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Diabetes & its Complications

Risk Factors Associated with COVID-19 Infection among Patients with Diabetes Mellitus

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ABSTRACT

The corona virus disease 2019 (COVID-19) pandemic has spread globally with increase in morbidity and fatality. Patients with diabetes mellitus (DM) are considerably vulnerable to the disease.

***Aim:** This study aims to explore the risk factors that contribute in susceptibility and severity of COVID 19 infection among patients with DM.*

***Method:** A systematic search of studies relating to DM and COVID 19 infection was conducted, using PubMed and Google scholar.*

***Result:** A total of 162 citations were initially identified. Seventy-four papers were removed for failing to address the aim of the study. Seventeen studies focused on age as risk factor, eighteen studies assesses the effects of glucose variability, nine studies evaluated the associated comorbidities, four assessed the risk of the job, eight addressed the susceptibility related DM, twenty four explored the effects of medications, fifteen concentrated on immune system, and sixteen addressed more than one risk factor.*

***Conclusion:** Old age, glucose variability, comorbidities, susceptibility factors related to DM, medications and impair immune response are considerable risk factors contributing in COVID 19 pathogenesis among patients with DM.*

Keywords

Diabetes mellitus, Corona virus, COVID-19, SARS-CoV-2.

Introduction

Diabetes mellitus (DM) is markedly increasing worldwide, with a global prevalence in adults in 2017 being 8.8% and expect to increase to 9.9% by 2045 [1]. The prevalence increases with age which was lowest in younger age group (35–39years) (5%), compared to old age one (65-69 years) 20%. Recent data from United States of America, revealed that up to10.1% of adult American had DM [2]. Viral infection, in particular that related to influenza virus represents a significant medical problem as most of the individuals may expose to more than one medical ailment annually [3]. The tendency to affect patients with chronic disease was evident after the 2009 H1N1 influenza pandemic [4]. Likewise, similar finding was documented during the last two world-wide respiratory infection outbreaks (influenza A (H1N1) in 2009 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012) which considered DM as host-independent risk factors and associated with severe morbidities and increased mortalities [5,6]. The same trend was adopted for patients with diabetes mellitus during the current COVID 19 pandemic [7,8]. COVID-19 infection is associated with increased severity of the disease, higher morbidity and mortality among old people with comorbidities [9,10]. This was strengthened by the outcome of recently released reports that linked the associated comorbidities to the poor prognosis [11-15]. Additionally, patients suffering COVID-19 with hyperglycemia may have a higher risk and a poorer outcome compared with those with normal blood sugar levels [16,17].

The synergistic effects of COVID-19 on immune system (lymphocytopenia, thrombocytopenia and leukopenia) and the impaired immune response of patients with DM are essential contributors to predict the final outcome [13,18]. Many other factors may have an influence on the disease progression that may attract the researcher to shed light on it. For all reasons mentioned above, I conducted this review to identify the possible contributing risk factors that affecting the outcome of COVID 19 among patients with DM.

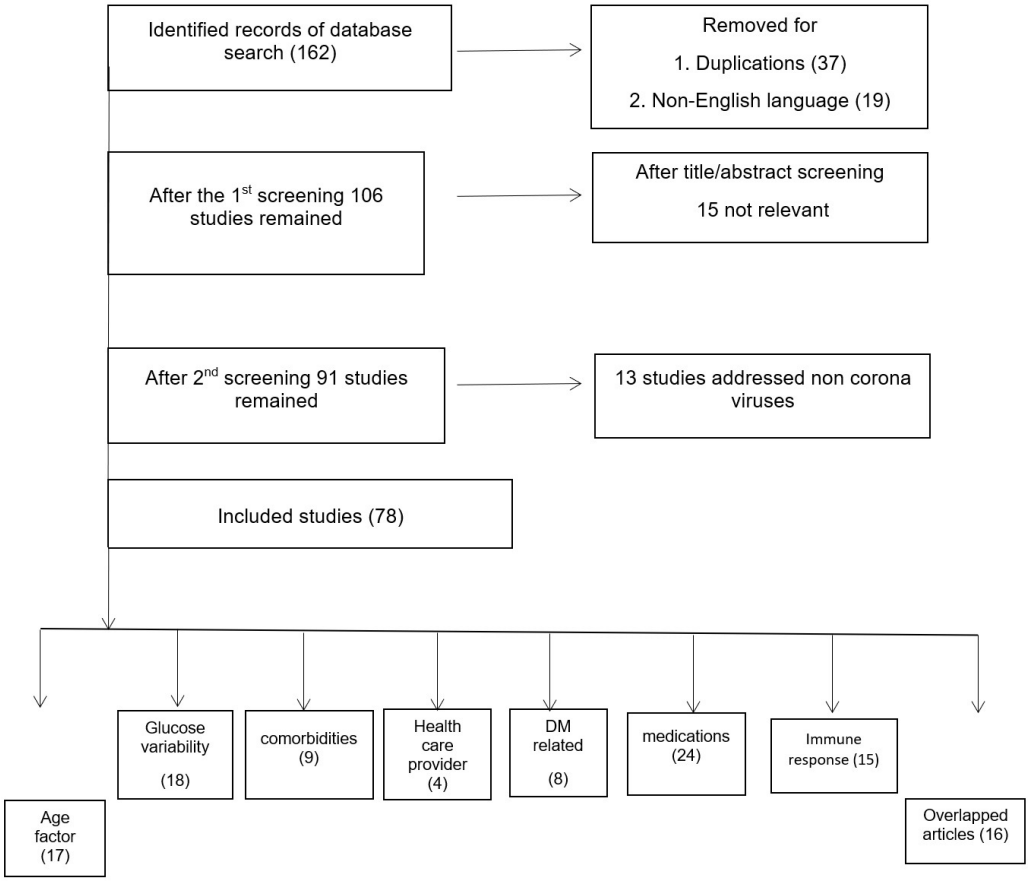
Method

A systematic search of studies addressing diabetes mellitus and COVID 19 and related corona virus infection was conducted without frame time limit, using PubMed and Google scholar, with the key the words; "diabetes mellitus" "corona virus" "COVID-19", and "SARS-CoV-2".

The electronic database search yielded 162 studies. Seventy-four studies were removed for not addressing the aim of the study, duplication, lacking proper citation, and language issue. Titles and abstracts were assessed to determine eligibility for full screening. Studies that employed acceptable quantitative and/or qualitative methods, including randomized controlled trials, observational studies (such as cross-sectional, experimental, and interventional studies), review articles, ideas, editorials, reports, letters to the editor and opinions were included. All studies focusing on the pathogenesis of COVID 19 in patients with DM, the mechanism of entry, risk factors, effect of blood sugar, immune response, medications, morbidity, and mortality were eligible for inclusion. The summary of the literature search procedure is illustrated in Figure 1. Once all relevant studies had been identified, full-text manuscripts were retrieved for assessment. The studies were grouped according to the primary aims, old age, blood glucose variability, associated comorbidities, health care provider with DM, DM related factors, medications and impaired immune response. This enabled identification of papers that addressed specific topics and issues relevant to my objectives and facilitated the retrieval of information.

Result

A total of 162 citations were initially identified. Seventy-four studies were removed for not addressing the target of the study, duplication, lacking proper citations and language issue. After screening titles and abstracts, seventy-eight full-text articles were retrieved for eligibility analysis. Seventeen studies focused on age as risk factor [2,12,13,19-31], eighteen studies assesses the effects of glucose variability [5,6,910,16,17,32-43], nine studies evaluated the associated comorbidities [11-15,18,19,44,45], four assessed the risk for health care providers, [46-49] eight addressed the susceptibility related DM [50-57] twenty four explored the effects of medications [9,27-31,50,58-74] fifteen concentrated on immune system, [5,13,18,39,40,42,75-83] and sixteen addressed more than one risk factor [5,9,12-14,18,19,27-31,39,40,42,50]. There risk factors appear to have a predictor value for increasing susceptibility to COVID 19 infection and worsening the outcome among individuals with DM.



Discussion

Patients with diabetes mellitus, have the same the risk of contracting a viral illness as those without diabetes mellitus, but might have severe presentation if they had [19]. Old patients with DM are considerably at a higher risk for COVID 19 infection as documented recently in some clinical data [12,14,20]. Increase age, itself, is a known risk for developing DM because the prevalence varies with age, younger age group (35-39years), has lowest prevalence (5%), compared to old age one [(65–69 years) 20%] [2]. A markedly higher prevalence of DM was obtained with a mean age of 80 years (44%) [21]. Moreover, older patients with DM have a higher chance to develop the chronic complications related the DM or age-related chronic diseases. The prevalence of peripheral vascular disease in patients with DM was almost twice as high compared to those without DM among adults age 60 years and older [22], and significantly very higher in patients aged 70 years and older (60.6%) [23]. Additionally, the prevalence of myocardial infarction was significantly higher among both males and females (15.5% vs. 7.2%, P = 0.001) [24]. Aging has negative effects on the immune system that may worse influence COVID 19 infection. In experimental study that showed increase of age was associated with impaired T-cell and B-cell function and release of excess inflammation markers which could increase the susceptibility and delay clearance of COVID 19 infection, resulted in worsening disease severity and increased fatalities [13]. Likewise, cytokine storm syndrome, which is commonly triggered by viral infection and is characterized by a fulminant and fatal hypercytokinaemia with multiorgan failure [25]. This might represent the failure of immune system's attempts to damp down or normalize the persistent pro-inflammatory response in a timely effective manner [26]. Another factor that may contribute in this issue, is possibly the multiple drugs that are used for DM or the associated comorbidities. These medications may affect the COVID 19 pathogenesis through ACE2 and DPP4 expression or modify immune response such as glucagon-like peptide 1 agonists and thiazolidinediones, ACE inhibitors, and statins [27-31]. It is clear that being old is not only risk factor but also hiring many potential associated synergistic risky elements.

In general people with DM have been found to be prone to infectious diseases, especially those caused by bacteria and viruses affecting lower airways [10]. High glucose levels and chronicity of DM play a relevant role in hindering antibacterial function of neutrophil [5]. As a result, such patients are prone to the risk of infectious diseases, in particular those caused by bacteria and viruses with tendency to affect lower airways [10,32,33]. This may explain why COVID-19 infection is associated with severe course of the disease, high morbidity and mortality especially among old people with uncontrolled DM [9,10]. Recent evidences demonstrated micro-angiopathic changes that might occur in the respiratory tract of patients with DM, leading to impairment of gas exchanges and reduced lung compliance. Moreover, it might create a favorable the environment for atypical microorganisms to grow and complicate severe pneumonia as a result of lower respiratory tract infection [5]. This observation was documented during the last two decades, world-wide respiratory infection outbreaks [6]. During these outbreaks, DM was confirmed to be one of host-independent risk factors and might fatal complications [5]. There is now a growing body of evidence linking glycemic oscillations with endothelial dysfunction, irrespective of blood sugar control [34,35]. Patients with DM generally have a significant reduction in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), that is corelated positively with higher plasma glucose levels [36]. Hyperglycemia, impaired glucose metabolism and development of acute complications of diabetes (e.g., ketoacidosis) were frequently seen in patients with DM who had COVID-19 infection. It was possibly triggered by higher stress state, leading to greater release of insulin counter regulatory hormones, e.g., glucocorticoids and catecholamines. The resultant is increase in blood glucose levels and abnormal glucose variability [37]. Likewise, the use of glucocorticoids during hospitalization, may favor a great glycemic excursion, especially among those with DM [37]. Hyperglycemia among patients suffering COVID-19 is considered to be a higher risk factor and predictor of poorer outcome compared with those who have normal blood glucose levels [16,17]. Hyperglycemia may result from pancreatic damage mediated by ACE2 expression on the pancreatic cell that facilitates direct corona virus invasion and possibly contributing to worse outcomes in subjects with DM. A Chinese study compared 39 SARS-CoV patients without previous DM, who did not receive steroid treatment, with 39 matched healthy siblings. The study showed that 20 of the 39 SARS-CoV patients developed DM during hospitalization. Moreover, immunostaining for ACE2 was strongly present in the pancreatic islet cell, indicating SARS-CoV might have damaged islet cells and caused acute insulin dependent diabetes mellitus [38]. Hyperglycemia has negative effects on the immune system at different levels may contribute in the severity of COVID 19 infection and increase mortalities [39,40]. Likewise, it is associated with increased risk of diabetic ketoacidosis during infection process or during management [22,37]. Thus, vigilant professional care skills are highly recommended to modify the prognosis and improve the outcome. On the other hand, documented hypoglycemia was reported that in 10% of the patients with T2DM and COVID-19 who suffered at least one episode of hypoglycemia (<3.9 mmol/L) [41]. Hypoglycemia has been associated with mobilization of pro-inflammatory monocytes and increase platelet reactivity, leading to a higher cardiovascular mortality in patients with diabetes mellitus [42]. The inflammatory and immune response occurs in these patients, with hyper- or hypoglycemia events may contribute in the SARS-CoV-2 virulence. Moreover, the virus itself may interfere with insulin secretion or glycemic control. As well as, the impact of usual diabetes drug treatment on COVID-19 outcomes and variation in the therapeutic approaches adopted for controlling blood sugar [43].

Not only with increase of age increases age-related comorbidities, but also a higher chance for appearance of diabetes related complications. In Morbidity and Mortality Weekly Report from United State of America, demonstrated that approximately one third of these patients (37.6%), had at least one underlying medical condition or risk factor: Diabetes mellitus (10.9%),chronic lung disease (9.2%), and cardiovascular disease (9.0%) were the most

frequently registered among all of patients [11]. Another study, recruited 1099 patients with confirmed COVID-19, reported the severity of the disease among of hypertensive patients (15.0%) and those with diabetes mellitus (7.4%) [18]. Likewise, many studies revealed that the presence of comorbidities is directly related to higher percentage of cases infected with COVID-19 [12-15]. The presence of comorbidities is essential to predict the severity and the outcome as reported in some recent studies: 12% of the admitted patients had only DM [44], and a higher percentage of patients with comorbidities (22%-26.1%) that requiring intensive care management for COVID 19 disease [12]. Although patients with diabetes mellitus, have the same the risk of contracting a viral illness as general population, but presented with the severe form of disease if they had [19]. This was supported by recently published reports from the Wuhan province in China that demonstrated those with diabetes mellitus and hypertension were the most group of patients who succumbed to COVID-19 infection and overrepresented among the most severely ill one [18]. Hence, they deserve vigilant evaluation and prompt health-care in case they have the disease because they are more vulnerable to severity of illness in particular if presented with the shortness of breath and fever) [45].

Health care provider with DM are prone to the potential risk of COVID 19 infection, in particular those providing care for sick patient who had COVID 19 disease. A recent report showed that nearly 9,300 U.S. health care workers contracted COVID-19 while at work, 27 have died and 55% of those whom were tested, turned to be positive [46]. Furthermore, two updated reports from China CDC on 44 672 confirmed cases and from Italy 139,377 positive test for COVID-19 a, revealed different percentages of infected health care providers, which were 1688 (3.8%) and 15 314 (11%) respectively [47,48]. I believe the risk for health care providers who have DM is considerably higher than these rates as no recent enough data to assess the risk among this vulnerable group. Health care providers, in particular anesthetists, dentists, head and neck surgeons, maxillofacial surgeons, ophthalmologists and otolaryngologists with chronic disease including diabetes mellitus are at high risk of contracting the COVID 19 disease from infected patients. They represent 3.8% to 20% of the infected population and 15% of them will develop severe form of the disease and many might lose their lives [49]. Those who are working around the oral cavity and nostrils of patients as mentioned above, are exposed to potential great risk hence the recommendation for them to avoid dealing with infected patients with COVID 19 and using proper preventive equipment.

There are some evidences that patients with DM hire characters that increase their vulnerability to contract COVID-19 infection. One of these mechanisms is facilitating binding and entry of the corona virus in the human cells. Angiotensin-converting enzyme 2 (ACE2) is known a recognition site for binding coronavirus to facilitate its entry and is expressed by epithelial cells of human organs [50]. Basically, patients with diabetes mellitus have increased expression of ACE2 and the risk is magnified among those taking either ACE inhibitors or angiotensin II type-1 receptor blockers (ARBs) [50]. DM is causally linked to increase ACE2 expression levels in the lung [51] and facilitate viral entry by cleaving the S1 and S2 domain of the spike protein [52]. Interestingly, a recent study linked the delayed clearance of SARS-CoV-2 virus to the over expression of ACE2 in patients with DM, besides prediction of worse prognosis [53]. Another issue, is the possible role of dipeptidyl peptidase IV (DPP-4) in coronavirus infection which is emerging issue related to DM. Corona virus binds to the human DPP-4 receptor as recognition site. In experimental trail, using type 2 diabetic transgenic mouse models expressing DDP-4 receptor on pulmonary alveolar cells to study the effect of DM on MERS-coronavirus infection. Not only a significant association of DM that corelated clinically with the severity of the disease, but also a similar greater weight loss and pulmonary inflammation was demonstrated with macrophage infiltrates [54]. Likewise, another study linked the expression of human and bat DPP4 to susceptibility to infection [55]. Further researches are needed to assess the therapeutic benefits or the risk expected from exploiting DPP4-inhibitors in patients with type 2 DM who have COVID-19 infection. On the same issue, one study pointed the important role of DPP4 in regulation of chemokine and cytokine responses, favoring downregulation of the immune response, hence proposing potential therapeutic at this level [56]. Interestingly, one study identified the polymorphisms of DPP4 and fortunately enough, four of them (K267E, K267N, A291P and Δ346-348) strongly inhibit the binding of MERS-CoV S to DPP4 and S protein-driven host cell entry. Moreover, two of them (K267E and A291P) have extra potential effects in attenuating viral replication [57].

Some medications used for patients with diabetes mellitus are under focus and their impact on the clinical course of COVID-19 has been widely debated. ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used by those with diabetes and hypertension [58]. Surprisingly, some studies have reported decreased mortality and endotracheal intubation in patients with viral pneumonia who continued using of ACEIs and ARBs [59,60]. This group of medications is postulated to have significant immunomodulatory effects [61] and reduce pulmonary and systemic inflammatory response by decreasing cytokines production and activation [59,60]. In experimental trial, mice injected with SARS-CoV Spike presented with worsened acute lung failure, which could be attenuated by blocking the renin-angiotensin pathway because SARS-CoV infection and the virus Spike protein reduce ACE2 expression [62]. On the same issue, one study strengthened the potential beneficial actions and promoted it as tentative medication for COVID 19 infection to reduce the aggressiveness and mortality [63]. On the other hand, when considering ACE2 is a functional receptor for SARS-CoV-2 and its levels can be increased by ACE inhibitors and ARBs, this might affect negatively the outcome in patients with COVID-19 disease [64]. Hence people on angiotensin-converting enzyme (ACE) inhibitors might expose to higher risk for clinically severe forms of infection. Basically, patients with diabetes mellitus have increased expression of ACE2 and the risk is magnified among those taking either ACE inhibitors or angiotensin II type-

1 receptor blockers (ARBs) [50]. In contrast to what mentioned above, no significant difference was obtained in the proportion of ACEI/ARB medication between survivors and non-survivors in a retrospective analysis recruiting 112 patients with COVID-19 and cardiovascular disease [65]. In absence of solid evidence of risk or benefit regarding ACEI/ARB medications, the American College of Cardiology, the American Heart Association, and the American Society of Hypertension have recommended to continue their usual antihypertensive therapy [66]. As we know that DPP-4 inhibitors are commonly used in the management of diabetes mellitus worldwide, future research should explore whether DPP-4 may also act as receptor for SARS-CoV-2. Recently, some studies proposed a potential protective effect of these drugs against COVID-19 [67]. Interestingly, some two studies, documented that DPP-4 inhibitors could inhibit ACE with the cardio-renal benefits [68,69], and regulate the function of the immune system, by reducing inflammatory reactions and by improving oxidative stress [70]. In addition to that it prevents coronaviruses from entering cells as a result of competitive binding to ACE2, which might help to protect and restore pulmonary function [69,71]. There is emerging concern regarding some medications that are commonly used by patients with DM and may have potential influence on COVID 19 infection. The main mechanism is through upgrading expression of ACE2, which include thiazolidinediones, statin and ibuprofen [9,27-31,72]. Thus, generating questions regarding the safety of these drugs in these patients with COVID-19. On the other hand, insulin therapy is associated with attenuation of ACE2 expression, a site of recognition for corona virus [73,74]. Furthermore, metformin and SGLT-2 inhibitors drugs are not recommended for use for managing moderate to severe illness as both are associated with lactic acidosis and diabetic ketoacidosis, respectively.

Diabetes mellitus is a chronic inflammatory disease characterized by multiple metabolic and vascular abnormalities that reflect the body response to pathogens [5]. Moreover, atherosclerosis, vascular inflammation and endothelial dysfunction are also part of the pathogenesis of other chronic conditions that has association with DM (hypertension and cardiovascular disease [75]. Hyperglycemia and insulin resistance are associated with increased production of glycosylation end products (AGEs), pro-inflammatory cytokines, oxidative stress and promoting production of adhesion molecules that mediate tissue inflammation process [5,75]. This may explain a higher propensity to infections, leading to worse outcomes in patients with DM [5,76]. Several defects in immune system have been related to hyperglycemia despite being still not fully understood [39]. Inhibition of lymphocyte proliferative response to different kinds of stimuli has been observed in in patients with uncontrolled DM [40]. Likewise, hindering the functions of monocyte, macrophage, neutrophils [5] and complements [77] with abnormal delayed type hypersensitivity reaction [39]. Evidences from many studies have linked pulmonary epithelial cells exposure to high glucose concentrations significantly increases vulnerability to influenza virus infection and replication [78-80]. In animal models, DM is associated with structural lung changes leading to increase vasculature permeability and collapsed alveolar epithelium [81], On the other hand, hypoglycemia has been shown to potentiate host's innate immune reaction to endotoxins by stimulating pro-inflammatory monocytes with increased risk of cardiovascular mortality [42].

Patients with COVID-19 at increased risk of lymphocytopenia, thrombocytopenia and leukopenia, which are more prominent in severe cases [18]. Furthermore, elevated levels of pro-inflammatory cytokines, C-reactive protein, and increased coagulation activity were also linked to severity of the disease [13,18]. Interestingly, among different cytokines, Interleukin-6 (IL-6) was significantly higher in COVID 19 positive patients with diabetes mellitus compared to those without [82]. Basically, this cytokine level is already higher in patients with T2DM and may be responsible for the severity and deterioration in COVID-19 infection. Hence targeting the over expression of Il-6 effects is a potential option of treating patients with T2DM with a monoclonal antibody against IL-6 receptor or Janus Kinase inhibitors [82]. Both insulin resistance and T2DM are associated with endothelial dysfunction, and enhanced platelet aggregation and activation. These abnormalities favor the development of a hypercoagulable pro-thrombotic state [83]. Animal studies involving SARSCoV reported older age was associated with impaired T-cell and B-cell function and release of excess inflammation markers. This might be applied to T2DM alone or in combination with older age, hypertension and/or CVDs contributing to COVID 19 infection severity and fatalities. It is worth to mention that most of these risk factors coexist and synergistically work together to shape the worse prognosis for COVID 19 infection among those patients with DM.

Conclusion

Old age, associated comorbidities, on multiple medications, uncontrolled glycemia, impaired immune status and being health care provider in risk environment are major contributing risk factors that can predict the COVID 19 infection susceptibility and severity among patients with DM.

Limitation

This study used only Pubmed and Google scholar database and some valuable data are not included. Another limitation is related to the article selection criteria that were used.

References

1. Standl E, Khunti K, Hansen TB, et al. The global epidemics of diabetes in the 21st century Current situation and perspectives. Eur J Prev Cardiol. 2019; 26: 7-14.
2. Norris T, Schiller JS, Clarke TC. Early Release of Selected Estimates Based on Data from the National Health Interview Survey. 2018.
3. Vos T, Barber RM, Bell B, et al. Global regional and national incidence prevalence and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries 1990-2013 A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 386: 743-800.
4. Kumar A. Critically Ill Patients With 2009 Influenza A H1N1

Infection in Canada. JAMA Internet. 2009; 302: 1872.
5. Knapp S. Diabetes and infection Is there a link- A mini-review. Gerontology. 2013; 59: 99-104.
6. Alqahtani FY, Aleanizy FS, Ali El Hadi Mohamed R, et al. Prevalence of comorbidities in cases of Middle East respiratory syndrome coronavirus A retrospective study. Epidemiol Infect. 2019; 147.
7. Bhatnagar T, Murhekar M, Soneja M, et al. Lopinavir ritonavir combination therapy amongst symptomatic coronavirus disease 2019 patients in India Protocol for restricted public health emergency use. Indian J Med Res. 2020.
8. Gentile S, Strollo F, Ceriello A. COVID-19 infection in Italian people with diabetes Lessons learned for our future an experience to be used. 2020.
9. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection. The Lancet Respiratory Medicine. Lancet Publishing Group. 2020; 8: 21.
10. Badawi A, Ryoo SG. Prevalence of diabetes in the 2009 influenza A H1N1 and the middle east respiratory syndrome coronavirus: A systematic review and meta-analysis. J Public health Res. 2016; 5: 130-138.
11. Free H, Groenewold MR, Luckhaupt SE. Morbidity and Mortality Weekly Report. 2020.
12. Yang X, Yu Y, Xu J, 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.
13. Zhou F, Yu T, Du R, et al. Articles Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China a retrospective cohort study. 2020.
14. Liu M, Liu SW, Wang LJ, et al. Burden of diabetes, hyperglycaemia in China from to 2016 Findings from the 1990 to 2016, global burden of disease study. Diabetes Metab. 2019; 45: 286-293.
15. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506.
16. Wu C, Chen X, Cai Y, 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.
17. Wang Y, Wang Y, Chen Y, et al. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia COVID-19 implicate special control measures. J Med Virol. 2020.
18. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020.
19. Kaiser UB, Mirmira RG, Stewart PM. No Title. J Clin Endocrinol Metab Internet. 2020; 105: 1-3.
20. 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: 146-50.
21. Ness J, Nassimiha D, Feria MI, et al. Diabetes mellitus in older African-Americans Hispanics and whites in an academic hospital-based geriatrics practice. Coron Artery Dis. 1999; 10: 343-346.
22. Kalyani RR, Saudek CD, Brancati FL, et al. Association of diabetes comorbidities and A1C with functional disability in older adults: results from the National Health and Nutrition Examination Survey NHANES, 1999-2006. Diabetes Care. 2010; 33: 1055-1060.
23. Escobar C, Blanes I, Ruiz A, et al. Prevalence and clinical profile and management of peripheral arterial disease in elderly patients with diabetes. Eur J Intern Med. 2011; 22: 275-281.
24. Motta M, Bennati E, Ferlito L, et al. Cardio-cerebrovascular complications in elderly with diabetes. Arch Gerontol Geriatr. 2007; 44: 261-269.
25. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020; 395: 1033-1034.
26. Rea IM, Gibson DS, McGilligan V, et al. Age and age-related diseases: Role of inflammation triggers and cytokines. Frontiers in Immunology Frontiers Media SA. 2018; 9.
27. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005; 111: 2605-2610.
28. Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, et al. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression reversing right ventricle hypertrophy and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology. 2015; 156: 3559-3569.
29. Tikoo K, Patel G, Kumar S, et al. Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: Role of epigenetic histone modifications. Biochem Pharmacol. 2015; 93: 343-351.
30. Wösten Van Asperen RM, Lutter R, Specht PA, et al. Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. J Pathol. 2011; 225: 618-627.
31. Zhang W, Xu YZ, Liu B, et al. Pioglitazone Upregulates Angiotensin Converting Enzyme 2 Expression in Insulin-Sensitive Tissues in Rats with High-Fat Diet-Induced Nonalcoholic Steatohepatitis. Scientific World Journal. 2014.
32. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care. 2003; 26: 510-513.
33. Muller LMAJ, Gorter KJ, Hak E, et al. Increased Risk of Common Infections in Patients with Type 1 and Type 2 Diabetes Mellitus. Clin Infect Dis. 2005; 4: 281-288.
34. Azuma K, Kawamori R, Toyofuku Y, et al. Repetitive fluctuations in blood glucose enhance monocyte adhesion to the endothelium of rat thoracic aorta. Arterioscler Thromb Vasc Biol. 2006; 26: 2275-2280.
35. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes. 2008; 57: 1349-1354.
36. Lange P, Groth S, Kastrup J, et al. Diabetes mellitus plasma glucose and lung function in a cross-sectional population

study. Eur Respir J. 1989; 2: 14-19.
37. Wang A, Zhao W, Xu Z, et al. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease COVID-19 is urgently needed. Diabetes Res Clin Pract. 2020; 162.
38. Yang JK, Lin SS, Ji XJ, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010; 47: 193-199.
39. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus DM. FEMS Immunol Med Microbiol. 1999; 26: 259-265.
40. Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus Analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete et Metabolisme. 1992; 18: 187-201.
41. Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism Clinical and Experimental. 2020; 107: 154216.
42. Iqbal A, Prince LR, Novodvorsky P, et al. Effect of hypoglycemiaon inflammatory responsesand the response to low-dose endotoxemia in humans. J Clin Endocrinol Metab. 2019; 104: 1187-1199.
43. Hussain A, Bhowmik B, Cristina do Vale Moreira N. COVID-19 and Diabetes Knowledge in Progress. Diabetes Res Clin Pract. 2020.
44. Zhang J jin, Dong X, Cao Y yuan, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy Eur J Allergy Clin Immunol. 2020.
45. Gupta R, Ghosh A, Singh AK, et al. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diabetes and Metabolic Syndrome: Clinical Research and Reviews. Elsevier Ltd. 2020; 14: 211-212.
46. https://www.poughkeepsiejournal.com/story/news/health/2020/04/14/cdc-report-thousands-health-care-workers-infected-coronavirus/2988120001/
47. http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51
48. https://www.epicentro.iss.it/en/coronavirus/bollettino/Infografica_10aprile%20ENG.pdf
49. Kowalski LP, Sanabria A, Ridge JA, et al. COVID-19 pandemic Effects and evidence-based recommendations for otolaryngology and head and neck surgery practice. Head Neck. 2020.
50. Wan Y, Shang J, Graham R, et al. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol. 2020; 94.
51. https://doi.org/10.1101/2020.03.04.20031237
52. Fernandez C, Rysä J, Almgren P, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. J Intern Med. 2018; 284: 377-387.
53. Chen X, Hu W, Ling J, et al. Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. medRxiv. 2020.
54. Kulcsar KA, Coleman CM, Beck SE, et al. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight. 2019; 4.
55. Caì Y, Yú S, Postnikova EN, et al. CD26/DPP4 cell-surface expression in bat cells correlates with bat cell susceptibility to middle east respiratory syndrome coronavirus MERS-CoV infection and evolution of persistent infection. PLoS One. 2014; 9.
56. Lambeir AM, Durinx C, Scharpé S, et al. Dipeptidyl-peptidase IV from bench to bedside An update on structural properties functions and clinical aspects of the enzyme DPP IV. Critical Reviews in Clinical Laboratory Sciences. Informa Healthcare. 2003; 40: 209-294.
57. Kleine-Weber H, Schroeder S, Krüger N, et al. Polymorphisms in dipeptidyl peptidase 4 reduce host cell entry of Middle East respiratory syndrome coronavirus. Emerg Microbes Infect. 2020; 9: 155-168.
58. Chamberlain JJ, Herman WH, Leal S, et al. Pharmacologic therapy for type 2 diabetes Synopsis of the 2017 American diabetes association standards of medical care in diabetes. Ann Intern Med. 2017; 166: 572-578.
59. Henry C, Zaizafoun M, Stock E, et al. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. Baylor Univ Med Cent Proc. 2018; 31: 419-423.
60. Mortensen EM, Pugh MJ, Copeland LA, et al. Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia. Eur Respir J. 2008; 31: 611-617.
61. Gullestad L, Aukrust P, Ueland T, et al. Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. J Am Coll Cardiol. 1999; 34: 2061-2067.
62. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 ACE2 in SARS coronavirus-induced lung injury. Nat Med. 2005; 11: 875-879.
63. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Development Research. Wiley Liss Inc. 2020.
64. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nature Reviews Cardiology. Nature Research. 2020; 17: 259-260.
65. Peng YD, Meng K, Guan HQ, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi. 2020; 48: E004.
66. Danser AHJ, Epstein M, Batlle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. HYPERTENSION. 2020.
67. Fadini GP, Morieri ML, Longato E, et al. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020; 28: 1-3.
68. Abouelkheir M, El-Metwally TH. Dipeptidyl peptidase-4 inhibitors can inhibit angiotensin converting enzyme. Eur J Pharmacol. 2019; 862: 172638.
69. Bornstein SR, Dalan R, Hopkins D, et al. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol. 2020; 1-2.

70. Zhang J, Chen Q, Zhong J, et al. DPP-4 inhibitors as potential candidates for antihypertensive therapy Improving vascular inflammation and assisting the action of traditional antihypertensive drugs. Frontiers in Immunology. Frontiers Media SA. 2019; 10: 1050.
71. Simões E Silva AC, Silveira KD, Ferreira AJ, et al. ACE2 angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. British Journal of Pharmacology. 2013; 169: 477-492.
72. Qiao W, Wang C, Chen B, et al. Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats. Cardiol. 2015; 131: 97-106.
73. Roca-Ho H, Riera M, Palau V, et al. Characterization of ACE and ACE2 expression within different organs of the NOD mouse. Int J Mol Sci. 2017; 18.
74. Wysocki J, Ye M, Soler MJ, et al. ACE and ACE2 activity in diabetic mice. Diabetes. 2006; 55: 2132-2139.
75. Petrie JR, Guzik TJ, Touyz RM. Diabetes Hypertension and Cardiovascular Disease Clinical Insights and Vascular Mechanisms. Canadian Journal of Cardiology. Elsevier Inc. 2018; 34: 575-584.
76. Ceriello A, Kilpatrick ES. Glycemic variability Both sides of the story. Diabetes Care. 2013; 36: S272-S275.
77. Ilyas R, Wallis R, Soilleux EJ, et al. High glucose disrupts oligosaccharide recognition function via competitive inhibition A potential mechanism for immune dysregulation in diabetes mellitus. Immunobiology. 2011; 216: 126-131.
78. Kohio HP, Adamson AL. Glycolytic control of vacuolar-type ATPase activity A mechanism to regulate influenza viral infection. Virology. 2013; 444: 301-309.
79. Short KR, Kroeze EJBV, Fouchier RAM, et al. Pathogenesis of influenza-induced acute respiratory distress syndrome. The Lancet Infectious Diseases. 2014; 14: 57-69.
80. Perrone LA, Plowden JK, García-Sastre A, et al. H5N1 and 1918 Pandemic Influenza Virus Infection Results in Early and Excessive Infiltration of Macrophages and Neutrophils in the Lungs of Mice. Baric RS editor. PLoS Pathog. 2008; 4: e1000115.
81. Popov D, Simionescu M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. Eur Respir J. 1997; 10: 1850-1858.
82. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020; e33213321.
83. Dunn E, Grant P. Type 2 Diabetes An Atherothrombotic Syndrome. Curr Mol Med Internet. 2005; 5: 323-332.