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Diabetes Mellitus with Uncontrolled Glycemia and its Impact on Mortality from the Novel Coronavirus: A Narrative Review

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Abstract

Introduction: The novel coronavirus pandemic characterized by its growing potential for dissemination and the rapid spread of infection around the world. During the pandemic, control of chronic conditions such as Diabetes Mellitus (DM) has become more demanding.

Objectives: To evaluate the most frequent conditions leading to uncontrolled glycemia in patients with diabetes infected with the novel coronavirus, verifying the association between disease severity and mortality.

Methods: We conducted a narrative review of studies on the novel coronavirus that contained information on DM and its metabolic control. The Science Direct, Lilacs, Scielo, VHL Regional Portal, and PubMed databases were assessed as part of the bibliographical search strategy using the search terms "diabetes mellitus" and "glycemic index" or "glycemic load" or "blood glucose" and "novel coronavirus" or "COVID-19" and "mortality." Studies published from December 1st, 2019 to May 1st, 2020 (date of search) identified. We included studies in adult humans infected with the novel coronavirus in which there was an association of DM. The chosen languages were English and Spanish. We excluded animal studies, studies involving children and adolescents, abstracts of congresses or symposia, and book chapters.

Results: For the proposed review, 74 articles identified in PubMed and 11 studies in Science Direct, but no articles with the descriptors found in Scielo, BSV, Lilacs, or VHL Regional Portal. After further screening, 17 articles were included for this review.

Final Comments: Patients with diabetes infected with the novel coronavirus frequently also had a lack of glycemic control, which was associated with a greater severity of the infectious disease, greater number of hospitalizations, and higher mortality than was found in infected patients without diabetes. Glycemic control during the course of COVID-19 considered a goal. To explain the relationship between diabetes and COVID-19, several mechanisms proposed and reported.

Keywords: Diabetes mellitus; Glycemic load; Novel coronavirus; COVID-19; Mortality

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Introduction

In December of 2019, the city of Wuhan, the capital of Hubei Province in China, gained international attention as the epicenter of a viral outbreak with unknown epidemiology, manifesting itself primarily as a pneumological phenomenon with peculiar characteristics [1]. On January 7th, 2020, Chinese scientists succeeded in isolating a novel coronavirus that caused a syndrome initially named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) and later designated as Coronavirus Disease (COVID-19) by the World Health Organization (WHO) [2]. It was declared officially a pandemic on March 11th, 2020, because of the growing potential for spread, with the incidence of severe disease multiplying around the world [1]. 89,048,345 cases of COVID-19 and 1,930,265 deaths were confirmed worldwide by January 12th, 2021 [3].

Chronic conditions in patients with COVID-19 have been reported as a frequent cause of greater complications and increased morbidity and mortality, which are also associated with the highest age group and male sex [4-7]. Admission to an intensive care unit, the necessity of invasive ventilation, and death were considered severe predictors to outcomes of COVID-19. Therefore, reinforcing what

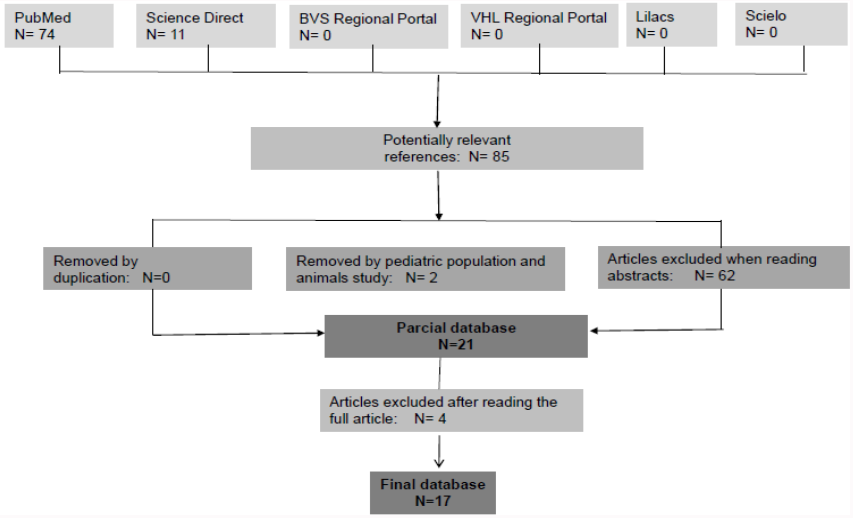

Figure 1: Bibliografics search results.

has been reported, although a large proportion of patients present with mild symptoms or asymptomatic, elderly individuals and those with comorbidities such as metabolic, cardiovascular, immunological, and respiratory disorders have a greater susceptibility to developing severe forms of the disease [5-7].

During the pandemic, control of a chronic condition such as Diabetes Mellitus (DM) has become more demanding owing to social distancing and difficulty in maintaining healthier lifestyles with limited physical activity. Limited supplies of high-quality food could also be a factor in the greater difficulty in sustaining adequate eating habits [8]. In addition, acquiring anti-diabetic drugs in most nations of the world as well as the challenges of self-monitoring have become more difficult. Routine medical follow-up during the pandemic period has also become much more challenging, and fine-tuning diabetes treatment has become more complex. As an example of the negative repercussion of this set of contingencies, there has been more uncontrolled glycemia in elderly patients with diabetes during the COVID-19 pandemic [8].

Given the current situation, we have noted numerous social, economic, and health crises combined with high viral spread and lethality [8]. It is essential to address the possible consequences of uncontrolled glycemia within this already complex equation, taking into consideration the prognostic implications of patients infected by the novel coronavirus in association with chronic conditions, especially DM. Thus, the present review aimed to evaluate the most frequent conditions that lead to uncontrolled glycemia in patients with diabetes infected with the novel coronavirus and verify the association between disease severity and mortality.

Methods

We conducted a narrative review of studies on the novel coronavirus that contained information on DM and its metabolic control. The objectives based on the PICO strategy (population, interventions, comparisons, and outcomes) and choice of descriptors [9]. The Science Direct, Lilacs, Scielo, VHL Regional Portal, and PubMed databases were assessed as part of the bibliographical search strategy using the search terms "diabetes mellitus" and "glycemic index" or "glycemic load" or "blood glucose" and "novel coronavirus" or "COVID-19" and "mortality." Studies published from December 1st, 2019 to May 1st, 2020 (date of search) identified.

For this review, we developed a data extraction spreadsheet, adhering to a study eligibility form, describing the type of study, inclusion criteria, exclusion criteria, examiners' assessment, agreement for inclusion, number of participants, clinical outcomes, stroke and mortality prevalence, suggested assumptions, risk of bias, statistical methods used, and additional analyses.

Four reviewers conducted the search. As initial identification criteria, all the articles selected in accordance with the chosen descriptors. We opted for studies of adult humans infected with the novel coronavirus in which there was an association of DM. In addition, we selected peer-reviewed articles or reviews of primary research, gray literature including policy papers, guides or guidelines, letters, editorials, and comments. The chosen languages were English and Spanish. We excluded animal studies, studies involving children and adolescents, abstracts of congresses or symposia, and book chapters. We also excluded articles in which DM mentioned but was not associated with the novel coronavirus infection. We documented all the steps of identifying, selecting, including, and excluding articles. Owing to the nature of the review study, approval by the Research Ethics Committee was not required.

Results

For the proposed review, 74 articles identified in the PubMed database and 11 studies in the Science Direct database. No articles found in Scielo, BSV, Lilacs, or VHL Regional Portal using the descriptors. Two articles excluded at this stage: A study of a pediatric population and an animal study. There were no duplicate articles in this search. Thus, 83 articles selected to read the abstracts in full. Some of these articles did not cover the subject of the proposed review, presenting specific information about the clinical management of COVID-19 infection without correlation with chronic conditions including DM. After the screening at this stage, 21 articles proved suitable for reading in full. Finally, 17 articles were included for this review (Figure 1).

Regarding the origin of the identified works, five articles were from India, five from North America, four from China, one each from Norway and Korea, and one joint publication from Nigeria and Canada. Regarding the type of studies, there was one meta-analysis,

Table 1: Characteristics of the studies included in the analyses version.

Publication date	Authors	Journal	Location	Study Type	Infected COVID-19 population	Diabetes prevalence	Severity disease (COVID-19)	Hospitalization prevalence	Mortality prevalence	Glycemic control x outcomes
2020 april	Kumar A et al.	Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2020; 1-31.	New Delhi, India	Meta analysis	16003	9.80%	yes		yes	
2020 april	Singh AK et al.	Diabetes Metab Syndr 2020;14(3):241-246. doi: 10.1016/j.dsx.2020.03.011.	Mumbai and Kolkata; India.	Systematic Review	157*		yes		yes	yes
2020 march	Pal R, Bhadada SK.	Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2020; 1-27.	Chandigarh, India	Systematic Review	72314*		yes		yes	yes
2020 april	Abdullahi in et al.	Infez Med 2020; 28(2):166-173.	Calabar, Nigeria and Edmonton, Canada.	Narrative Review			yes	yes	yes	
2020 march	Muniyappa R et al.	Am J Physiol Endocrinol Metab 2020; 318: E736–E741. Doi:10.1152/ajpendo.00124.2020	Maryland, USA.	Narrative Review			yes	yes	yes	yes
2020 april	Banerjee M et al.	Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2020; 351e354352.	Kolkata, India	Narrative Review			yes		yes	yes
2020 february	Giwa A et al.	Emerg Med Pract 2020; 22(2 Suppl 2):1-21.	New York, USA	Narrative Review	240*		yes		yes	yes
2020 july	Ghosh A et al.	Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2020; 14: 273-276.	New Delhi, India	Guideline						yes
2020 april	Khera A et al.	American Journal of Preventive Cardiology 2020; 1 100009; 1-10.	Dallas, USA	Scientific Recommendations	75924*		yes	yes	yes	yes
2020 april	Hussain A et al.	Diabetes Research and Clinical Practice 2020;162: 1-9.	Nord University, Norway	Short Review	78020*		yes	yes	yes	yes
2020 june	Zhu l et al.	Cell Metabolism 2020; 1-14.	Wuhan, China	Retrospective Cohort Study	7337	13%	yes	yes	yes	yes
2020 march	Zhou F et al.	Lancet 2020; 395: 1054–62.	Beijing, China	Retrospective Cohort Study	191	19%	yes		yes	
2020 april	Yan Y et al.	BMJ Open Diabetes Research Care 2020; 8(1).	Wuhan, China	Case Controle Study	193	24.90%	yes	yes	yes	yes
2020 april	Zhao XY et al.	BMC Infectious Diseases 2020; 20(1):	Wuhan, China.	Case Controle Study	91		yes			
2020 april	Kim N et al.	Diabetes and Metabolism Journal 2020; 44(2).	Daegu, Korea.	Case Report	2		yes		yes	yes
2020 april	Angelidi AM et al.	Metabolism Clinical and Experimental 2020:1-6.	Boston, USA	Editorial	72522*		yes	yes	yes	yes
2020 june	Hill MA et al.	Metabolism Clinical and Experimental 2020; 107 154217; 1-2.	Columbia, USA	Comments	73605*		yes		yes	yes

two systematic reviews, four narrative reviews, one guideline, one recommendation, two retrospective studies, two control cases, one case report, two comments, and one editorial.

The present review included population samples of individuals infected with the novel coronavirus ranging from 2 to 78,020 patients. The estimated prevalence of DM among those infected was from 9.8% to 24.9%. In approximately half of the studies evaluated, diabetes in infected patients was associated with hospitalization, whereas almost all of the studies found the greatest severity of the disease among this population. The highest mortality among patients with diabetes also observed in 14 of the 17 studies analyzed (82.35%), whereas the association between lack of glycemic control and worse outcomes found in 13 of the 17 studies review (76.47%) (Table 1).

COVID-19 can develop into an acute and severe respiratory syndrome, with substantial morbidity and mortality [7]. Comparing patients with and without diabetes infected by the novel coronavirus, Kumar et al. [1] pointed out that there was a dual effect, an increase in both greater severities of the disease as well as a higher mortality due to infection. Similarly, Khera et al. [2] found a two to three times higher mortality among patients with diabetes, similar to results found in the study by Singh et al. [10]. Recent studies have shown advanced age along with DM, hypertension, obesity, and cardiovascular disease as important factors for significantly increasing the risk of hospitalization and death in patients with COVID-19 [7,8,10,11]. Hussain et al. [12] reinforced this information in their study. Patients with diabetes in a critical state, when compared to patients without diabetes, were also characterized as older and more likely to require mechanical ventilation and admission to an intensive care unit, with a worsened Kaplan-Meier survival curve and, consequently, a higher risk of mortality [12,13].

Some authors stated that glycemic control in patients with diabetes infected with the novel coronavirus considered as one of the indicators of management and follow-up of the disease [14]. Pal et al. [5] observed the development of a vicious cycle between diabetes and COVID-19, with worsening of dysglycemia due to severe exacerbation of the infectious condition. The worsening of glycemic control during the pandemic could be evidence of greater difficulty in self-care in patients with diabetes, which pointed out by Banerjee et al. [8] as an important and unfavorable factor for the prognosis of this population concerning COVID-19. Moreover, uncontrolled glycemia shown to represent greater inflammatory potential, with increased serum levels of Tumor Necrosis Factor (TNF)-alpha and Interleukin (IL)-10 [13].

Acute hyperglycemic crises such as diabetic ketoacidosis and a hyperosmolar hyperglycemic state are serious acute metabolic complications of diabetes, commonly caused by infections. COVID-19 estimated to trigger acute hyperglycemic crises in patients with inadequately controlled diabetes, but the evidence for this association is still limited [15]. Acute hyperglycemic crises could be

precipitated by COVID-19 and culminate in catastrophic results for patients with diabetes with poor glycemic control [15]. An additional and interesting finding was that groups of patients with diabetes using telemedicine during the pandemic showed better glycemic control, verified by a significant reduction in glycated hemoglobin levels [16].

In a recent study, the presence of greater alterations in laboratory test results, larger oscillations in oxygen saturation, and exacerbation of the peculiar symptoms of viral infection in patients with diabetes noted compared to the group without comorbidities [17]. In the cohort of Zhu et al. [18], the authors reinforced the presence of diabetes as a marker of higher severity of COVID-19, a greater need for medical interventions, and a more prominent risk of mortality. Similarly, Yan et al. [13] reported that 24.9% of 193 patients infected by the novel coronavirus with severe disease had diabetes as comorbidity. Zhao et al. [19], also corroborated the association of COVID-19 with diabetes (among other comorbidities), including the risks associated with the higher age range.

As a final observation, comments in the studies included the importance of glucose control in patients with diabetes, as high levels of glucose could increase *in vitro* viral replication and suppress the antiviral immune response, automatically affecting lung function [20]. Mantovani et al. [21] highlighted that maintaining glycemic control among patients infected by the novel coronavirus should be a target.

Development of results

The present review demonstrated that DM, a chronic disease highly prevalent worldwide, was associated with greater severity and higher mortality secondary to infection by the novel coronavirus and that a lack of glycemic control was associated with worse outcomes.

Evidence of the risks associated with the concomitant presence of DM and COVID-19 in the human body is increasingly consistent. A previous meta-analysis of studies comparing patients with and without diabetes (33 studies including 16,003 patients) concluded that patients with diabetes had a twofold increased mortality and severity of disease [1]. The study by Huang et al. [22] also indicated a two times greater risk of serious illness as well as a three times greater risk of in-hospital death in patients with diabetes.

Notably, the presence of DM is itself associated with increased morbidity and mortality in patients infected with COVID-19, even if glycemic control is adequate. According to the Center for Disease Control (CDC), patients diagnosed with COVID-19 and who had comorbidities had worse outcomes than patients without underlying clinical conditions, including DM, chronic obstructive pulmonary disease, and cardiovascular disease (present in 10.9%, 9.2%, and 9% of infected patients, respectively) [10]. Data from the CDC, released on March 28th, 2020, estimated that 10.9% of infected patients and 32% of those requiring intensive care unit admission were also diabetic [23]. A report by the Chinese Center for Disease Control and Prevention (based on an analysis of 72,314 cases), revealed significantly higher mortality rates for those with cardiovascular disease (10.5%), arterial hypertension (6%), and DM (7.3%) compared to the total average of 3% to 4% [3,10]. Although the available evidence does not indicate an increased risk of patients with diabetes contracting the disease [3,10]. According to a retrospective and multicenter report carried out in 7,337 patients admitted to 19 hospitals in Hubei Province in China, individuals with DM have greater fatigue (38% *vs.* 31.4%) and dyspnea (20.5% *vs.* 15.4%) than the control group. Furthermore, more frequent bilateral lung injuries (88.1% *vs.* 80.4%) and a greater association with previous arterial hypertension, coronary heart disease, cerebrovascular disease, and chronic kidney disease observed [13]. Documents released by the National Institute of Health in Italy described the prevalence of patients with diabetes who died was approximately 35% among those infected with COVID-19 [24].

Regarding mechanisms responsible for the greater severity of outcomes from the COVID-19 in diabetes, especially those with inadequate glycemic control, several hypotheses presented, including pathophysiological mechanisms inherent to viral aggression as well as immunological, clinical, sanitary, and psychosocial mechanisms. Thus, the presence of DM was associated with higher circulating levels of furin, a protease that facilitates penetration of the virus through a greater affinity between the viral particle and the cell receptor, and, consequently, more efficient viral entry [6]. Another report suggested a lower viral clearance, less T cell activity, greater susceptibility to hyper inflammatory states, and cardiovascular dysfunction. The latter was corroborated by reports of elevations in high-sensitivity cardiac troponin in 10% to 20% of infected patients, greater risk of atherosclerotic plaque rupture, hypercoagulability, and the development and decompensation of heart failure [10], which is related to respiratory impairment associated with hypoxia, cytokine storm, myocarditis induced by direct viral infection, and hemodynamic imbalance resulting from systemic infection [10].

In patients with diabetes infected with COVID-19, pulmonary dysfunction involving pulmonary volume, pulmonary diffusion capacity, ventilation control, bronchomotor tone, and noradrenergic bronchial innervation has been described [14]. Animal studies have suggested that alveolar microangiopathy and interstitial fibrosis are induced by the glycosylation of collagen in lung tissue, processes mediated by nicotinamide adenine dinucleotide phosphate and Angiotensin Converting Enzyme 2 (ACE-2) [13,16]. Apparently, aggressive glycosylation resulting from a hyperglycemic state is also related to dysfunction of immunoglobulins, causing greater susceptibility to infectious diseases and less clearance of antigens *via* phagocytic cells [15,16]. A recent study also showed that structural proteins from SARS-CoV-2 are able to attack the hemoglobin B1 chain, triggering dissociation between iron and porphyrin and impairing oxygen transport, suggesting a negative impact of hemoglobin glycosylation in patients with diabetes [3].

Along with diabetes come several aspects of immunological dysregulation, such as a deficit of phagocytic cells, altered production of cytokines, decreased immune response *via* T cells, and ineffective microbial clearance, among others. Thus, in patients with severe COVID-19, this characteristic could result in an immunological profile similar to that found in secondary hemophagocytic lymphohistiocytosis [1]. Lim et al. [25] conducted an animal experiment using a diabetic rat model made susceptible to infection by MERS-CoV by expressing the human receptor Dipeptidyl Peptidase 4 (DPP4). After being infected, a prolonged phase of the disease was observed, with increased severity and decreased recovery, regardless of viral load, as well as a lower number of monocytes/macrophages, CD4 T cells, TNF-alpha, IL-6, IL-12b, and arginase 1 and increased levels of IL-17a, among other findings [1,6,12]. Diabetes as well as obesity could also trigger the differentiation of CD4 T cells to Th1 and Th2 cells, leading to an immune state of dysfunction of Th17 cells and regulatory T cells, significantly affecting the balance between the mechanisms and anti-inflammatory drugs [6,16]. Such

immunological processes, associated with increased serum levels of fetuin-A, could also be responsible for intensifying insulin resistance, which in conjunction with the frequent presence of hypokalemia in patients infected with COVID-19, would directly affect glycemic control in patients with diabetes [3].

Regarding ACE-2, its reduced expression in DM could be associated with a worse prognosis. In the pulmonary system, the ACE-2/angiotensin set (1,7) plays an important anti-inflammatory and antioxidant role [3]. As described in an experimental model, the ACE-2/ACE ratio tends to reduced in patients with diabetes with advanced disease [19]. Paradoxically, a recent study indicated increased expression of the enzyme in the lungs, kidneys, heart, and pancreas of rodents with DM [6]. Following this line of thought, Rao et al. [6,18] observed an increase in the ACE-2 levels in patients with diabetes.

DM and the infection associated with the novel coronavirus share a similar pathophysiology, using enzymes (ACE-2 and DPP-4) that play key roles in viral entry and act on the metabolic pathways of glucose homeostasis and renal and cardiovascular physiology as well as in inflammatory processes [1]. In addition, patients with diabetes with SARS, despite not treated with glucocorticoids, have increased plasma fasting blood glucose levels compared to the patients without such an infection. An investigation of the damage caused by SARS-CoV in pancreatic islets found that ACE-2 is also expressed in this tissue [3,13,16]. The fact that ACE-2 expressed almost threefold higher in men than in women could perhaps explain why men have higher levels of mortality [16]. Additional data illustrate that ACE-2 in the kidneys is 100 times greater than in the lungs. Indeed, DM has been shown to coexist with the development and progression of chronic kidney disease and is associated with arterial hypertension, factors that would increase the severity of the disease and worsen poor outcomes such as hospitalization and increased mortality [11,12]. This fact is corroborated by the underlying state of hypercoagulability favoring the formation of thrombi, leading to fatal thromboembolic complications, especially if associated with over activation of the coagulation cascade resulting from COVID-19 (usually accompanied by elevation of D-dimer levels) [3].

The current context of the health crisis, with guidelines throughout the world recommending social distancing, quarantine, and significant changes in lifestyle, has presents a potential obstacle to adequate management of patients with diabetes, both for self-care and for patients who need hospitalization. Confinement alone represents several psychosocial developments secondary to the current pandemic [7], including limitations on physical activities required by social distancing and the risk of viral spread. In addition, there were also dietary changes imposed both by difficulties in obtaining high-quality food and by coping mechanisms to cope with the psycho-emotional impact. Medicines and supplies necessary for self-care in patients with diabetes also became difficult to purchase owing to travel restrictions and greater difficulty in accessing health services. Furthermore, healthcare professionals often directed to cases of COVID-19, thus postponing assistance to patients with chronic conditions, reflecting deficits in routine clinical monitoring. This profile was very common in low-income countries [7,8,10]. The reduction in purchasing power triggered by mass unemployment can also be considered, and all of these factors, acting together, could contribute to the development uncontrolled glycemia, thus making this population even more susceptible to a worsening prognosis after infection [7,11].

In contrast, adequately managing the blood glucose of patients with diabetes hospitalized with SARS-CoV-2 has proven to be a challenge for health teams and a goal to be pursued [21]. There is a need for a precise balance between correcting hyperglycemia without relying on hypoglycemic conditions, as these could trigger adverse cardiovascular events by activating the sympathetic nervous system and by platelet reactivity and mobilization of inflammatory cells [3,13]. In addition, attention should be paid to the effects of drugs commonly used in the management of infection on glycemic control, among which it is worth mentioning corticosteroids, lopinavir, ritonavir, interferon-B1, azithromycin, camostate mesylate, tocilizumab, chloroquine, and hydroxychloroquine as well as others [2,3,8,20,21].

Studies have demonstrated the significant role of telemedicine in reducing glycated hemoglobin in patients with diabetes when compared to control groups [16]. Likewise, Andres et al. [26] concluded that integrative telemedicine, with flexible scheduling and simultaneous multi professional participation in a virtual space, had potential benefits for the care of patients with diabetes [8]. Therefore, the expanded use of telehealth, encompassing the importance of an adequate diet, maintaining physical activity, handling mood swings and sleep, smoking cessation, and glucose self-monitoring, can enable such patients to properly recognize hypoglycemic conditions and maintain the use of their medications, including ACE inhibitors and angiotensin receptor blockers when prescribed [7,10].

Finally, long-term studies needed to assess the cardiometabolic sequelae related to COVID-19 in patients with diabetes. Previously, a survey of 25 patients who had recovered from SARS after a 12-year interval found greater changes in glycemic and lipid metabolism as well as in serum metabolites than was found in a group of healthy individuals of similar age [20].

Final Comments

The present review demonstrated a frequent lack of glycemic control in patients with diabetes infected with the novel coronavirus and a greater severity of the infectious disease, greater number of hospitalizations in intensive care units, and higher mortality than in infected patients without diabetes. During the course of COVID-19, the glycemic control considered a goal and several mechanisms proposed to explain this phenomenon. It has assumed that success in coping with the current scenario requires a joint effort between the health team and the patient, taking into account the complexity of diabetes and its vulnerabilities, often associated with other comorbidities.

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