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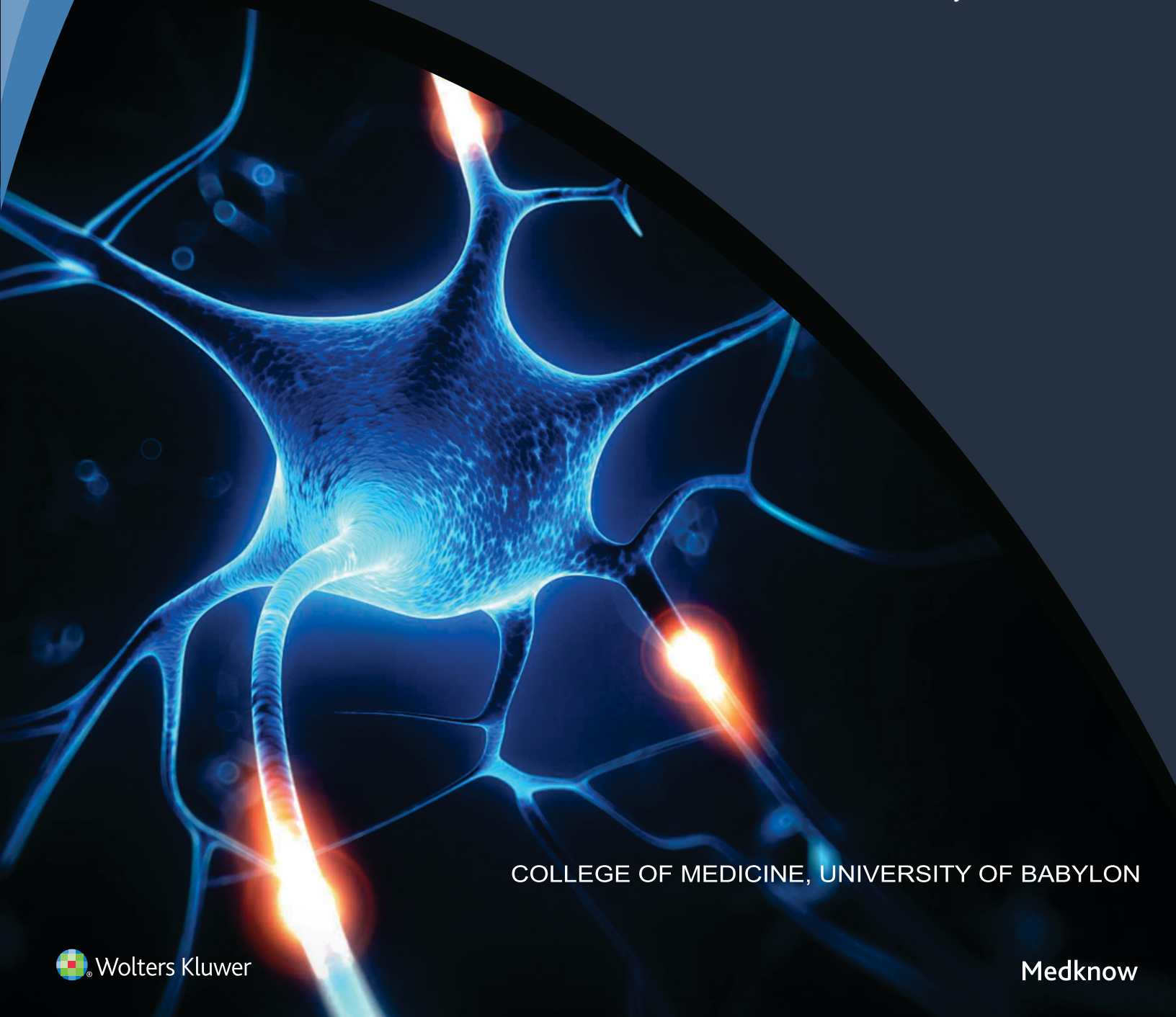

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Review Article

The Interrelationship between Diabetes Mellitus and COVID-19

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Abstract

The pandemic of coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has involved more than 100 million individuals, including more than 2 million deaths. Diabetes represents one of the most prevalent chronic conditions worldwide and significantly increases the risk of hospitalization and death in patients with COVID-19. In this review, we discuss the prevalence, the pathophysiological mechanisms, and the outcomes of COVID-19 infection in people with diabetes. We propose a rationale for using drugs prescribed in patients with diabetes and some pragmatic clinical recommendations to deal with COVID-19 in this kind of patient.

Keywords: Coronavirus, COVID-19, diabetes

Introduction

Diabetes mellitus (DM) is a well-known risk factor for worse clinical outcomes in patients with coronavirus disease-2019 (COVID-19). However, the relationship between these two entities seems to be bidirectional. The ongoing pandemic of COVID-19 has significantly affected blood glucose control in patients with DM. The results of these effects can be classified into direct effects (those directly related to the viral infection) and indirect effects (those related to the impact of the pandemic on the management of blood glucose or the use of proposed treatments for the infection that also affect glucose homeostasis).[1]

As a direct effect, the COVID-19 infection has resulted in striking changes in patients' metabolism with significant elevations in blood glucose. It is attributed to the increased release of cytokines and inflammatory mediators, which led to increased insulin resistance and the associated hyperglycemia.[2] In addition, it has been suggested that COVID-19 might be involved in developing acute DM in certain patients by targeting angiotensin-converting enzyme 2 (ACE2) receptors located in pancreatic islets resulting in pancreatic injury.[3]

Many therapies have been repurposed for the management of COVID-19. For instance, glucocorticoids have a remarkable impact on blood glucose. The use of glucocorticoids has been associated with a decreased mortality in critically ill patients infected with COVID-19.[4] It is well known that glucocorticoid use results in a significant change in glucose homeostasis due to increased gluconeogenesis and a simultaneous increase in insulin resistance in various tissues.[5]

Several studies have described the indirect effects of the COVID-19 pandemic on diverse populations during the lockdown. Some studies indicated that there is an improvement in glycemic control, whereas others state there is no significant change[6] or that the glycemic control in this population has worsened.[7] Herein, we will review the available literature related to COVID-19 and DM.

Prevalence of Diabetes and Its Clinical Severity in Patients With COVID-19

Emerging data suggest that COVID-19 is common in patients with diabetes, hypertension, and cardiovascular diseases (CVDs), even if the prevalence rate changed

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in different studies and country-wise data. The rates of type 2 diabetes in subjects affected by SARS-CoV-2 vary, depending on the median age, the severity of illness, the location of the study population, and the method of testing.[8]

Data show that the prevalence of diabetes and sex differences (with a higher prevalence of men than women), increases according to the increase of median age.

A similar trend regarded hypertension. Current evidence indicates that fatality rates are higher in men than in women. A report on April 23, 2020, from the Italian National Institute of Health, shows that of 23.188 deaths from COVID-19 infection in Italy, approximately 70% were in men.[9] In addition, our previously published data in elderly inpatients[10] have shown a higher prevalence of diabetes in men than women. This evidence might explain the higher prevalence of diabetes in elderly patients affected by COVID-19. It could justify an exclusively epidemiological association between diabetes and COVID-19 and not the virus's ability to affect diabetic patients specifically.[11]

There are two other aspects to consider: how much does diabetes affect clinical severity? Since its relationship to, how does obesity? Some data might clarify these issues.

First, USA Centers for Disease Control and Prevention reported data for laboratory-confirmed SARS-CoV-2 infections in the United States from February 12 to March 28, 2020. Data regard 7162 subjects with completed case information and revealed a prevalence rate for diabetes of 6%, 24%, and 32%, for nonhospitalized, hospitalized but not requiring intensive care unit (ICU) admission versus hospitalized in the ICU, respectively. In Italy, a diabetes prevalence of 17% was reported in patients admitted to ICUs for severe COVID-19. Recent data confirmed the findings mentioned above, outlining a diabetes prevalence of 18.3% in English people with severe COVID-19 requiring critical care treatment (high dependency unit or ICU).[12,13]

Second, prevalence rates of diabetes (31.8% versus 5.4%) and obesity (39.8% versus 14.5%) were more significant in the hospitalized versus nonhospitalized subgroups, respectively. In addition, a body mass index (BMI) >40 was among the risk factors most predictive of the need for hospitalization (odds ration [OR] 6.2, 95% confidence interval [CI], 4.2–9.3). In addition, obesity represented by BMI has still increased the mortality (obesity class I HR 1.23; obesity class II HR 1.81) (25). Severe obesity (BMI ≥ 35 kg/m^2), increasing age, and male sex are independently associated with mortality and need for intubation and increasing oxygen requirements during hospitalization.[14] An analysis of 124 consecutive ICU admissions in a single center in Lille, France from February 27 to April 5, 2020, revealed higher obesity rates and severe obesity among patients with SARS-CoV-2, relative to historical no SARS-CoV-2 controls. In this observational study, the frequency of obesity was 47.5% compared to 25.8% in a control group of ICU individuals with the non-SARS-CoV-2 illness. In subjects affected by obesity, the requirement for intubation and mechanical ventilation was higher.[15]

Type II Diabetes as a Risk Factor for COVID-19

Type 2 diabetes mellitus (T2DM) is considered a risk factor for a poor prognosis in COVID-19. Many mechanisms have been described to explain the poorer prognosis of COVID-19 in diabetics. Some of these mechanisms include impaired neutrophil degranulation and complement activation, increased glucose concentration in airway secretion, which significantly increases viral replication, exaggerated pro-inflammatory cytokine response in diabetes, decreased viral clearance, and a more significant presence associated comorbidities.[1]

One of the essential aspects of the relationship between COVID-19 and T2DM is that the information on the condition of hyperglycemia at the time of hospital admission is more relevant for prognostic purposes than the HbA1c. It is thought that COVID-19 predisposes infected individuals to hyperglycemia, leading to hyperglycosylation of the ACE2, the natural viral receptor on the host cell surface.[16] The acute hyperglycemia in these patients induces inflammation, endothelial dysfunction, and thrombosis via the generation of oxidative stress. This may also enhance tissue tropism and viral penetration into the cells leading to increased virulence, pathogenicity, and susceptibility to severe infections. It has been hypothesized that the COVID-19 might affect pancreatic B-cells to produce insulin, which would aggravate underlying lack of glycemic control in the setting of T2DM.[17]

Regardless of the mechanisms, when comparing COVID-19 patients with and without T2DM, the patients with T2DM tend to develop more severe forms of the disease and have a significant increase in inflammatory markers compared to nondiabetics (i.e., higher levels of C-reactive protein, pro-calcitonin, ferritin, lactate dehydrogenase, and d-dimer). Furthermore, the prevalence of diabetes among the patients admitted to ICUs for COVID-19 is two- to threefold higher, along with the mortality rate which is twice that of nondiabetic patients. There is limited evidence suggesting that newly diagnosed diabetes might be associated with a higher admission rate to ICU, invasive mechanical ventilation, and mortality risk than pre-existing diabetes.[18]

Studies have shown that a family history of T2DM might also be a significant risk factor for this infection. Healthy individuals with a family history of T2DM tend to develop early endothelial dysfunction. Endothelial

dysfunction has been reported to be a critical event in the pathophysiology of COVID-19, which has been associated with pulmonary microvascular thrombosis. Hyperinsulinemia and hyperglycemia observed in this population could promote the expression of ACE2 in various tissues, including microvascular endothelial cells known to act as a receptor for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[19]

Based on these findings, T2DM affects the disease severity and is one of the independent risk factors for inadequate therapeutic response in patients with COVID-19.[20] Understanding the interactions between these two diseases is crucial in developing appropriate therapeutic approaches. Further studies are warranted to elucidate the mechanisms by which diabetes affects these patients' prognosis and how these pathways can be modified to generate better outcomes in COVID-19 patients with diabetes.

COVID-19 and Type I Diabetes Mellitus

The prevalence of type 1 diabetes mellitus (T1DM) in patients with COVID-19 ranges from 0.15% to 28.98%. Hyperglycemia has been observed to be a risk factor for COVID-19-related complications. According to preliminary findings from a multicenter surveillance study in the United States that assessed clinical outcomes of COVID-19 in patients with T1DM, a total of 48.5% of patients had high blood glucose levels; 45.5%, elevated temperature; 39.4%, dry cough; 33.3%, excess fatigue, and vomiting; 30.3%, shortness of breath; 27.3%, nausea; and 21.2%, body/headaches. In addition, abdominal and chest pain, chills, loose stools, and loss of taste and smell were reported by <15% of patients. In these patients with COVID-19 and T1DM, obesity (39.4%) and hypertension or CVD (12.1%) were the most prevalent comorbidities, whereas diabetic ketoacidosis was the most common adverse outcome.[21]

In a whole-population study that assessed the independent effects of diabetic status and its type on in-hospital death in English patients with COVID-19, 1.5% of in-hospital COVID-19-related deaths were occurred in patients with T1DM versus 31.4% in those with T2DM. Over the 72 days of the study, unadjusted mortality rates per 100,000 individuals were 138 for those with T1DM versus 27 for those without diabetes. Interestingly, when adjusted for age, sex, deprivation, ethnicity, and geographical region, the odds ratio (OR) for in-hospital COVID-19-related death was 3.51 (95% CI ¼ 3.16e3.90) in the patients with T1DM.[22]

Impaired T-cell Function and Increased Susceptibility to Inflammation

The activation of pro-inflammatory cytokines or chemokines causes infected cells apoptosis or necrosis and triggers inflammatory responses, which leads to the recruitment of inflammatory cells. Through interferon-gamma (I.F.N) production, CD4 T helper (Th1) cells are involved in regulating antigen presentation against intracellular pathogens such as CoV. The recruitment of neutrophils and macrophages is induced by Th17 cells by producing interleukin-17 (IL-17), IL-21, and IL-22. SARS-CoV-2 increases apoptosis of lymphocytes (CD3, CD4, and CD8 T cells) and infects circulating immune cells leading to lymphocytopenia.[23]

Lower T cell function diminishes the inhibition of innate immune system resulting in the secretion of high amounts of inflammatory cytokines. This phenomenon is called "cytokine storm." Neutrophil chemotaxis, the intracellular killing of microbes, and phagocytosis were inhibited by diabetes. In the beginning, a delay in the activation of Th1 cell-mediated immunity and a late hyper-inflammatory response is often observed in diabetics.[24]

In line with this evidence, in patients with COVID-19, the number of CD4+ and CD8+ T cells are low. However, a higher proportion of highly pro-inflammatory Th17 CD4+ T cells, along with elevated cytokine levels was present. It is possible to speculate that patients with DM may have weakened anti-viral I.F.N. responses, and the delayed activation of Th1/Th17 may accentuate inflammatory responses.[25]

Several cytokines are increased in COVID-19 infection. At baseline, cytokines such as TNF, IL-1, and IL-6 are more active in diabetics and subjects affected by obesity. Therefore, it is believed that SARS-CoV-2 infection may enhance the cytokine response of such patients, thereby exacerbating the cytokine storm that seems to cause multiple organ failure in COVID-19.[26]

The baseline pro-inflammatory state found in diabetes and obesity may serve to exacerbate this. Diabetes occurs in part because the increase of activated innate immune cells in metabolic tissues leads to the overproduction of inflammatory mediators, especially IL-1β and TNFα, which can promote systemic insulin resistance and b cell damage.[9]

Conclusion

DM carries a significant risk of complications, extended hospital stays, and mortality in patients with COVID-19. Therefore, insulin is preferred to oral hypoglycemic medications in the management of hospitalized COVID-19 infected diabetic subjects. This review has recommended frequent blood sugar checks and prompts management of hypoglycemia, hyperglycemia, and DKA.

Ethical consideration

Not applicable.

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Conflicts of interest
There are no conflicts of interest.

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