospective study from the National Health Insurance Service-National Sample Cohort followed up 66,426 T2D patients in South Korea and 18,911 controls for nine years and investigated their susceptibility to infection. The results showed that T2D patients have a higher risk for almost all the types of infections considered in the study. Adjusted incidence rate ratios (aIRRs) for infection-related hospitalizations showed a higher risk for hepatic abscess (aIRR, 10.17; 95% confidence interval [CI], 7.04–14.67), central nervous system infections (aIRR, 8.72; 95% CI, 6.64–11.45), and skin and soft tissue infections other than cellulitis (aIRR, 3.52; 95% CI, 3.20–3.88) [34]. A systematic review of 243 cohort studies and 3102 case-control studies showed that T2D patients have an increased

incidence of skin (OR 1.94, CI 1.78–2.12), respiratory (OR 1.35, CI 1.28–1.43), blood (OR 1.72, CI 1.48–2.00), genitourinary (OR 1.61, CI 1.42–1.82), head and neck (OR 1.17, CI 1.13–1.22), gastrointestinal (OR 1.48, CI 1.40–1.57), and of special interest to us now, viral infection (OR 1.29, CI 1.13–1.46) [35]. A likely explanation for this is the known association between hyperglycemia and immune dysfunction.

7. T2D and immune dysfunction

The main objective of the immune system is to protect the body against a wide variety of threats. Innate immunity is responsible for controlling infection [36] and for protection against pathogens through pattern recognition receptors (PRRs), and inflammation [37]. The effectiveness of immunity, therefore, depends on the perfect coordination and regulation of all these components. In this sense, immune malfunction can trigger inadequate infection control. One such case is what occurs with patients with uncontrolled T2D that have impaired or delayed wound healing and susceptibility to infection [38].

Monocytes obtained from healthy volunteers were cultured at high concentrations of glucose and the levels of IL-6 and TNF-α were subsequently determined. The results showed alterations in the production of TNF-alpha and IL-6 [39]. One possible explanation for these results is the binding of advanced glycation end products (AGEs) to proteins expressed in peripheral blood T lymphocytes, which has been related to IFN-gamma production [40]. Human and mice neutrophils cultured with high glucose levels showed impaired chemotaxis [41]. Similarly, macrophages obtained from T2D patients had less phagocytic activity than macrophages from non-diabetic subjects [42].

8. T2D and antiviral mechanism

The current COVID-19 pandemic has made evident the highly increased susceptibility of diabetic patients to the SARS-CoV-2 infection and to the development of heightened severity of manifestation [43]. Importantly, blood sugar fluctuation has been related with severity of viral infections [44]. Diabetic patients are highly susceptible to hepatitis C virus (OR: 3.6, CI: 2.7–4.9), human herpes virus 8 (OR: 2.7, CI: 1.3–5.4), influenza virus (OR: 2.1, CI: 1.7–2.5), hepatitis B virus (OR: 1.6, CI: 1.2–2.13), virus herpes simplex 1 (OR: 1.5, CI: 1.1–2.0), SARS-CoV-2 (OR: 10.8, CI: 10.3–11.4) and cytomegalovirus infection (OR: 3.5, CI: 0.6–18.3) [45,46].

Interestingly, T cells lacking insulin receptors were found to have reduced antigen-specific proliferation and less production of inflammatory cytokines during the H1N1 infection [47]. Sestan et al. reported that virus-induced IFN-γ downregulates the insulin receptor in skeletal muscle while simultaneously enhancing antiviral immunity via CD8 T cells [48]. According to the expression of peptidylarginine deiminase 4 (PAD4) and citrullinated histone 4 (H3Cit), neutrophils obtained from humans and diabetic mice are primed to produce neutrophil extracellular traps (NETs) [49]. During COVID-19, NETs formation was related to acute lung injury, multi-organ damage, and mortality [50]. This showed a higher predisposition of neutrophils obtained in diabetic individuals to produce NETs and therefore raising the probability of producing tissular damage. Peripheral blood mononuclear cells (PBMCs) cultured with high glucose also showed a higher production of TGF-β and decreases in IL-2, IL-6, and IL-10 production [51], suggesting that TGF-β produced as a result of high glucose levels may impair the immune response by reducing the inflammatory response, thereby permitting the spread of infection. Additionally, alteration in TLRs expression and functions can lead to susceptibility to viral infections. *In vitro* studies showed that high glucose concentration was shown to alter TLRs pathway [52]. TLR9, a DNA sensor, is significantly upregulated in the kidneys of diabetic mice. This has been linked with the activation of NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome [53].

The NLRP3 inflammasome is a multiprotein complex crucial to IL-1b and IL-18 maturation. Like TLRs, NLRP3 recognizes viral components and can trigger an antiviral immune response. Human and diabetic rats show elevation of IL-1β and IL-18 in a NLRP3-dependent manner [54]. During the H1N1 infection, the production of IL-1beta and IL-18 was associated with inflammation in lung cells [55]. Meanwhile, IL-18 deficient mice challenged with the influenza A virus had reduced viral loads indicating that IL-8 impairs viral clearance [56].

DNA sensors such as absent in melanoma 2 (AIM2), cGAS, STING, and DNA-PK, could be affected during diabetes. High glucose concentration has been shown to down-regulate the expression of MDA-5 and IRF-3 [57]. The expression of AIM2 was enhanced in diabetic and aging conditions and correlated with the inflammatory state. However, importantly metformin was shown to alleviate macrophage dysfunction in an AIM2-dependent manner [58]. The cGAS-cGAMP-STING pathway has been associated with chronic inflammation and obesity-induced insulin resistance [59]. Similar results were reported for DNA-PK. Park et al. showed that DNA-PK activates HSP90-alpha dampening mitochondrial activity, promoting weight gain, and insulin resistance, and

Table 1
Immunomodulatory mechanisms of sugar lowering drugs with potential effects on monkeypox infection.

DRUG	ACTION MECHANISM	EFFECT	REFERENCE
Glyburide	Inhibits ATP-sensitive K+ channels, ASC ensemble, and NLRP3 inflammasome.	Reduces inflammatory mediators production, such as IL-1b, which is associated with severe manifestation during viral infection.	61
Angiotensin 1–7, NorLeu^3-A	Induce activation of Mas receptor, vasodilation, and reduce of oxidative stress.	Promote oxidative stress and may accelerate immunity. Oxidative stress is also linked to inflammation and damage.	62
Evogliptin and sitagliptin	Inhibits dipeptidyl peptidase 4 (DDP4) activity.	Control the activation and proliferation of T cells. A key cell population during viral infection.	64
Thiazolidinedione	Inhibit peroxisome proliferator-activated receptor γ (PPAR γ), a regulator of glucose metabolism.	Inhibits T cell apoptosis. During viral infection, T cells are induced to apoptosis as a mechanism of immune evasion.	66,67
Metformin	Inhibits mitochondrial complex I, ATP production, fructose-1,6-bisphosphatase, and gluconeogenesis.	Promotes p38MPAK pathway activation and B-cell activity. Therefore, metformin enhances innate immune response and antibody production, respectively.	71,72
Sodium-glucose cotransporter type 2	Inhibits empagliflozin.	Reduces the production of TNF-α, PCR, and IL-6, which prevents exacerbated inflammation associated with viral infections.	73

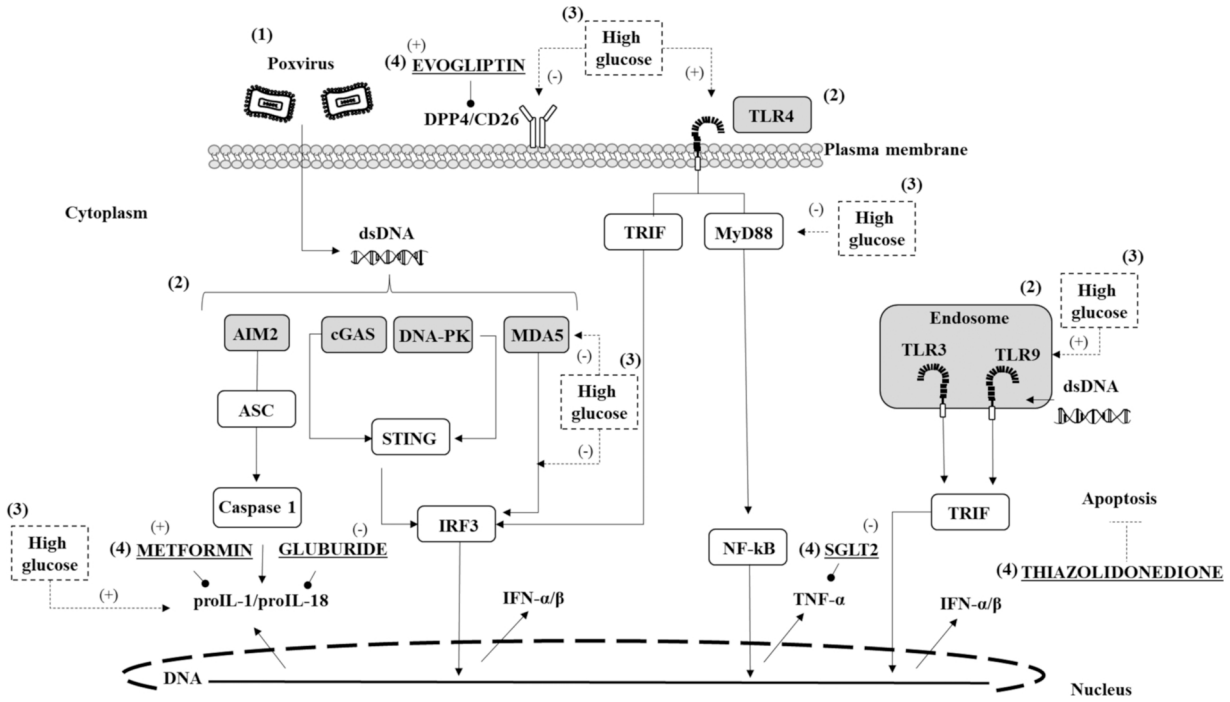

Fig. 1. During poxvirus infection (1), sensor proteins (enclosed and highlighted in grey color) activate adaptor proteins (enclosed without color), which promote the synthesis of IFNs, and inflammatory cytokines (2). High glucose levels impair virus recognition (3), which is associated with the overexpression^{+} or reduction^{-} of cytosolic membranal sensors, and/or adaptor proteins. Hypoglycemiant such as metformin, gluburide, evogliptin, SGLT2, and Thiazolidonedione (4) can induce the overexpression^{+} or reduction^{-} of membranal and cytosolic protein related to antiviral defense. cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; AIM2, absent in melanoma 2; DNA-PK, DNA-dependent protein kinase; MDA5, Melanoma differentiation-associated gene 5; TLR9, Toll-like receptor 9; TLR3, toll-like receptor 3; TLR4, Toll-like receptor 4; DPP4, Dipeptidyl peptidase 4; IRF3, interferon regulatory factor 3; STING, stimulator of interferon genes; ASC, apoptosis-associated speck-like protein containing a CARD; MyD88, myeloid differentiation factor 88; TRIF, TIR-domain-containing adapter-inducing interferon-β; IFN, Interferon, IL-1/18, Interleukin 1/18, and TNF-α, Tumor necrosis factor α; DNA-PK, DNA-dependent protein kinase.

increasing the risk of diabetes [60].

9. Hypoglycemiants as protective drugs against viral infections

In this section, we analyzed some antidiabetic drugs (summarized in Table 1) and their immunomodulatory properties which might have a beneficial role during monkeypox infection (Fig. 1).

9.1. Glyburide, and angiotensin 1–7 and NorLeu^{3}-A

Glyburide, a sulfonylurea drug used to treat T2D, reduces the inflammatory environment inhibiting the production of IL-1beta in an NLRP3-dependent manner [61]. Angiotensin 1–7 and NorLeu^{3}-A (a bioactive peptide of RAS and RAS-modifying peptides, respectively), were used in diabetic mice with respiratory infections. Interestingly, mice treated with these bioactive peptides had better preservation of the structure of pulmonary architecture, an increase in myeloid progenitors, and a reduction in oxidative stress production [62].

9.2. Evogliptin

Dipeptidyl peptidase 4 (DPP4 or CD26), a key regulator of the expression of incretins, also regulates the activation and proliferation of T cells. DDP4 is commonly dysregulated in cells obtained from diabetic patients. Likewise, high circulation of DPP4 levels has been correlated with the risk of vascular dysfunction [63]. Yoon et al. reported that evogliptin or sitagliptin (anti-diabetic drugs) inhibits DPP4 enzymatic activity on Th1 cells [64] which suggests that evogliptin and sitagliptin could be used to control T cells function.

9.3. Thiazolidinedione

Thiazolidinedione (TZD) targets the peroxisome proliferator-activated receptor γ (PPARγ), a protein responsible for regulating genes involved in glucose metabolism. This drug is used for the treatment of T2D [65]. It is known that the influenza A virus and HIV promote apoptosis in T cells [66,67]. Wang et al. published that TZD-dependent activation of PPARγ protects T cells from apoptosis [65].

9.4. Metformin

The use of metformin has been associated with lower severity and mortality in diabetic patients with COVID-19 in a 2021 study [5]. This might be related to the reduction of the inflammatory stimuli [68]. It is known that poxviruses have evolved various mechanisms to evade immune responses. Poxvirus and MPI infection have already been associated with the impaired innate immune response: monkeypox E3 protein has been associated with the blocking of activation of innate immune cells [69]. Meanwhile, IL-1β-binding protein secreted by Vaccinia and cowpox virus has been related to impaired B cell function [70]. In animal models, metformin treatment was shown to increase the innate immune response in a p38MAPK-dependent manner. Clinical studies using metformin showed that B-cell stimulation and antibody production improved in diabetic patients with seasonal influenza [71,72]. Therefore, metformin use could have beneficial results not only to restore euglycemia but also to improve innate immune response and B cell activation.

9.5. Sodium-glucose cotransporter type 2

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors represent

another treatment option for TD2 diabetics. It was demonstrated that SGLT2 inhibitors may decrease the levels of various inflammatory mediators, such as TNF-alpha, PCR, and IL-6 [73]. Many viral infections such as dengue, HIV, and even monkeypox disease are characterized by elevated cytokine levels and severe clinical manifestations [22,74,75]. Therefore, SGLT2 inhibitors could play a key role in both glucose control and viral treatment. Consequently, controlling the fluctuations in blood glucose levels in diabetic patients could aid to obtain a better prognosis and reduce the risk of death during the current monkeypox infection outbreak.

10. Conclusions

Although the current worldwide monkeypox infection represents a considerable risk to the general population, this is especially so for diabetics. Therefore, most countries should be more cautious regarding their diabetic populations, particularly today with an unfortunate increase in the MPI outbreak. The cessation of smallpox vaccination due to eradication in 1980 resulted in increased monkeypox outbreaks. This cessation of smallpox vaccination has left large numbers of the human population unprotected. While there is no specific treatment for monkeypox infection, the best option for the population remains confined to the prevention of infection, until large-scale vaccination programs are instituted or alternative therapy is developed. The intensification of health care, general nutrition, and optimal control of blood glucose levels in diabetic populations to avoid immunological alterations and minimize risk factors during the monkeypox outbreak, are essential.

11. Summary

Poor glucose control was recognized early in the COVID-19 pandemic to predispose to susceptibility and severity of infection; however, its implication on monkeypox is poorly understood. The recent rapid rise in monkeypox infection cases worldwide calls for consideration of the results of glycemic treatment during the COVID-19 pandemic, given the known immunological alterations in diabetics. Although the mortality rate of monkeypox infection is around 10% compared with the mortality rate of variola major at 30%, the high incidence of diabetes mellitus in many countries, leads us to explore what we can glean from the COVID-19 experience.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict interest

No competing financial interests exist.

Acknowledgments

We wish to thank Dr. M. Teresa Horn-Copeland for her help with the presentation of this work in English.

References

[1] ⟨https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html⟩.
[2] ⟨https://www.cdc.gov/poxvirus/monkeypox/considerations-for-monkeypox-vaccination.html⟩.
[3] Sapra, A., P. Bhandari, *Diabetes Mellitus*, in *StatPearls*. 2022: Treasure Island (FL).
[4] A. Zahid, et al., Molecular and structural basis of DNA sensors in antiviral innate immunity, Front. Immunol. 11 (2020), 613039.
[5] R.E. Tamura, et al., Outcome and death risk of diabetes patients with Covid-19 receiving pre-hospital and in-hospital metformin therapies, Diabetol. Metab. Syndr. 13 (1) (2021) 76.
[6] I.V. Babkin, I.N. Babkina, The origin of the variola virus, Viruses 7 (3) (2015) 1100–1112.
[7] Z. Jezek, et al., Human monkeypox: disease pattern, incidence and attack rates in a rural area of northern Zaire, Trop. Geogr. Med 40 (2) (1988) 73–83.
[8] R. Grant, L.L. Nguyen, R. Breban, Modelling human-to-human transmission of monkeypox, Bull. World Health Organ 98 (9) (2020) 638–640.
[9] J. Heskin, et al., Transmission of monkeypox virus through sexual contact - a novel route of infection, J. Infect. (2022).
[10] N. Sklenovska, M. Van Ranst, Emergence of monkeypox as the most important orthopoxvirus infection in humans, Front Public Health 6 (2018) 241.
[11] M.G. Reynolds, et al., Improving the care and treatment of monkeypox patients in low-resource settings: applying evidence from contemporary biomedical and smallpox biodefense research, Viruses 9 (12) (2017).
[12] I.D. Ladnyj, P. Ziegler, E. Kima, A human infection caused by monkeypox virus in basankusu territory, Democratic Republic of the Congo, Bull. World Health Organ 46 (5) (1972) 593–597.
[13] G. Hobson, et al., Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, Eur. Surveill. 26 (32) (2021).
[14] https://www.ecdc.europa.eu/en/publications-data/monkeypox-multi-country-outbreak-first-update#:~:text=Since%20early%20May%202022%20and, c.r.w.i.
[15] ⟨https://www.cdc.gov/poxvirus/monkeypox/outbreak/us-outbreaks.html⟩.
[16] R.F. Johnson, et al., Comparative analysis of monkeypox virus infection of cynomolgus macaques by the intravenous or intrabronchial inoculation route, J. Virol. 85 (5) (2011) 2112–2125.
[17] H. Adler, et al., Clinical features and management of human monkeypox: a retrospective observational study in the UK, Lancet Infect. Dis. 22 (8) (2022) 1153–1162.
[18] A.M. McCollum, I.K. Damon, Human monkeypox, Clin. Infect. Dis. 58 (2) (2014) 260–267.
[19] H. Song, et al., Poxvirus antigen staining of immune cells as a biomarker to predict disease outcome in monkeypox and cowpox virus infection in non-human primates, PLoS One 8 (4) (2013), e60533.
[20] G.M. Zaucha, et al., The pathology of experimental aerosolized monkeypox virus infection in cynomolgus monkeys (Macaca fascicularis), Lab Invest 81 (12) (2001) 1581–1600.
[21] H. Song, et al., Monkeypox virus infection of rhesus macaques induces massive expansion of natural killer cells but suppresses natural killer cell functions, PLoS One 8 (10) (2013), e77804.
[22] S.C. Johnston, et al., Cytokine modulation correlates with severity of monkeypox disease in humans, J. Clin. Virol. 63 (2015) 42–45.
[23] E. Hammarlund, et al., Monkeypox virus evades antiviral CD4+ and CD8+ T cell responses by suppressing cognate T cell activation, Proc. Natl. Acad. Sci. USA 105 (38) (2008) 14567–14572.
[24] C. Samuelsson, et al., Survival of lethal poxvirus infection in mice depends on TLR9, and therapeutic vaccination provides protection, J. Clin. Invest 118 (5) (2008) 1776–1784.
[25] M. Hutchens, et al., TLR3 increases disease morbidity and mortality from vaccinia infection, J. Immunol. 180 (1) (2008) 483–491.
[26] M.A. Hutchens, et al., Protective effect of Toll-like receptor 4 in pulmonary vaccinia infection, PLoS Pathog. 4 (9) (2008), e1000153.
[27] S.R. Scutts, et al., DNA-PK is targeted by multiple vaccinia virus proteins to inhibit DNA sensing, Cell Rep. 25 (7) (2018), p. 1953-1965 e4.
[28] A.G. Dias Junior, N.G. Sampaio, J. Rehwinkel, A balancing act: MDA5 in antiviral immunity and autoinflammation, Trends Microbiol 27 (1) (2019) 75–85.
[29] N. Yang, et al., Lung type II alveolar epithelial cells collaborate with CCR2(+) inflammatory monocytes in host defense against poxvirus infection, Nat. Commun. 13 (1) (2022) 1671.
[30] K.L. Karem, et al., Monkeypox-induced immunity and failure of childhood smallpox vaccination to provide complete protection, Clin. Vaccin. Immunol. 14 (10) (2007) 1318–1327.
[31] J. Reed, S. Bain, V. Kanamarlapudi, A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives, Diabetes Metab. Syndr. Obes. 14 (2021) 3567–3602.
[32] ⟨https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf⟩.
[33] J.L. Harding, et al., Global trends in diabetes complications: a review of current evidence, Diabetologia 62 (1) (2019) 3–16.
[34] E.J. Kim, et al., Diabetes and the risk of infection: a national cohort study, Diabetes Metab. J. 43 (6) (2019) 804–814.
[35] W. Abu-Ashour, et al., The association between diabetes mellitus and incident infections: a systematic review and meta-analysis of observational studies, BMJ Open Diabetes Res Care 5 (1) (2017), e000336.
[36] H. Kumar, T. Kawai, S. Akira, Pathogen recognition by the innate immune system, Int Rev. Immunol. 30 (1) (2011) 16–34.
[37] T. Kawasaki, T. Kawai, Toll-like receptor signaling pathways, Front Immunol. 5 (2014) 461.
[38] J. Chavez-Reyes, et al., Susceptibility for some infectious diseases in patients with diabetes: the key role of glycemia, Front Public Health 9 (2021), 559595.
[39] M. Morohoshi, et al., The effect of glucose and advanced glycosylation end products on IL-6 production by human monocytes, Ann. N. Y Acad. Sci. 748 (1995) 562–570.
[40] F. Imani, et al., Advanced glycosylation endproduct-specific receptors on human and rat T-lymphocytes mediate synthesis of interferon gamma: role in tissue remodeling, J. Exp. Med 178 (6) (1993) 2165–2172.
[41] R. Roy, et al., Overriding impaired FPR chemotaxis signaling in diabetic neutrophil stimulates infection control in murine diabetic wound, Elife 11 (2022).
[42] A. Lecube, et al., Phagocytic activity is impaired in type 2 diabetes mellitus and increases after metabolic improvement, PLoS One 6 (8) (2011), e23366.

[43] K. Subbaram, P.S.S. Ali, S. Ali, Enhanced endocytosis elevated virulence and severity of SARS-CoV-2 due to hyperglycemia in type 2 diabetic patients, Gene Rep. 26 (2022), 101495.
[44] R.J. Marshall, et al., Glycemic variability in diabetes increases the severity of influenza, mBio 11 (2) (2020).
[45] E. Lontchi-Yimagou, et al., Non-autoimmune diabetes mellitus and the risk of virus infections: a systematic review and meta-analysis of case-control and cohort studies, Sci. Rep. 11 (1) (2021) 8968.
[46] B.W. Roberts, I. Cech, Association of type 2 diabetes mellitus and seroprevalence for cytomegalovirus, South Med J. 98 (7) (2005) 686–692.
[47] S. Tsai, et al., Insulin receptor-mediated stimulation boosts T cell immunity during inflammation and infection, Cell Metab. 28 (6) (2018), p. 922-934 e4.
[48] M. Sestan, et al., Virus-induced interferon-gamma causes insulin resistance in skeletal muscle and derails glycemic control in obesity, Immunity 49 (1) (2018), p. 164-177 e6.
[49] S.L. Wong, et al., Diabetes primes neutrophils to undergo NETosis, which impairs wound healing, Nat. Med 21 (7) (2015) 815–819.
[50] M. Szturmowicz, U. Demkow, Neutrophil extracellular traps (NETs) in severe SARS-CoV-2 lung disease, Int J. Mol. Sci. 22 (16) (2021).
[51] D. Reinhold, S. Ansorge, E.D. Schleicher, Elevated glucose levels stimulate transforming growth factor-beta 1 (TGF-beta 1), suppress interleukin IL-2, IL-6 and IL-10 production and DNA synthesis in peripheral blood mononuclear cells, Horm. Metab. Res 28 (6) (1996) 267–270.
[52] M.R. Dasu, et al., High glucose induces toll-like receptor expression in human monocytes: mechanism of activation, Diabetes 57 (11) (2008) 3090–3098.
[53] J. Shen, et al., TLR9 regulates NLRP3 inflammasome activation via the NF-kB signaling pathway in diabetic nephropathy, Diabetol. Metab. Syndr. 14 (1) (2022) 26.
[54] J. Wang, et al., High glucose mediates NLRP3 inflammasome activation via upregulation of ELF3 expression, Cell Death Dis. 11 (5) (2020) 383.
[55] K.S. Kim, et al., Induction of interleukin-1 beta (IL-1beta) is a critical component of lung inflammation during influenza A (H1N1) virus infection, J. Med Virol. 87 (7) (2015) 1104–1112.
[56] K.F. Van Der Sluijs, et al., Enhanced viral clearance in interleukin-18 gene-deficient mice after pulmonary infection with influenza A virus, Immunology 114 (1) (2005) 112–120.
[57] G. Kocic, et al., Hyperglycemia, oxidative and nitrosative stress affect antiviral, inflammatory and apoptotic signaling of cultured thymocytes, Redox Rep. 15 (4) (2010) 179–184.
[58] L. Nie, et al., Diabetes induces macrophage dysfunction through cytoplasmic dsDNA/AIM2 associated pyroptosis, J. Leukoc. Biol. 110 (3) (2021) 497–510.
[59] J. Bai, et al., DsbA-L prevents obesity-induced inflammation and insulin resistance by suppressing the mtDNA release-activated cGAS-cGAMP-STING pathway, Proc. Natl. Acad. Sci. USA 114 (46) (2017) 12196–12201.
[60] S.J. Park, et al., DNA-PK promotes the mitochondrial, metabolic, and physical decline that occurs during aging, Cell Metab. 25 (5) (2017), p. 1135-1146 e7.
[61] A. Zahid, et al., Pharmacological inhibitors of the NLRP3 inflammasome, Front Immunol. 10 (2019) 2538.
[62] M. Soto, K.J. Gaffney, K.E. Rodgers, Improving the innate immune response in diabetes by modifying the renin angiotensin system, Front Immunol. 10 (2019) 2885.
[63] D. Rohrborn, N. Wronkowitz, J. Eckel, DPP4 in diabetes, Front Immunol. 6 (2015) 386.
[64] H. Yoon, J.H. Sung, M.J. Song, Effects of the antidiabetic drugs evogliptin and sitagliptin on the immune function of CD26/DPP4 in Th1 cells, Biomol. Ther. 29 (2) (2021) 154–165.
[65] H. Yki-Jarvinen, Thiazolidinediones, N. Engl. J. Med 351 (11) (2004) 1106–1118.
[66] Y. Zhang, et al., Apoptosis and reduced influenza A virus specific CD8+ T cells in aging mice, Cell Death Differ. 9 (6) (2002) 651–660.
[67] D. Cao, et al., A Matter of life or death: productively infected and bystander CD4 T cells in early HIV infection, Front Immunol. 11 (2020), 626431.
[68] T.S. Postler, et al., Metformin selectively dampens the acute inflammatory response through an AMPK-dependent mechanism, Sci. Rep. 11 (1) (2021) 18721.
[69] W.D. Arndt, et al., Evasion of the innate immune type I interferon system by monkeypox virus, J. Virol. 89 (20) (2015) 10489–10499.
[70] M.K. Spriggs, et al., Vaccinia and cowpox viruses encode a novel secreted interleukin-1-binding protein, Cell 71 (1) (1992) 145–152.
[71] Y. Xiao, et al., Metformin promotes innate immunity through a conserved PMK-1/p38 MAPK pathway, Virulence 11 (1) (2020) 39–48.
[72] D. Frasca, et al., Metformin enhances B cell function and antibody responses of elderly individuals with type-2 diabetes mellitus, Front Aging 2 (2021), 715981.
[73] F. Bonnet, A.J. Scheen, Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease, Diabetes Metab. 44 (6) (2018) 457–464.
[74] A.R.K. Patro, et al., Cytokine signature associated with disease severity in dengue, Viruses 11 (1) (2019).
[75] D.M. Muema, et al., Association between the cytokine storm, immune cell dynamics, and viral replicative capacity in hyperacute HIV infection, BMC Med. 18 (1) (2020) 81.