Type 2 Diabetes Mellitus and COVID-19 in Mexico. A comprehensive Assessment

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BACKGROUND

Diabetes mellitus is a pre-existing pandemic that has not been controlled, being linked to the current one by COVID-19, which results in catastrophic damage to health, increasing morbidity and mortality in Mexico from all causes and also generating lack of metabolic control in previously controlled patients. The strategy generated to reduce the rate of infections generated an increase in cardiometabolic diseases derived from confinement, sedentary lifestyle and anxiety. It is important to analyze these two etiologies together to reduce the risk of complications that both involve, knowing the pathophysiology, clinical symptoms, clinical picture, diagnosis, treatment and complications.

Keywords: Diabetes; COVID-19; Telemedicine; Protein S; ACE 2; Lack of Metabolic Control

Introduction

On February 11, 2020, the International Committee for Taxonomy in Viruses named SARS-CoV-2. Composed of a genome of 30,000 base pairs, belonging to the Coronaviridae family of the order Nidovirales. Phylogenetically coronaviruses are classified into alpha, beta, gamma and delta. Coronaviruses were identified 50 years ago as pathogens responsible for the common cold, mainly HCoV-OC43, HCoV-229E among other variants. At the beginning of 2002, coronaviruses were considered exclusively veterinary pathogens, however, by 2019 they were identified in biological samples from patients diagnosed with pneumonia [1-4]. Showing an age trend initially with geriatric patients, it has been shown that the risk of mortality increases after 75 years [5]. However, today age is no longer a dependent factor for infection. It is important to mention this since it may be due to multiple etiologies in addition to infection, such as: comorbidities, lack of metabolic control, suspension of work in the outpatient clinic due to hospital oversaturation derived from the pandemic, sedentary lifestyle, among others.

Hence it is important to emphasize the lack of metabolic control derived from all those cardiometabolic diseases, such as: obesity, hypertension, dyslipidemias and mainly diabetes mellitus, which turns out to be the first pandemic that has not been adequately controlled since ancient times [6]. All these factors are directly and proportionally related to the risk of severe progression and poor prognosis due to the chronic inflammatory state that generate more the acute systemic inflammatory response derived from COVID-19. In the case of obesity, another factor shared by both pathologies increased even more derived from confinement due to the forced closure of sports centers, favoring a sedentary lifestyle. The anxiety derived from the pandemic favors a greater consumption of foods with low nutritional power, again favoring obesity and lack of metabolic control. Therefore, in the context of a controlled diabetic patient, the measures that had to be implemented as a strategy to reduce the rate of infections are one of the factors to generate lack of control. The percentage of uncontrolled diabetics since the beginning of the pandemic is more and more common and
continues to rise, which entails greater spending on health, greater generation of medical supplies and resources. There is an excess of mortality in the Mexican Republic derived from the pandemic, not only due to COVID-19, but also due to other causes [7,8] without forgetting to mention the possibility of under-registration that exists, for example, in marginalized areas or those who could not have hospital access derived from the same scenario. That is why the relevance of this article where a comprehensive scenario is proposed for the knowledge and management of COVID-19 in those patients who already have a chronic damage such as Diabetes Mellitus.

**Pathophysiology**

The incubation period for SARS-CoV-2 is 5 days with a range of 2 to 14 days [9]. The spectrum of diseases generated by coronavirus infection is mainly acute respiratory, chronic, enteric, hematological, endothelial and of the central nervous system. The mechanism of transmission of the disease by SARS-CoV-2 is from person to person through the airway by the drops of Flügge that are exhaled when coughing, sneezing or speaking and are inhaled or deposited in the mouth and ocular conjunctiva, as well as surfaces, which can function as fomites [10]. The main structural proteins found on the membrane surface of the SARS-CoV-2 viral particles participate within the pathophysiology, which are: Spike (S), membrane (M) and envelope (E). Among other, these are responsible for the anchorage and entry of these microorganisms to the host’s cells. It should be noted the type 2 angiotensin converting enzyme (ACE 2) which is a type I membrane protein that contains receptors in the lung, heart, kidney and intestine, endothelium, nervous system, mainly: The ACE2 receptors that are located in the lower respiratory tract of humans are the cellular receptors for SARS CoV-2. Since the virion has the S-glycoprotein or Spike protein, which projects through the viral envelope and forms the spicules of the crown, this is glycosylated and is responsible for mediating the binding of the receptor (protein S + ACE 2), as well as its fusion with the host cell [11,12].

This strong bond unites the entire SARS-CoV-2 membrane with the host cell membrane, entering it through endocytosis. Viral particles release their RNA that binds to viral DNA, initiating the viral replication cycle, which leave the host cell through exocytosis. Once the RNA of the SARS-CoV-2 particles begins its translation and transcription, two processes are generated: the first related to the high demand for manufacturing viral proteins causing cellular stress that ends in apoptosis of the target cells; while in the second, the viral RNA acts in a molecular pattern associated with pathogens, which leads it to be recognized by the cells of the immune system, initiating the activation of the cytokine cascade and the migration of neutrophils. Hypercoagulability, venous stasis and endothelial damage is another of the main characteristics mediated by the ACE 2 receptors that SARS-CoV-2 particles possess, being observed in the endothelium of the veins, arteries and arterial smooth muscle cells of the brain; This produces dysfunction and inflammation of the microvasculature that alters vascular flow and initiates platelet activation, increasing risk for macrovascular and microvascular thrombosis, pulmonary thromboembolism, deep vein thrombosis, catheter-related thrombosis, ischemic cerebrovascular disease, atherosclerotic, and capillary leak syndrome in organs such as lungs, kidneys and heart, increasing mortality, one of the main complications [13] (Figure 1).
**SARS-COV2 as a Diabetogenic Agent**

Diabetes is associated with a chronic low-grade inflammatory state that favors the development of an exaggerated and constant inflammatory response. At the molecular level, there is an increase in the levels of IL-6 and C-reactive protein (CRP), so the pro-inflammatory state typical of diabetes can favor the cytokine storm and the systemic inflammatory response that accompanies the acute respiratory distress syndrome (ARDS) in patients with COVID 19 [14]. This is why diabetics infected with SARS-CoV-2 have a higher rate of hospital admission, severe pneumonia, and higher mortality compared to non-diabetic subjects [15]. SARS-CoV-2 is considered diabetogenic since it is also capable of causing direct damage to the pancreas, due to the expression of ACE 2 (mainly in islet cells) even in a higher proportion than at the lung level, which could worsen hyperglycemia and even induce the onset of diabetes in previously non-diabetic subjects [16]. It should be noted that only 1-2% of patients with mild COVID-19 infection present pancreatic lesions, while 17% of patients with severe cases present with lesions of the pancreas, which can accentuate the systemic inflammatory response and, therefore, accelerate the appearance of ARDS [17]. On the other hand, the current scenario of the pandemic even in uninfected subjects may favor the deterioration of metabolic control due to difficulties in accessing the health system, lack of physical activity and increased stress associated with confinement.

Therapeutic strategies should be aimed at facilitating access to the health system through telemedicine to advise the patient on the adaptation of treatment or any other remotely manageable medical situation and guide patients and caregivers in the control of diabetes in order to prevent hospitalization [18]. Clinical symptoms. Different stages of SARS-CoV-2 disease have been described in humans depending on the clinical severity, which can range from mild symptoms such as: fever, myalgia, headache, cough, anosmia. Up to severe symptoms characteristic of pneumonia with severe respiratory impairment [19,20-25]. Table 1 Mild and moderate infections comprise 80.9% of the registered cases; the severe ones, 13.8% and the critical ones, 4.7%. In the adult population it is 1.2%; while in pediatric population it is 15.8% [26]. The prevalence of asymptomatic patients differs according to the age group and can be reported by up to 40% [27]. Due to the high percentage of asymptomatic patients not only in Mexico, but also worldwide, it is vitally important to continue using a facial mask in our daily lives in order to reduce the risk of contagion. Even people with a full vaccination schedule are not exempt from COVID-19 infection.

**Table 1:** Clinical symptoms of COVID-19 severity.

| Clinical Severity COVID-19 | Asymptomatic | Mild | Moderate | Serious | Critical |
|---------------------------|--------------|------|----------|---------|----------|
| No apparent symptoms or imaging changes, but with positive RT-PCR | Symptoms confined to the upper respiratory tract, including fever, malaise, and cough. No positive RT-PCR images changes | Pneumonia symptoms, imaging changes RT-PCR positive | Dyspnoea and respiratory rate ≥ 30 breaths/min. At rest, an oxygen saturation ≤ 93% or PaO2 ≤ 300 mmHg Imaging lesions that progress >50% in a period of 24-48 hours and positive RT-PCR | Rapid progression of the disease accompanied by respiratory failure, need for mechanical ventilation, shock or multi-organ failure and positive RT-PCR |

Prognostic factors for serious and severe disease are considered: cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cerebrovascular disease, cancer; chronic kidney disease, obesity and smoking [28,29]. Some alterations in laboratory parameters associated with a pro-inflammatory and procoagulant state are indicative of a poor prognosis, such as multi-organ failure [30]:

- Lymphopenia.
- Elevated liver enzymes.
- Elevated LDH.
- Elevation of acute inflammation markers (CRP, ferritin, procalcitonin).
- D-dimer elevation.
- Prothrombin time lengthening.
- Elevation of troponins.
- CPK elevation.
- Markers of kidney damage (elevated creatinine, anuria).

**Diagnosis.** There are different detection techniques for SARS-CoV-2, each with different sensitivity and specificity. We currently have three types of diagnostic tests [17,18]:

a) Nucleic acid detection tests (PCR). In the case of the gold standard. Being its high cost the main limitation for its application.

b) Antigen (Ag) detection tests.

c) Antibody detection tests (Ab): IgM / A and IgG.
We must emphasize that a negative result does not exclude infection, therefore, if the clinical suspicion is high (clinical data, epidemiological context, radiological findings, sometimes earlier in computed tomography than the positivity of the PCR and analytical studies), it is recommended repeating the same sample in 48-72 hours or trying to obtain it from the lower respiratory tract, especially in severe or progressive disease [16]. Throughout the pandemic, a high percentage of false negatives has been observed in the practice of antigenic tests, the most used in Mexico due to the difference in cost between PCR, which has perpetuated in the patient the uncertainty of being or not with the infection, which means that they do not follow the medical indications and finally contribute to continue perpetuating the contagion. Educating the patient about what a negative result implies despite high clinical suspicion is part of our work in this pandemic and therefore, as health professionals, we should not base our treatment on a laboratory test and the recommended measures should be initiated in the context of isolation, symptomatic treatment and continuous monitoring of associated comorbidities in order to avoid complications as explained in detail.

Treatment of diabetes mellitus in patients with COVID-19. Treatment depends on the clinical characteristics of each patient, risk of complications, age, ease of access to the health area, socioeconomic status, risk of drug interactions especially in patients with polypharmacy, etc. Treatment for COVID-19 infection should be symptomatic, that is, based on the clinical picture presented by each patient, which can be: antihistamines, cough suppressants, thromboprophylaxis, analgesics and anti-inflammatories, educate for self-monitoring of vital signs and provide all the necessary alarm data. As outpatient management in non-serious patients and mild symptoms, the following should be taken into account: prevention of infection, healthy lifestyle, general measures to improve diabetes control, treatment of hyperglycemia, treatment of comorbidities and support doctor (Figure 2). For the treatment of asymptomatic or non-severe patients, the following is recommended: home management, follow usual treatment for diabetes control, goal of fasting glucose 70-130 mg / dL, HbA1c <6.5%, use of telemedicine to clarify doubts and education, indicate alarm and isolation measures, adjust the medication only if there is lack of control. Speaking of telemedicine, Mexico is not fully prepared, since it has a technological development of around 25%, however, thanks to portable technology such as a cell phone that facilitates the use of telemedicine, it can favor the medical attachment of chronic degenerative diseases and likewise surveillance of the clinical evolution of COVID-19 in those patients with a high risk of complications. Up to 70% of the population could benefit from these programs [22,24,30].

In the case of patients with mild-moderate infection: home management with close monitoring, assess risk of progression and assess the need for in-hospital management, medication adjustments according to glycemic control, fasting blood glucose target of 72-144 mg / dL, HbA1c <7%, close medical contact. For those with severe-critical infection: use insulin in continuous intravenous infusion or basal-bolus-correction regimen, fasting glycemic goal of 72-180 mg / dL, HbA1c <8%, strict monitoring of plasma glucose, electrolytes, ketone bodies, renal and cardiovascular function, procoagulant markers among others. Always in-hospital (22,30). (Figure 3). With the above mentioned, the need for extra medication should be taken into account depending on the symptoms of COVID-19 according to the evidence reported so far. It is intended to exemplify the treatment of these two entities together, since if we only dedicate
ourselves to treating the patient based exclusively on the diagnosis of COVID-19, forgetting about their underlying pathology, in this case diabetes mellitus, we increase the risk of complications and mortality. Special considerations for drugs for diabetes mellitus in COVID-19 should be taken into account, such as: Metformin, SGLT2-i, GLP-1 analogs, DPP-4 inhibitors, sulfonylureas, and insulin. Each one with specific indications, making the appropriate dose adjustments according to the patient’s needs, to optimize therapeutic goals, but it is important to emphasize that for those who require hospitalization derived from COVID-19, the drug of choice for glycemic control will be insulin [22].

In diabetes hospitalized for COVID-19, the use of prophylactic doses of low molecular weight heparin, such as Enoxaparin, is suggested in the absence of contraindications (active bleeding or platelet count <25 × 109 / l, and others), with dose adjustment for patients with frank elevation of D-dimer and those that present severity criteria [15]. It is important to individualize the prothrombotic risk according to the age and associated comorbidities of each patient, even in patients with mild symptoms thromboprophylaxis is indicated, the duration of this measure will also depend on how many associated risk factors present and the clinical severity, which requires a minimum of 2 weeks in those asymptomatic or mild symptoms and up to 6 weeks in severe conditions. Even with the resolution of the symptoms and / or the hospital discharged, this measure must continue for a minimum of 7 days [30].

Conclusions

The union of protein S with ACE 2 is the most important point within the pathophysiology since it culminates in a systemic inflammatory response and endothelial damage, which opens the door for a wide panorama of complications in the organism, even that a patient debut as diabetic from infection. At the beginning of 2020, when the first case of COVID-19 was registered, to date, the Mexican population presents data of exhaustion derived from isolation. Despite this, the vaccination program that was established in Mexico has not been fast enough, placing itself practically in the last place in Latin America for complete coverage of vaccines and reducing the rate of infections to be able to restore daily activities in a greater proportion and better still reduce morbidity and mortality in vulnerable groups. In addition to this, the lack of supplies and medical personnel in the health sector remains constant, which does not favor the scenario of both pandemics since it also worsens the medical adherence required by patients with chronic degenerative diseases, leading to a greater risk of complications, greater risk of contagion and finally higher mortality; thus, generating a vicious circle. Offering a broad panorama as a comprehensive evaluation of what COVID-19 implies in a patient with Diabetes Mellitus offers us new opportunities to reduce complications and serious progression of the disease, emphasizing the need to establish strategies such as telemedicine if necessary for better medical surveillance, promote pharmacological adherence and provide timely help in case of seriousness, always treating together.

We are in a century where two pandemics converge with each other, increasingly diabetic patients with lack of metabolic control, generating catastrophic damage to health, psychosocial and the economy. It is necessary to control both, starting with preventive measures to be able to modify the impact that has been generated so far. The points to follow in the context of DM2 and
COVID-19 will be prevention measures where isolation is the most important, educating the patient, surveillance of comorbidities and glucose self-monitoring to be able to adjust the dose or change the medication in case of lack of control, monitor alarm signs and offer symptomatic treatment according to the needs of the patient, without forgetting the necessary use of telemedicine as a support tool.

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