Severity of Symptoms and Mortality in Diabetic Patients with COVID- 19 Infection. Review

Zahraa ALBasry*, Abeer Abdulhadi Rashid*, Shaymaa Hasan Abbas*
**** Department of Clinical Pharmacy, College of Pharmacy, Mustansiriyah University, Iraq.***

Article Info:

Received Nov 2022
Accepted Feb 2023
Corresponding Author email:
zahraalbasy@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0002-1816-5466

DOI: https://doi.org/10.32947/ajps.v23i1.991

Abstract:

Background: COVID-19 pneumonia is an illness that was spreading rapidly around the world and causes many deaths. Diabetes, is considered as a risk factor which adds severity and mortality to COVID-19 infected persons. There are many studies aiming to explain the exact association between diabetes and COVID-19. This review aims to link between diabetes and COVID-19 risk factors, discuss the management of patients with diabetes and COVID-19 and provide perception into the COVID-19 disease complications relevant to diabetes .In this review, many scientific articles and reports about COVID- 19 and Type 2 DM were collected from different databases (e.g., PubMed, Google Scholar, and Web of Science) using keywords such as SARS-CoV2, COVID-19, TYPE 2 DM, Mortality, and CO-morbidities .The result from this study found that diabetic patients has poor prognosis, severe symptoms, worsen outcomes, and the mortality rate is higher among COVID-19 patients who have diabetes mellitus. Many complications associated with diabetes like peripheral neuropathy and vascular insufficiency can make patients more susceptible to infections. One of the sever complication of Covid-19 infection is, the cytokine storm, that result in excessive release of inflammatory cytokines (TNF-a, IL-6, IL-10), and this may be aggravated by the inflammatory process together with the hyper-coagulable condition in diabetic patients. In conclusion: Hyperglycemia is established as risk factor for increased morbidity and mortality in covid 19 infection.

Key words: SARS-CoV2, COVID-19, TYPE 2 DM, Mortality, and CO-morbidities

شدة الأعراض والوفيات لدى مرضى السكري المصابين بعدوى COVID- 19:بحث مراجعة

زهراء عبد الغني محمد علي*،عبير عبد الهادي*،شيماء حسن عباس*
****فرع الصيدلة السريرية/الجامعة المستنصرية/كلية الصيدلة***

الخلاصة:

COVID-19 هو مرض ينتشر بسرعة في جميع أنحاء العالم ويسبب العديد من الوفيات. يعتبر مرض السكري من عوامل الخطر التي تساهم في شدة ووفيات الأشخاص المصابين بـ COVID-19. هناك العديد من الدراسات التي تهدف إلى شرح العلاقة الدقيقة بين مرض السكري و COVID-19. تهدف هذه المراجعة إلى تلخيص الأدلة حول مرض السكري وتفشي COVID-19 ، وتقديم تصور لمضاعفات مرض COVID-19 ذات الصلة بمرض السكري. في هذه المراجعة تم استخدام العديد من المقالات والتقارير العلمية حول COVID-19-and Type 2 DM من قواعد بيانات مختلفة (مثل PubMed و Google Scholar و Web of Science) باستخدام كلمات رئيسية مثل SARS-CoV2 و COVID-19 و TYPE 2 DM والوفيات . وجدت الدراسة أن مرضى السكري يعانون من سوء التشخيص ، والأعراض الشديدة ، والنتائج المتدهورة ، ومعدل الوفيات أعلى بين مرضى COVID-19 الذين يعانون من داء السكري. واحدة من المضاعفات الشديدة لعدوى Covid-19 هي عاصفة السيتوكينات ، التي تؤدي إلى الإفراط في إطلاق السيتوكينات

الالتهابية (TNF، IL-6، IL-10) ، وهذه بدورها تتفاقم بسبب العملية الالتهابية مع حالة فرط التخثر في مرضى السكري. في الختام: قد ثبت ارتفاع السكر في الدم هذا كعامل خطر لزيادة المرض والوفيات في عدوى كوفيد 19.
الكلمات المفتاحية: السارس ، كوفيد -19 ،السكري النوع 2 ، الوفيات والامراض المشتركة.

Introduction

Over the last two decades, a sever acute respiratory infection flare up as a generalized global health problem. The main two coronaviruses that have been found to cause high mortality and pathogenicity among humans, are sever acute respiratory syndrome coronavirus (SARS-COV-1) and middle east respiratory syndrome coronavirus (MERS-COV) [1]. In 2002 and 2003, SARS-COV-1 discovered and resulted in over than 8000 cases of infection and approximately 800 deaths, on the other hand MERS-COV, which is discovered in 2012 has reported more than 2300 people around the world. [1,2]. Despite that both these coronaviruses, never reached a level to be pandemic.In December 2019 a new novel Coronavirus called (SARS-COV-2 or COVID-19) has been recognized in Wuhan, China and associated with many pneumonia cases without knowing their etiology [3]. After that, the world Health Organization (WHO) stated a public health emergency in January, 2020, because of the increase in number of cases. Later more information is collected, and the number of new cases doubled up rapidly, which made the WHO to declare the virus as a global pandemic in March,2020 [4]. Then SARS-COV-2 has spread more exponentially worldwide, and despite the low mortality rate of COVID-19, but many patients with co-morbidities like cardiovascular disease, hypertension, and diabetes mellitus are exposed to more severe symptoms and have higher rate of mortality compared to general population [5]. Furthermore, obese patients showed a bad prognosis when infected with COVID-19, especially in young people who are more prone to more serious infection [6]. It was found that most of persons with type 2 diabetes are overweight individuals, obesity led to insulin resistance and impaired suppression of glucose production by the liver, causing hyperglycemia and hyperinsulinemia [7].

Aim of the study: This review aims to link between diabetes and COVID-19 risk factors, discuss the management of patients with diabetes and COVID-19 and provide perception into the COVID-19 disease complications relevant to diabetes.

Diabetes mellitus as risk factor for the progression of COVID-19:

Many complications associated with diabetes like peripheral neuropathy and vascular insufficiency can make patients more susceptible to infections [8] and there is an increased risk in diabetic patients with poor glycemic control [9]. Insulin resistance in diabetes and obesity are resulted from the increase in the secretion of adipose tissue hormones like leptin, in addition to the effect of Interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) [10]. Furthermore,hyper-coagulable prothrombotic state risk, that developed from endothelial dysfunction and increased platelets aggregation and activation, are related to diabetes and insulin resistance [11]. One of the sever complication of Covid-19 infection is, the cytokine storm, that result in excessive release of inflammatory cytokines (TNF, IL-6, IL-10), and this may aggravate by the inflammatory process together with the hyper-coagulable condition in diabetic patients [12]. A retrospective Chinese study of 174 patients, compared the laboratory parameters, of 37 diabetic and 137 non-diabetic covid -19 patients, and found that, C-reactive protein (CRP), absolute neutrophil counts, d-dimers, IL-6, serum ferritin, erythrocyte sedimentation rate and fibrinogen were all higher in diabetic patients compared with non-diabetic patients [12].

An observational retrospective study conducted by Yan et al in China found a higher CRP, White cell count, d-dimer, neutrophil count,IL-2R IL-6, lL-8, N-terminal pro-B- type natriuretic peptide (NT-proBNP), and lactate dehydrogenase(LDH) in diabetic patients more than that present in non-diabetic patients This study also found that diabetic patients with covid-19 admitted to the intensive care unit need more artificial ventilation, and had higher rate of mortality [14]. In a multi-center study conducted also in China, included 7337 COVID-19 patients with Diabetes, this study found a higher inflammatory marker including d-dimer, CRP and pro calcitonin. Also, this study showed that diabetic patients with well glycemic control had less inflammatory response compared to diabetic patients with poor glycemic control, which emphasize the importance of good glycemic control before and during infection with Covid-19[15].

The pathophysiology of diabetic lung is problematic and may include autonomic neuropathy, oxidative stress, glycosylation of tissue proteins, collagen and elastin changes, variation in connective tissue, surfactantdysfunction, micro /macroangiopathy of alveolar capillaries and pulmonary arterioles, and failure of respiratory muscles, in addition to hyperglycemia and hyperinsulinemia [16].

Prevalence of diabetes among COVID-19 infected patients

Hu et al. Reported diabetes as a predicting factor for poor clinical outcomes of covid 19 infection [17]. While in other study conducted by Xu et al. showed that comorbidity associated with diabetes is an independent risk factor that predict acute kidney injury among patients with Covid-19[18]. In Onder et al. Study, from 355 died patients, 126 patients had diabetes (35.5%) versus, three patients (0.8%) died had no disease [19].

Wang's study in a hospital of changsha city,China, included 242 patients, found a predominance of diabetes among patients with severe infection (10.8%) compared to patients with non-sever infection (5.4%) [20]. Hu et all also reported an increased prevalence of diabetes among critical and sever cases (42.3% and 15.1% respectively) compared to non-sever cases (9.3%) [17]. Additionally, Guan et al. study reportedd similar results to the wang and Hu studies, in which the higher prevalence of diabetic patients is among sever infected cases than non-sever (16.2 % versus (5.7%) [21]. Wu study showed that the mortality rate of diabetic patients infected with covid-19 was (7.3%), which is higher than overall mortality rate (2.3%) [23]. In other study, the prevalence rate of diabetes among 52 critically ill patients was (2/20, 10%) among survivors and (7/32, 22%) among non-survivors [24]. In Zhang Study, the prevalence of diabetes was (8/58, 13.8%) in severe cases and (9/82, 11%) in non-sever cases, among a total of 140 patients [25]. Similarly, in Zhou et al study which are conducted on 191 patients conducted that diabetes is one of severe comorbid illness [26]. *Liu et al* study reported a significant relationship between diabetes and acute respiratory distress syndrome (ARDS)($p=0.002$), with a higher prevalence of diabetes in ARDS patients (11/53, 20.8%) and lower prevalence in non-ARDS (1/56, 1.8%) [27]. In other study by Wu, found a significant correlation between diabetes and glucose level with (ARDS) ($p=0.002$, $p<0.001$), and the prevalence of diabetes was more in ARDS patients comparing to non-ARDS (16/84, 19%) and (6/117, 5.1%) respectively [28].

Clarifying the cross-link between Diabetes Mellitus and COVID-19:

There are many reasons behind increasing the susceptibility of diabetic patients to COVID-19 infection, which are decreased in viral clearance, low T-cell activity, higher cellular binding affinity, increasing liability to cytokine storm and hyper

inflammation, in addition to association with higher risk of cardiovascular diseases [29]. Diabetic patients who have complications associated with bacterial activity, neutrophil chemotaxis and cell-mediated innate immunity have been found to have disorder in phagocytosis by macrophages, monocytes and neutrophils [30]. Also, hyperglycaemia is found to suppress the innate immune response [31]. As a result of that diabetic patients have an improper innate immune system in addition to a damaged adaptive immune response [32].

Management of COVID-19 infected diabetic patients

Diabetic patients with COVID-19 should be managed for good glycemic control with many options including, self-monitoring, telemedicine, office visits and in-home visit. Physicians recommended that all unnecessary admissions of diabetic patients to the hospital should be reduced immediately. In addition, these individuals are recommended to give special attention to the healthy diet, intake of protein, regular exercise, and administration of vaccines like influenza and pneumonia [33-36]. For diabetic patients with Covid-19, the recommendations included good glycemic control, decreasing side effects of drugs, decreasing the dose of anti-diabetic medications, and discontinuation of oral agents in critically ill patients, especially metformin and sodium glucose cotransporter-2 inhibitors. These patients should be isolated for 14 days or until the disappearance of their symptoms. In case of association of fever with hyperglycemia, then they may need to maintain sufficient hydration, and give a symptomatic treatment with acetaminophen, inhalation, monitoring of blood glucose and ketones in urine in type 1 diabetes and replace the use of insulin instead of oral hypoglycemic agents (table1). [35,36].

Table (1): Anti-diabetic medication uses in COVID-19 patients with diabetes, special consideration about their risks and benefits.

Anti-diabetic medications	BENEFITS	RISKS
Insulin.	-Recommended in critically ill conditions [37] -One study reported improvement in the COVID-19-associated outcomes of patients use insulin and achievement of glycemic targets and improvement [38].	-Hypoglycaemia side effect. -Requirement for high doses. -Intravenous administration need [37] -There is some research mentioned that insulin use in diabetic patients to be related with a larger COVID-19 associated morbidity and mortality [39-41].
Metformin	-A beneficial impact of metformin in COVID-19 infected persons is the prevention of virus entry into cells by activation of adenosine monophosphate-activated protein kinase and activation of phosphatidylinositol-3-kinase–protein kinase B–mam malian target of rapamycin signalling pathway [42]. -Better outcomes have been reported in patients with COVID-19 that having	-Lactic acidosis is sever side effect especially in patients with respiratory distress, renal failure, or heart failure [46,47]. -Metformin is contraindicated or avoided in people with sepsis or severe hepatic or renal impairment [48]. -If the patient had dehydration and multi-organ failure, metformin

	diabetes and treated with metformin by reduced mortality and levels of inflammation [43,44]. -metformin treatment should be kept for all patients hospitalized with COVID-19, as long as they have not developed kidney or liver failure [45].	should be stopped if severe organ failure developed such as renal or hepatic dysfunction and monitoring of renal function is necessary during illness [48].
Sodium-glucose transport protein2 inhibitors [SGLT2-inhibitors]	-SGLT2-inhibitors has antiviral effect by decrease intra-cellular pH and rise lactate concentrations that could decrease the viral load [49]. -In patients with type-2 diabetes it exert cardioprotective and renoprotective effect [50]. SGLT2 inhibitors may be effective in patients with COVID-19 with cardiovascular complications, acute myocardial infarction and renal or acute kidney damage [51].	-Risk of diabetic ketoacidosis in diabetic patient use SGLT2 inhibitors So, a- require optimal hydration to prevent hypovolemia and electrolyte disturbance b-require suitable adjustment of insulin doses [51], -SGLT2 inhibitors should be discontinued in patients with renal dysfunction or severe infection who are dehydrated or have a risk of ketoacidosis [52].
Glucagon-like peptide-1 agonists [GLP-1 receptor agonists]	- GLP-1 receptor agonists have anti-inflammatory properties, which is considered beneficial effect in low-grade inflammation [53,54] - GLP-1 receptor agonists also have renoprotective effects [55].	-GLP-1 receptor agonists might exaggerate anorexia - potential risk of aspiration pneumonia and should be stopped in severely ill patients with COVID-19 [56]. - In one Scottish study, a risk of sever COVID-19 was even found to be amplified in patients using GLP-1 receptor agonists [57]. - some preclinical studies have proposed that GLP-1 receptor agonists might weaken pulmonary inflammation,introducing such therapies in acute or critical states (such as sever COVID-19) was not advised because they will take time to become effective [58].
Dipeptidyl peptidase4 inhibitors DPP-4 inhibitors	- The risk of hypoglycaemia is low and can be used in patients with renal function disease. -DPP-4 inhibitors considered well tolerated in general and, they were found that it minimizes inflammatory response [59].	-One study reported that DPP-4 act as a co-receptor for a subset of coronaviruses [60].

Sulfonylureas	-One study reported that treatment with sulfonylurea might be safe for patients with COVID-19 and diabetes without additional risks also lower mortality was found in sulfonylurea users [61].	-Sulfonylureas should be stopped in patients with diabetes with COVID-19 if there is risk of hypoglycaemia, particularly if oral intake is reduced or chloroquine is concurrently used [62].
Pioglitazone	-Pioglitazone have anti-inflammatory activity, and in experimental researches it shows reduced lung inflammation and fibrosis [63,64]	-Management with pioglitazone in patients with diabetes and COVID-19 is controversial because if the patients were haemodynamically unstable there is a risk of fluid retention and oedema [64].

Table (2): Outcomes of covid 19 infection in diabetic individuals according to different studies:

Author	Type of study	No.of patients	Outcomes of covid 19 in diabetic patient
Zhang et al [65]	Retrospective cohort study	258	33.3% critical condition
Kumar et al [66]	Meta-analysis	16 003	Severe disease (two-fold increase of both mortality and severity)
Li Bet al [67]	Meta-analysis	1527	11.7% of ICU/severe cases
Fadini et al [68]	Meta-analysis	1687	worsen outcome
Petrilli et al [69]	Retrospective	1195	Hospital admission associated with critical illness
Roncon et al [70]	Meta-analysis	1382	Second comorbid risk for-ICU admission
Wu C et al [71]	Cohort	201	19% have acute respiratory distress
Zhou et al [72]	Retrospective cohort study	191	31%Mortality
Zhu et al [73]	Retrospective	7337	7.8%Mortality
Yan et al [74]	Retrospective observational study	193	81.3%Mortality
Yang X et al [75]	Retrospective observational study	52	22% mortality
Yang et al [76]	Meta-analysis	4648	Most prevalent comorbid illness
Barron et al [77]	Cohort study	61414470	High mortality in type1 and type 2
Huang et al [78]	Meta-analysis	6452	poor outcome and mortality
Hussain et al [79]	Meta-analysis	23007	higher mortality and ICU admission
AbdulKhader	A cross-sectional study	1582	increased risk of poorer

et al [80]			clinical outcomes
Mainak Banerjee et al [81]	systematic review	110	Diabetic ketoacidosis /Hyperglycemic hyperosmolar syndrome is higher mortality than DKA alone.
Wu et al [82]	View point	44 672	2.3% mortality
Guo W et al [83]	retrospective	174	4% mortality
Yan Y et al [84]	retrospective, observational study	193	24.9% sever symptoms
Chung SM et al [85]	Retrospective cohort study		17.2% mortality
Zhu L et al [86]	retrospective longitudinal, multi-centered study	7,337	7.8% mortality

ICU/intensive care unit, DKA/ Diabetic ketoacidosis.

Discussion:

Diabetes has been linked to a rise in the incidence of COVID-19 disease. The pathology, on the other hand, is unclear. Understanding the relationship between diabetes and COVID19 could lead to therapeutic interventions, but there is a scarcity of data on the topic. According to the findings of a report on MERS and diabetes, virus replication and clearances was unaffected by diabetes [87]. Chen, on the other hand, came to the conclusion that diabetes would slow COVID19 clearance [88]. This debate may be caused by variations in viruses or samples. The other explanation put forward is that antidiabetic drugs inhibit the action of the Dipeptidyl Peptidase IV (DPP4) enzyme. These medications, known as gliptin, work by inhibiting DPP4 activity, resulting in increased insulin secretion and lower blood glucose levels. DPP4 is an aminopeptidase that is found in the cell membrane and is involved in a variety of physiological processes, including immune responses [89-91]. Some researchers believe that reduced macrophage activity is another factor contributing to the incidence of COVID-19 in diabetic patients [92]. Chronic Hyperglycemia and inflammation are listed in Iacobellis' study as possible causes of an irregular and ineffective immune response. This is due to reduced polymorphonuclear leukocyte mobilization, chemotaxis, phagocytic activity, lower cytokine secretion in response to lipopolysaccharides, inhibition of T-cell Tumor Necrosis Alpha (TNFα) activity, and immunoglobulin glycation [93].

Patients with viral pneumonia who were continued on ACE inhibitors had lower rates of death and intubation, according to a retrospective review [94]. However, it has the potential to increase the risk of COVID-19 infection, especially in diabetic patients [95]. Antibiotics (meropenem, linezolid) and antiviral agents (ganciclovir, oseltamivir) were given in this case [96]. Other research offered additional recommendations, such as that a diabetic patient should monitor blood glucose levels and improve hygienic standards [97]. Remote surveillance systems and home visits, as well as the use of social media will reduce hospital referrals and health care systems are encouraged to accept these recommendations [98,99].

Conclusion:

Hyperglycemia resulted in impaired glucose homeostasis due to insulin resistance or deficiency. And this is established as risk factor for increased morbidity and mortality in several diseases

such as in cancer, cardiovascular diseases and infectious diseases.

As approved by many studies, during the Hyperglycemic environment, the virulence of some pathogens is increased. Poor blood glucose control in diabetic patients with Covid-19 can result in damaged immune response. In summary, poor glycemic control at admission and hospitalization lead to poor outcomes of COVID-19 patients. So COVID-19 patients with Hyperglycemia, both therapeutic strategies and glycemic control should be used to decrease the risk of mortality and sever outcomes.

Acknowledgment: The authors would like to acknowledge Al Mustansiriyah University (www.uomustansiriyah.edu.iq), Baghdad - Iraq for its support in this study work.

References:

1- Abbas S H, Abbas R S, Nafea LT, Severity and Risk of Death Due to COVID 19, Al Mustansiriyah Journal of Pharmaceutical Sciences, 2020, Vol. 20, No.4
2- Hui DS, Azhar EI, Memish ZA, Zumla A. Human Coronavirus Infections—severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), and SARS-CoV-2. Reference Module in Biomedical Sciences [Internet]. 2020.
3- Nsoesie EO, Rader B, Barnoon YL, Goodwin L, Brownstein J. Analysis of hospital traffic and search engine data inWuhan China indicates early disease activity in the fall of 2019. 2020.
4- Velavan TP, Meyer CG. The COVID-19 epidemic. Tropical Medicine & International Health [Internet]. 2020 Feb 16;25(3):278–80.
5- Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020 Feb 28;382(18).
6- Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. The Lancet. 2020 May; 395(10236): 1544–5.
7- Najim HD, Majeed IA, Rahmah AM. Effects of Metformin &/or Glimepiride on Resistin Level and Related Biochemical Markers in Type 2 Diabetes Mellitus. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2014 Dec 1;14(2):78–88.
8- Alves C, Casqueiro J, Casqueiro J. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian Journal of Endocrinology and Metabolism [Internet]. 2012;16(7):27.
9- Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People with Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. Diabetes Care. 2018 Aug 13;41(10):2127–35.
10- Coelho M, Oliveira T, Fernandes R. State of the art paper Biochemistry of adipose tissue: an endocrine organ. Archives of Medical Science [Internet]. 2013;9(2):191–200.
11- Carr ME. Diabetes mellitus. Journal of Diabetes and its Complications. 2001 Jan;15(1):44–54.
12- Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes/metabolism research and reviews. 2020 Oct;36(7): e3319.
13- Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes/Metabolism Research and Reviews. 2020 Mar 31; e33213321.
14- Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Research & Care. 2020 Apr;8(1): e001343.

15- Zhu L, She Z-G, Cheng X, Qin J-J, Zhang X-J, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metabolism. 2020 May;31(6).
16- Kolahian S, Leiss V, Nürnberg B. Diabetic lung disease: fact or fiction? Reviews in Endocrine and Metabolic Disorders. 2019 Sep;20(3):303–19.
17- Hu L, Chen S, Fu Y, Gao Z, Long H, Wang J, et al. Risk Factors Associated with Clinical Outcomes in 323 COVID-19 Hospitalized Patients in Wuhan, China. Clinical Infectious Diseases. 2020 May 3.
18- Xu S, Fu L, Fei J, Xiang H-X, Xiang Y, Tan Z-X, et al. Acute kidney injury at early stage as a negative prognostic indicator of patients with COVID-19: a hospital-based retrospective analysis. medRxiv; 2020.
19- Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. Jama. 2020 May 12;323(18):1775-6.
20- Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. Epidemiological and clinical features of corona virus disease 2019 (COVID-19) in Changsha, China. China (3/1/2020); 2020.
21- Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. New England J Med; 2020
22- Abdi A, Jalilian M, Sarbarzeh PA, Vlaisavljevic Z. Diabetes and COVID-19: A systematic review on the current evidences. Diabetes research and clinical practice. 2020 Aug 1; 166:108347.
23- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020.
24- Yang X., Yu Y., Xu J., Shu H., Liu H., Wu Y., et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet. Respir Med. 2020.
25- Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy; 2020
26- Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z., et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020.
27- Liu Y, Sun W, Chen L, Wang Y, Zhang L, Yu L. Clinical characteristics and progression of 2019 novel coronavirus-infected patients concurrent acute respiratory distress syndrome. medRxiv; 2020.
28- Wu C., Chen X., Cai Y., Zhou X., Xu S., Huang H., et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Int Med. 2020
29- Muniyappa R, Gubbi S. COVID-19 pandemic, Corona viruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318: E736–41.
30- Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol. 1999;26(3–4):259–65.
31- Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. The American journal of the medical sciences. 2016 Feb 1;351(2):201-11.

32- Ma RCW, Holt RIG. COVID-19 and diabetes. Diabet Med. 2020; 37:723–5.
33- Iacobucci G. Covid-19: diabetes clinicians set up social media account to help alleviate patients' fears. BMJ 2020;368.
34- Rogers LC, Lavery LA, Joseph WS, Armstrong DG. All feet on deck—the role of podiatry during the COVID-19 Pandemic: Preventing hospitalizations in an overburdened healthcare system, reducing amputation and death in people with diabetes. J Am Podiatr Med Assoc 2020.
35- Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism. 2020 Jun; 107:154216.
36- Wang A, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res Clin Pract 2020; 162:108118
37- Papadokostaki E, Tentolouris N, Liberopoulos E. COVID-19 and diabetes: What does the clinician need to know? Primary care diabetes. 2020 Jul 3.
38- Sardu C, D'Onofrio N, Balestrieri ML, et al. Outcomes in Patients with Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? Diabetes Care (2020) 43(7):1408–15.
39- McGurnaghan SJ, Weir A, Bishop J, 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(2):82–93.
40- Cariou B, Hadjadj S, Wargny M, et al. Phenotypic Characteristics and Prognosis of Inpatients With COVID-19 and Diabetes: The CORONADO Study. Diabetologia (2020) 63(8):1500–15.
41- Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients with Diabetes and COVID-19 in Association with Glucose-Lowering Medication. Diabetes Care (2020) 43(7):1399–407.
42- Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: a possible role beyond diabetes. Diabetes Res Clin Pract 2020; 164: 108183.
43- Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients with Diabetes and COVID-19 in Association with Glucose-Lowering Medication. Diabetes Care (2020) 43(7):1399–407.
44- Cariou B, Hadjadj S, Wargny M, et al. Phenotypic Characteristics and Prognosis of Inpatients With COVID-19 and Diabetes: The CORONADO Study. Diabetologia (2020) 63(8):1500–15.
45- Lalau J-D, Al-Salameh A. Management of Diabetes in Patients With COVID-19. Lancet Diabetes Endocrinol (2020) 8(8):666–7.
46- Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, Boehm B, Amiel S, Holt RI, Skyler JS, DeVries JH. Practical recommendations for the management of diabetes in patients with COVID-19. The lancet Diabetes & endocrinology. 2020 Apr 23.
47- Cheng X, Liu YM, Li H, et al. Metformin is Associated with Higher Incidence of Acidosis, But Not Mortality, in Individuals With COVID-19 and Pre-Existing Type 2 Diabetes. Cell Metab (2020) 32(4):537–547 e533.
48- Raj VS, Mou H, Smits SL, Dekkers DH, Muller MA, Dijkman R, et al. Di¬peptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495:251-4.
49- Cure E, Cumhur Cure M. Can dapagliflozin have a protective effect against COVID-19 infection? A

hypothesis. Diabetes Metab Syndr Clin Res Rev 2020; 14: 405–06.
50- Cure E, Cumhur Cure M. Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes Metab Syndr Clin Res Rev 2020; 14: 405–06.
51- Dapagliflozin in Respiratory Failure in Patients With COVID-19 - Full Text View-ClinicalTrials.gov, (n.d.). https://clinicaltrials.gov/ct2/show/NCT04350593.(Accessed May 27, 2020).
52- Raj VS, Mou H, Smits SL, Dekkers DH, Muller MA, Dijkman R, Muth D, Demmers JA, Zaki A, Fouchier RA, Thiel V, Dro¬sten C, Rottier PJ, Osterhaus AD, Bosch BJ, Haagmans BL. Di¬peptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013; 495:251-4.
53- Ceriello A, Novials A, Ortega E, et al. Glucagon-Like Peptide 1 Reduces Endothelial Dysfunction, Inflammation, and Oxidative Stress Induced by Both Hyperglycemia and Hypoglycemia in Type 1 Diabetes. Diabetes Care (2013) 36(8):2346–50.
54- Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-Like Peptide-1. Cell Metab (2018) 27(4):740–56.
55- Lee YS, Jun HS. Anti-Inflammatory Effects of GLP-1-Based Therapies Beyond Glucose Control. Mediators Inflamm (2016) 2016:3094642.
56- Viby NE, Isidor MS, Buggeskov KB, Poulsen SS, Hansen JB, Kissow H. Glucagon-like peptide-1 (GLP-1) reduces mortality and improves lung function in a model of experimental obstructive lung disease in female mice. Endocrinology 2013; 154: 4503–11.
57- McGurnaghan SJ, Weir A, Bishop J, 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(2):82–93.
58- Nauck, M. A., and Meier, J. J. (2019). Management OF endocrine disease: are all GLP-1 agonists equal in the treatment of type 2 diabetes? Eur. J. Endocrinol. 181 (6), R211–r234.
59- Sun Q, Zhang Y, Huang J, Yu F, Xu J, Peng B, et al. DPP4 regulates the inflammatory response in a rat model of febrile seizures. Bio-Medical Materials and Engineering [Internet]. 2017 [cited 2023 Jan 20];28(s1): S139–52. Available from: https://pubmed.ncbi.nlm.nih.gov/28372289/ 101. Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract 2020; 162: 108125.
60- Palmer SC, Mavridis D, Nicolucci A, Johnson DW, Tonelli M, Craig JC, Maggo J, Gray V, De Berardis G, Ruospo M, Natale P. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. Jama. 2016 Jul 19;316(3):313-24.
61- Han T, Ma S, Sun C, Zhang H, Qu G, Chen Y, et al. Association Between Anti-diabetic Agents and Clinical Outcomes of COVID-19 in Patients with Diabetes: A Systematic Review and Meta-Analysis. Arch Med Res. 2022 Feb;53(2):186-195.
62- Aoki Y, Maeno T, Aoyagi K, Ueno M, Aoki F, Aoki N, et al. Pioglitazone, a Peroxisome Proliferator-Activated Receptor Gamma Ligand, Suppresses Bleomycin-Induced Acute Lung Injury and Fibrosis. Respiration. 2008 Oct 31;77(3):311–9.
63- Barbarin V, Nihoul A, Misson P, et al. The role of pro- and anti-inflammatory responses in silica-induced lung fibrosis. Respir Res 2005; 6: 112.
64- Zhang Y, Cui Y, Shen M, et al. Association of diabetes mellitus with

disease severity and prognosis in COVID-19: a retrospective cohort study. Diabetes Res Clin Pract 2020; 165: 108227.

65- Zhang Y, Cui Y, Shen M, et al. Association of diabetes mellitus with disease severity and prognosis in COVID-19: a retrospective cohort study. Diabetes Res Clin Pract 2020; 165: 108227.

66- Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A metaanalysis. Diabetes Metab Syndr Clin Res Rev 2020; 14: 535–45

67- Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 2020; 109: 531–38

68- Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest 2020; 43: 867–69.

69- Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. BMJ 2020; published online April 11.

70- Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol 2020; 127: 104354.

71- Wu C., Chen X., Cai Y., Xia J., Zhou X., Xu S., et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med. 2020

72- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.

73- 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 Metab 2020; 31: 1068–77.

74- Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ open diabetes research and care. 2020 Apr 1;8(1): e001343.

75- Yang X., Yu Y., Xu J., Shu H., Xia J., Liu H., et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir. Med. 2020 S2213-2600(20)30079-5.

76- Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. International Journal of Infectious Diseases [Internet]. 2020 Mar 12;0(0).

77- Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. The lancet Diabetes & endocrinology. 2020 Oct 1;8(10):813-22.

78- Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia–a systematic review, meta-analysis, and metaregression. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 Jul 1;14(4):395-403.

79- Salman Hussain, Harveen Baxi, Mohammad Chand Jamali, Nazima Nisar, Md Sarfaraj Hussain November–December 2020 Pages 1595-1602

80- Khader MA, Jabeen T, Namoju R. A cross sectional study reveals severe

disruption in glycemic control in people with diabetes during and after lockdown in India. Diabetes & Metabolic Syndrome: Clinical Research & Reviews [Internet]. 2020 Nov 1;14(6):1579–84.
81- Pal R, Banerjee M, Yadav U, Bhattacharjee S. Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: A systematic review of literature. Diabetes & Metabolic Syndrome [Internet]. 2020;14(6):1563–9.
82- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020.
83- Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020 Mar 31 [Epub].
84- Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe COVID-19 with diabetes. BMJ Open Diabetes Res Care 2020; 8: e001343.
85- Chung SM, Lee YY, Ha E, Yoon JS, Won KC, Lee HW, et al. The risk of diabetes on clinical outcomes in patients with coronavirus disease 2019: a retrospective cohort study. Diabetes Metab J 2020; 44:405-13.
86- Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020; 31:1068-77.
87- Chen X, Hu W, Ling J, Mo P, Zhang Y, Jiang Q, et al. Hypertension and diabetes delay the viral clearance in COVID-19 patients. medRxiv; 2020.
88- Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight 2019;4(20.
89- Deacon CF. Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes. Front Endocrinol 2019; 10:80.
90- Klemann C, Wagner L, Stephan M, von Ho¨ rsten S. Cut to the chase: a review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. Clin Exp Immunol 2016;185(1):1–21.
91- Hodgson K, Morris J, Bridson T, Govan B, Rush C, Ketheesan N. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. Immunology. 2015 Feb;144(2):171-85.
92- Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract 2020; 162:108125.
93- Baidya A, Shankar A, Ahmed R, Das K. Relevance and role of hydroxychloroquine in prophylaxis and therapy of COVID-19. J Med Sci Clin Res 2020;08.
94- Gupta R, Misra A. Contentious issues and evolving concepts in the clinical presentation and management of patients with COVID-19 infectionwith reference to use of therapeutic and other drugs used in Co-morbid diseases (Hypertension, diabetes etc). Diabetes Metabolic Syndrome: Clin Res Rev 2020;14(3):251–4.
95- Han X, Fan Y, Wan Y-L, Shi H. A diabetic patient with 2019- nCoV (COVID-19) infection who recovered and was discharged from hospital. J Thorac Imaging 2020.
96- Zhou J, Tan J. Diabetes patients with COVID-19 need better care. Metabolism 2020.
97- Rogers LC, Lavery LA, Joseph WS, Armstrong DG. All feet on deck—the role of podiatry during the COVID-19

Pandemic: Preventing hospitalizations in an overburdened healthcare system, reducing amputation and death in people with diabetes. J Am Podiatr Med Assoc 2020.

98- Iacobucci G. Covid-19: diabetes clinicians set up social media account to help alleviate patients' fears. BMJ 2020;368. https://doi.org/10.1136/bmj.m1262 m1262.

99- Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes & metabolic syndrome. 2020 May;14(3):211