Available online at www.rajournals.in

RA JOURNAL OF APPLIED RESEARCH
ISSN: 2394-6709
DOI:10.47191/rajar/v8i2.06
Volume: 08 Issue: 02 February-2022

International Open Access

Impact Factor- 7.036

Page no.- 88-93

Diabetes Mellitus and Covid-19: Modern Strategies

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ARTICLE INFO

Published Online:
12 February 2022

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ABSTRACT

The announcement of the COVID-19 pandemic in the world was followed by unprecedented measures to control the spread of the disease and find effective treatment and prevention regimens. The most vulnerable in these conditions were patients with diabetes mellitus.

In this article analyzes the literature data of recent years on the management, diagnosis, treatment and prevention of diabetes mellitus against the background of coronavirus infection.

KEYWORDS: COVID-19, diabetes mellitus, diagnosis, treatment, prevention, review.

INTRODUCTION

The infectious epidemic of COVID-19 caused by a new coronavirus - causing severe acute respiratory syndrome coronavirus 2 (Severity Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2), began its disastrous procession in December 2019 in Wuhan (China) and spread almost like lightning to all countries of the world.

The severity of this epidemic is largely due to the widespread (epidemic) prevalence of diabetes mellitus (DM) and obesity, the presence of which exacerbates the course of infection. Data from the first months of 2020 show that the majority of people with severe COVID-19 have comorbidities, the most common of which are diabetes, obesity, cardiovascular disease, and hypertension [1].

The "Asian" and "Hong Kong" influenza epidemics of 1957 and 1960, as well as the 2009 H1N 1 influenza A virus pandemic, have already shown that obesity and diabetes are associated with an increased risk of severe disease and higher mortality, even in the absence of other chronic conditions, which increase the risk of influenza [2, 3].

THE MAIN PART

In today's pandemic, data have accumulated, on the one hand, indicating the association of obesity and DM with a more severe course of COVID-19 and death [4,6], on the other hand, that COVID-19 is associated with the development of hyperglycemia, especially in elderly people with type 2 diabetes [7].

To understand the relationship between this infection and DM, some structural features of the virus and its interaction with human cells are important. Coronavirus 2 refers to RNA-3-containing viruses that have an envelope, the structure of which contains several elements (glycoproteins) that ensure the structural integrity of the virion and its penetration into the target cell. The virus uses a special surface glycoprotein called a "spike" to bind to angiotensin-converting enzyme 2 (ACE2) and enter the cell [8]. ACE2 as an element of the renin-angiotensin-aldosterone system (RAAS) was identified at the beginning of the 21st century [9]. Its long and well-studied homolog, angiotensin-converting enzyme, is a positive regulator of RAAS activity, providing the conversion of angiotensin I (AngI) to angiotensin II (AngII) by removing the dipeptide from the C-terminal end of the AngI decapeptide. AngII is a profibrogenic, vasoconstrictor, pro-inflammatory peptide that binds and activates the angiotensin type 1 receptor (AT1R). ACE2 proved to be a negative regulator of RAAS activity, since, by cleaving the AngII residue elsewhere, it produces angiotensin (1-7), a heptapeptide that has a powerful vasodilating, anti-inflammatory and antioxidant effect. It can also cleave AngI, producing angiotensin (1-9), which has similar properties [10]. In the experiment, genetic or pharmacological modeling of low ACE2 expression was accompanied by the development of impaired glucose tolerance and a decrease in the first phase of insulin secretion [11]. A decrease in ACE2 expression was observed in animal models of DM and in kidney biopsies of patients with DM and was associated with an increase in albuminuria and the presence of morphological signs of diabetic nephropathy in biopsies [12]. It is believed that ACE2 deficiency plays an important role both in the development of DM and in the progression of its renal and cardiac complications [13].

Another important surface structure of the virus is the prM and E proteins, which are critical for the formation of the

final virion configuration [8]. These glycoproteins may be the point of application for some of the therapies that we will touch upon later.

ACE2 and changes in its expression play an important role in the mechanisms of interaction between DM and COVID-19. It is extremely important that the virus, by binding to ACE2, causes its down-regulation, which may give the following explanation for severe lung damage in diabetes and cardiovascular diseases - these patients initially have low expression of ACE2 due to type 2 diabetes and further its decrease under the influence of the virus leads to a severe deficiency of Ang1-7 and 1-9 and a pronounced dominance of the effects of AngII in the lung tissue, which determines severe lung damage [14].

The lung appears to be the most vulnerable target organ, firstly because the large surface area of the lungs makes them highly susceptible to inhaled viruses. In addition, Y. Zhao et al. (2020) demonstrated that 83% of cells expressing ACE2 were type II alveolar epithelial cells, and these cells can presumably serve as a reservoir for viral invasion [15]. High expression of the ACE2 receptor, in addition to the lungs, has also been found in many extrapulmonary tissues, including the aforementioned pancreas and kidneys, as well as the heart, endothelium, and intestines [16].

Acute hyperglycemia has been shown to increase the expression of ACE2 in cells, which may facilitate entry of viral cells. However, chronic hyperglycemia, as already noted, reduces the expression of ACE2, making cells vulnerable to the inflammatory and damaging effects of the virus. The interaction between COVID-19 and DM may be bidirectional. As noted above, SARS-CoV-2 enters human cells through ACE2 [17]. ACE2 is widely expressed in the liver and pancreas, and its deficiency plays a role in the development of insulin resistance and impaired insulin secretion. After endocytosis of the viral complex, ACE2 expression decreases [18], which leads to two types of consequences. First, entry of SARS-CoV-2 into pancreatic islet cells can directly exacerbate damage to beta cells [19]. Second, suppression of ACE2 after viral entry can lead to angiotensin II production without counteraction, which impairs insulin secretion [20].

These data suggest that infection may cause the development of DM or at least severe stress hyperglycemia [19, 21]. The fact that COVID-19 infection causes hyperglycemia in people without pre-existing diabetes has already been documented by some researchers. Hyperglycemia has been shown to persist for 3 years after recovery from SARS, indicating transient damage to beta cells [19]. Today we cannot yet talk about the consequences of exposure to SARS-CoV-2, but in the near future the long-term consequences of this infection will certainly be assessed.

Meanwhile, pronounced ACE2 inhibition is not the only reason for the more severe course of COVID-19 disease in patients with DM. There are several additional mechanisms that explain the increased incidence and severity of COVID-19 infection in people with DM.

People with all forms of DM already have impaired both humoral and cellular immunity (primary immunodeficiency), which contributes to an increased risk of infection and a more severe course of infection. Poor glycemic control impairs the immune response to viral infection in the lungs (secondary immune dysfunction) [22].

Patients with type 2 diabetes are characterized by the presence of obesity, which contributes to the risk of developing severe forms of COVID-19. Obese patients have chronically higher concentrations of leptin (a pro-inflammatory adipokine) and lower concentrations of adiponectin (an anti-inflammatory adipokine). This unfavorable hormonal environment also leads to dysregulation of the immune response [23]. Patients with obesity and diabetes have a higher concentration of a number of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF alpha), monocytic chemotactic factor 1 (MCP-1) and interleukin 6 (IL-6), mainly produced by visceral and subcutaneous adipose tissue. tissue [22]. Obesity has been shown to impair adaptive immune responses to influenza virus, and dysregulation of the pro-inflammatory response has contributed to the severe lung injury seen in influenza pandemic victims [24]. This is likely the case with COVID-19 as well. The presence of obesity in a patient with type 2 diabetes may increase the risk of thromboembolic complications. The development of disseminated intravascular coagulation and a high frequency of venous thromboembolism accompany severe forms of COVID-19 with a higher frequency in patients with a body mass index (BMI) > 35 kg/m^2. Obesity also affects lung function, reducing forced expiratory volume and vital capacity. Together, these cardiometabolic, thrombotic, and cardiorespiratory consequences of obesity in type 2 DM lead to an attenuated metabolic response and increased severity of COVID-19. In a French study, the risk of mechanical ventilation in patients with COVID-19 infection admitted to intensive care was more than seven times higher in people with a BMI > 35 kg/m^2 compared to those with a BMI < 25 kg/m^2 [5].

Another mechanism that may play a significant role in the development of severe forms of coronavirus infection in type 2 diabetes with obesity is associated with a change in the activity of the dipeptidyl peptidase-4 (DPP-4) enzyme. DPP-4 is a type II transmembrane glycoprotein that is expressed in many tissues, including immunocytes. DPP-4 is involved in the degradation of many hormones and peptides, its functions are diverse and not fully understood [25]. Nevertheless, it has now been established that DPP-4 plays an important role in the metabolism of glucose and insulin, providing a rapid breakdown of incretins - glucagon-like peptide 1 and glucose-dependent insulinotropic peptide, which modulate insulin secretion in response to food intake. In visceral obesity, which invariably accompanies type 2 DM,

DPP-4 expression is increased in visceral adipose tissue and directly correlates with inflammation and insulin resistance [26]. An increase in DPP-4 activity leads to a decrease in insulin secretion and impaired metabolism of adipose tissue. DPP-4 also plays an important role in regulating the immune response by activating T cells and increasing inflammation activity in type 2 DM through both catalytic and non-catalytic mechanisms [27]. Meanwhile, DPP-4 has been identified as a functional receptor for the hCOV-EMC coronavirus spike protein. When bound to DPP-4hCOV-EMC also interferes with the regulation of the immune response. In vitro studies have shown that antibodies directed to DPP-4 inhibit hCOV-EMC infection of bronchial epithelial cells and Huh-7 cells [28, 29]. However, different coronaviruses may use different structures to enter the cell. Coronaviruses can be roughly divided into SARS-coronaviruses, which include both the SARS-CoV-2 virus that caused the current COVID-19 pandemic, and MERS-coronaviruses. At the same time, SARS-coronaviruses use ACE2 to penetrate the cell, and MERS-coronaviruses use DPP-4 for this purpose. In this regard, when infected with MERS-coronavirus, DPP-4 inhibition unequivocally reduces the penetration of viruses into cells, but this has not been proven for SARS-coronaviruses [30]. Meanwhile, there are substantial grounds for suggesting positive effects of DPP-4 inhibition in SARS-CoV-2 as well. This was the basis for the start of clinical trials aimed at evaluating the effect of DPP-4 inhibitors, in particular linagliptin, on the course of coronavirus infection caused by SARS-CoV-2 [31].

Particular attention should be paid to patients with type 1 diabetes with glycated hemoglobin levels above the target values due to the high risk of metabolic decompensation. Diabetic ketoacidosis (DKA) results from a deficiency in insulin and increased counter-regulatory responses that promote ketone production. In fact, any severe infection increases the risk of developing acute complications of diabetes with a high frequency. Infection is a causative factor in 30–60% of patients with hyperglycemic hyperosmolar state and in 15–58% of patients with DKA [32].

Interactions between SARS-CoV-2 and RAAS may provide another mechanism in the pathophysiology of DKA. The down-regulation of ACE2 described above under the influence of both SARS-CoV-2 and hyperglycemia can contribute to an acute deterioration in the function of pancreatic beta-cells and exacerbate the course of DKA.

In addition, the relationship between SARS-CoV-2 and RAAS may complicate the management of DKA. Excessive fluid administration may exacerbate acute respiratory distress syndrome, as angiotensin II increases pulmonary vascular permeability and worsens damage to the lung parenchyma [33]. Also, angiotensin II stimulates aldosterone secretion, increasing the risk of hypokalemia, which may require additional potassium to continue intravenous insulin to suppress ketogenesis.

Given the high risk of developing severe forms and death in DM, it is important to pay great attention to the prevention of COVID-19 in patients with DM. To this end, it is recommended to avoid scheduled visits to medical institutions, consultations of specialists, in particular an endocrinologist, if technically possible, should be replaced by telemedicine consultations, telemonitoring or consultations by phone and Skype [34]. Patients should pay close attention to maintaining euglycemia, adequate hydration, and weight control. It is useful to take vitamins C (standard doses for SARS) and D. Considering that vitamin D deficiency also worsens the immune response, and the self-isolation regime exacerbates this deficiency, high doses of vitamin D are recommended (taking vitamin D at a dose of 10,000 IU per day for several weeks, then switching to 5000 IU per day rather quickly raises the level of 25 (OH) D in the blood to the target and, possibly, contributes to the prevention of COVID-19) [35]. Elderly patients also benefit from taking zinc supplements (zinc sulfate at a dose of 20-45 mg/day is recommended), since zinc deficiency is very common in the elderly and is associated with a more severe course and high mortality of viral pneumonias [36]. The management of patients with DM and COVID-19 is determined by the form of the disease. Usually, 80% of people have a mild infection that does not require hospitalization of the patient, and patients receive treatment at home in self-isolation. As noted above, patients with DM are more likely to have severe forms. In the case of a mild course, the patient should increase the frequency of glycemic control to daily every 4-6 hours, patients with a high risk of developing ketoacidosis (type 1 diabetes, type 2 diabetes with absolute insulinopenia (with C-peptide level < 0.25 nmol / l) or its high risk (long-term receiving high doses of insulin)) with an increase in the level of glycemia above 13 mmol / l, ketonuria or ketonemia should be monitored. It is necessary to ensure sufficient hydration - consumption of at least 2.5-3 liters of water per day (in the absence of contraindications), conduct steam inhalations, take paracetamol with hyperthermia. Since the target level of glycemia for patients with COVID-19 has not been established, the standard target levels of glycemia for patients with diabetes, taking into account age and comorbid pathology, should be used [47]. For patients with mild COVID-19, a strict glycemic control goal (fasting plasma glucose 4.4–6.1 mmol/L, 2-hour postprandial plasma glucose 6.1–7.8 mmol/L) is recommended. Not only hyperglycemia should be avoided, but also excessive glucose lowering, especially < 3.9 mmol/l, due to the risk of hypoglycemia [37]. Patients with type 1 diabetes treated with continuous insulin delivery and continuous glycemic monitoring systems should be informed that some permanent glucose monitoring sensors (Dexcom G5, Medtronic Enlite and Guardian) are exposed to acetaminophen (paracetamol) and in they should only use the test strips during its intake [38]. If glycemic control is within the target range, you should continue taking antidiabetic drugs in the same volume, with the development of hyperglycemia, discuss the issue of intensifying therapy with

your doctor. The choice of drugs to enhance therapy is quite difficult in a patient with type 2 diabetes and COVID-19. The use of drugs that can cause dehydration (gliflozins) or hypoglycemia (glibenclamide, other sulfonylurea drugs) should be avoided. Therapy with gliflozins is associated with an increased risk of developing euglycemic DKA [39]. This risk increases significantly in acute conditions, so the FDA recommends interrupting gliflozin therapy in severe infections. A very balanced approach is also needed to address the issue of metformin withdrawal in patients with type 2 diabetes and COVID-19. On the one hand, the risk of developing lactic acidosis in patients receiving metformin is very low and amounts to 4.3 cases per 100,000 patients per year [40]. These cases occur mainly in patients who abuse alcohol, with severe impairment of liver or kidney function. Therefore, in patients with a mild course of coronavirus infection, discontinuation of metformin is more likely to lead to the development of severe hyperglycemia and an increased risk of worsening the course of the disease than to the development of lactic acidosis. Meanwhile, with the development of severe forms of coronavirus infection with severe respiratory failure, the risk of developing lactic acidosis becomes significant, and such patients should be treated with insulin. Glitazone therapy is associated with increased ACE2 expression and increased fluid retention [41]. The significance of increased ACE2 expression (benefit/risk ratio) is now being actively debated. It is known that treatment with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, which is received by almost all patients with type 1 and type 2 diabetes, can increase the expression of ACE2 and, accordingly, accelerate the penetration of the virus into cells. However, since SARS-CoV-2 can reduce ACE2 expression and increase angiotensin II activity, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may protect against severe lung injury after infection [42]. However, the risk of developing heart failure described for thiazolidinediones, combined with a high incidence of heart failure in severe forms of COVID-19, makes therapy with this group of drugs quite risky. Thus, if it is necessary to increase therapy, it is safest to increase therapy with DPP4 iD or "soft" sulfonylurea drugs (gliclazide, gliquidone). Therapy with DPP-4 i, taking into account the above-described role of DPP-4 in the development of coronavirus infection, requires a separate discussion. Data from a meta-analysis that assessed the effect of DPP-4 i on the course of respiratory infections showed a neutral effect [43], and the results of experimental studies do not exclude the possibility of reducing the risk of infection. In addition, in recent years, the possibility of safe use of this group of drugs even in fairly severe patients has been actively discussed [44].

Another group of drugs with probably positive effects on the course of COVID-19 are α-glycosidase inhibitors. These drugs attracted attention during the dengue fever epidemic, caused by a virus similar in structure to SARS-CoV-2 (DENV-1). These viruses, like SARS-CoV-2, have prM and E glycoproteins in the envelope structure. α-glucosidase 1 is an enzyme that plays a crucial role in viral maturation by initiating the formation of oligosaccharides of viral envelope glycoproteins (prM and E). α-glycosidase inhibitors inhibited the activity of SARS-CoV-2-like viruses (DENV-1) by interfering with the configuration of the structural proteins prM and E, which provide a critical step in virion secretion [45]. However, these drugs, while demonstrating a significant reduction in viral load in animal experiments, had a rather weak effect in humans. This may be due to the local action of these drugs in the gastrointestinal tract.

Patients with reduced appetite, gastrointestinal symptoms may require a reduction in the dosage of antidiabetic drugs or a switch from tablet preparations to insulin.

Patients who developed stress hyperglycemia during the course of COVID-19 should receive intensive treatment during hospitalization (maintaining glycemic levels of 6.1-7.8 mmol / l), and later, after discharge, they need periodic monitoring glycemic levels, as they have a high risk of developing diabetes.

CONCLUSION

Patient education with a detailed discussion of the importance of continuing all prescribed therapy, including RAAS blockers, statins, smoking cessation, maintaining targeted glycemic control, blood pressure, weight loss is an integral part of the management of patients with diabetes necessary to reduce the risks associated with COVID-19.

There is a certain feeling that nature has decided to join the fight against obesity and diabetes pandemics in such an extraordinary way as the development of COVID-19, putting our patients before a harsh choice - either normalization of body weight and tight control of glycemia, or a high probability of dying from a viral infection, demonstrating the vulnerability and impotence of such patients in the face of a new infection that will always lie in wait for humanity.

REFERENCES

1. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q. Prevalence of comorbidities and its effects in patients infected with SARS- CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–95.
2. Yang L, Chan KP et al. Obesity and influenza associated mortality: evidence from an elderly cohort in Hong Kong. Prev Med. 2013;56(2):118–123.
3. Morgan OW, Bramley A, Fowlkes A, Freedman DS, Taylor TH, Gargiullo P et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A (N 1) disease. PLoS One.

2010;15;5(3):e9694.
4. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell LF, Chernyak Y et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. Br Med J. 2020;369: m1966.
5. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring). 2020. [Ahead of print, published online 9 April 2020].
6. Lighter J, Phillips M, Hochman S, Sterling S, Johnson D, Francois F et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission. Clin Infect Dis. 2020. [Ahead of print, published online 9 April 2020].
7. Xue T, Li Q, Zhang Q, Lin W, Wen J, Li L et al. Blood glucose levels in elderly subjects with type 2 diabetes during COVID-19 outbreak: a retrospective study in a single center. medRxiv. 2020. [Published online 2 April 2020].
8. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE 2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020;46(4):586–590.
9. Turner AJ, Hooper NM. The angiotensin-converting enzyme gene family: genomics and pharmacology. Trends Pharmacol Sci. 2002;23(4):177–183.
10. Batlle D, Soler MJ, And Ye M. ACE 2 and Diabetes: ACE of ACEs? Diabetes. 2010;59(12):2994–2996. doi:10.2337/db10-1205
11. Tikellis C, Wookey PJ, Candido R, Andrikopoulos S, Thomas MC, Cooper ME. Improved islet morphology after blockade of the renin-angiotensin system in the ZDF rat. Diabetes. 2004;53(4):989–997.
12. Ye M, Wysocki J, William J, Soler MJ, Cokic I, Batlle D. Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes. J Am Soc Nephrol. 2006;17(11):3067–3075.
13. Reich HN, Oudit GY, Penninger JM, Scholey JW, Herzenberg AM. Decreased glomerular and tubular expression of ACE 2 in patients with type 2 diabetes and kidney disease. Kidney Int. 2008;74(12):1610–1616.
14. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S et al. SARS-CoV-2 cell entry depends on ACE 2 and TMPRSS 2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–280.
15. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single- cell RNA expression profiling of ACE 2, the putative receptor of Wuhan COVID-19. 2020.
16. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virology. 2020;94(7):127–120.
17. Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol. 2020;16(6):297–298.
18. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020;382(17):1653–1659.
19. Yang JK, Lin SS. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47(3):193–199.
20. Carlsson PO, Berne C, Jansson L. Angiotensin II and the endocrine pancreas: effects on islet blood flow and insulin secretion in rats. Diabetologia. 1998;41(2):127–133.
21. Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE and ACE 2 expression within different organs of the NOD mouse. Int J Mol Sci. 2017;18(3):563.
22. Richard C, Wadowski M, Goruk S, Cameron L, Sharma AM, Field CJ. Individuals with obesity and type 2 diabetes have additional immune dysfunction compared with obese individuals who are metabolically healthy. BMJ Open Diabetes Res Care. 2017;5(1): e000379.
23. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11(2):85–97.
24. Ussher JR, Drucker DJ. Endocrine Reviews. 2012; 33(2):187–215.
25. Sell H, Blüher M, Klöting N, Schlich R, Willems M, Ruppe F et al. Adipose dipeptidyl peptidase-4 and obesity: correlation with insulin resistance and depot-specific release from adipose tissue in vivo and in vitro. Diabetes Care. 2013;36(12):4083–4090.
26. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020;26(162):108–125.
27. Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013;495(7440):251–254.
28. Canton J, Fehr AR, Fernandez-Delgado R, Gutierrez- Alvarez FJ, Sanchez-Aparicio MT, García-Sastre A et al. MERS- CoV 4b protein interferes with the NF-κB-dependent innate immune

response during infection. PLoS Pathog. 2018;14(1):e1006838.
29. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5(4):562–569.
30. Guo W, Li M et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020: e3319.
31. Guo J, Hang Z, Lin L, Lv J. Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome Coronavirus 2 infection. J Am Heart Assoc. 2020;9(7): e016219.
32. Ma W-X, Ran X-W. The management of blood glucose should be emphasized in the treatment of COVID-19. Sichuan Da Xue Xue Bao Yi Xue Ban. 2020;51(2):146–150.
33. GrantWB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL at al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12(4):988.
34. Barnett JB, Hamer DH, Meydani SN. Low zinc status: a new risk factor for pneumonia in the elderly? Nutr Rev. 2010;68(1):30–37.
35. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes Metab Syndr. 2020;14(3):211–212.
36. Ma WX, Ran XW. The Management of Blood Glucose Should be Emphasized in the Treatment of COVID-19. Sichuan Da Xue Xue Bao Yi Xue Ban. 2020;51(2):146–150.
37. Amott C, Li Q, Kang A, Neuen BL, Bompoint S, Lam CSP et al. SGLT2i for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. J Am Heart Assoc. 2020;9(3): e014198.
38. StrugaruAM, Botnariu G,Agoroaei L, Grigoriu IC, Butnaru E. Metformin induced lactic acidosis-particularities and course. Rev Med Chir Soc Med Nat Iasi. 2013;117(4):1035–1042.
39. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4): e21.
40. de Simone G. Position statement of the ESC Council on hypertension on ACE-inhibitors and angiotensin receptor blockers. [Electronic resource]. URL: https://www.escardio.org/Councils/
41. Yang W, Cai X, Han X, Ji L. DPP-4 inhibitors and risk of infections: a meta-analysis of randomized controlled trials. Diabetes Metab Res Rev. 2016;32(4):391–404.
42. Pasquel FJ, Fayfman M, Umpierrez GE. Debate on insulin vs non-insulin use in the hospital setting-is it time to revise the guidelines for the management of inpatient diabetes? Curr Diab Rep. 2019;19(9):65.
43. Botta L. Drug repurposing approaches to fight Dengue virus infection and related diseases. Front Biosci (Landmark Ed). 2018;23:997–1019.