

# The role of diabetes mellitus and obesity in COVID 19 patients

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## Key words:

- COVID 19
- Diabetes Mellitus
- Obesity

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## ABSTRACT

Several risk factors (old age, hypertension, cardiovascular disease, immunodeficiency) have been related with coronavirus disease 2019 (COVID 19). Among them, Diabetes Mellitus (DM) and obesity are recognized to increase the susceptibility and severity of the infection. A higher inflammatory response observed in these patients, the immune system dysfunction and increased expression of angiotensin converting enzyme 2 (ACE2) which is a the target for SARS-CoV-2, contribute to the worse outcome of diabetic and obese patients. Adequate blood glucose control improves the prognosis, while critically ill COVID 19 patients with high metabolic risk should be monitored for new onset DM. *Pneumon 2020, 33(3):114-117.*

## INTRODUCTION

According to the World Health Organization, 820.000 deaths approximately are attributed to COVID -19 (coronavirus disease 2019) until August 2020. The disease is caused by SARS-CoV-2 virus and its clinical presentation ranges from mild respiratory symptoms to severe pneumonia with respiratory failure, Acute Respiratory Distress Syndrome (ARDS) and septic shock<sup>1</sup>. Elderly patients, mainly males, patients with comorbidities (hypertension, cardiovascular disease, diabetes mellitus [DM], chronic respiratory disease), patients with cancer and immunosuppression are at increased risk for severe COVID 19. However, emerging data show that young people without comorbidities are also susceptible and obesity is a significant risk factor for severe disease.

## DM AND OBESITY: PREVALENCE, INCIDENCE AND MORTALITY

DM is related to severe COVID 19 with a prevalence that varies and ranges from 7-20% in Chinese studies, to 33-35% in studies from Italy while Bhatraju et al, in USA, in a small study with 24 patients reported a prevalence of 58%<sup>2,3</sup>. In a meta-analysis of 21 studies from China with

47,344 patients, 7.7% of COVID 19 patients had DM, while in a retrospective study with 1591 critically ill patients in Lombardy-Italy, the incidence of DM was 17%<sup>4,5</sup>. In New York City in a study with 5700 patients the most common comorbidities were hypertension (56.6%), obesity (41.7%) and DM (33.8 %)<sup>6</sup>. An even 50% rise of mortality is reported in diabetics with COVID 19 while in the past DM was related to increased complications and mortality in Severe Acute Respiratory Syndrome (SARS-CoV-1) epidemic in 2002-2003 in China, in influenza A (H1N1) pandemic in 2009 and in Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreaks in 2012 in Middle East<sup>7</sup>. In the USA, according to the Centers for Disease Control and Prevention (CDC) the prevalence of DM in patients hospitalized in the ICUs was 32% while the Chinese Center for Disease Control and Prevention reported a case fatality rate of 7.3% in diabetic patients<sup>8,9</sup>. Zeng-Hong Wu et al in a meta-analysis, which included 9 studies, reported that DM was significantly related to COVID 19 mortality with odds ratio of 1,7 ( $p=0.006$ ) and in another study with 1099 patients 16% of patients who had severe disease and only 6% of those with mild disease were diabetics<sup>10,11</sup>. Ian Huang et al, in a meta-analysis of 30 studies concluded that DM was related to a worse outcome (Risk Ratio [RR] 2.38), increased mortality (RR 2.12), severe disease (RR 2.45), ARDS (RR 4.64) and disease progression (RR 3.31). Old age ( $p = 0.003$ ) and hypertension ( $p < 0.001$ ) influenced the association of DM to worse prognosis, which was stronger in young people and patients without hypertension according to a meta-regression analysis<sup>12</sup>.

Obesity seems to be an independent risk factor for severe COVID 19, especially in the younger patients and usually coexists with DM increasing further the risk of these patients<sup>13</sup>. Severe obesity ( $BMI \geq 35 \text{ kg/m}^2$ ) was independently related to mortality in 200 COVID 19 patients in New York City, while in Chinese studies obese patients had a 3.4 higher probability of having severe disease (OR 3.40,  $p < 0.007$ ) in comparison to patients with normal body weight<sup>14-16</sup>. In a Greek multi-centre observational study in 8 ICUs where 90 patients were included, 34.4% of patients were obese and 18.9% were diabetics. The mean BMI was  $28 \text{ kg/m}^2$  and younger patients ( $\leq 55$  years) had a significantly higher BMI ( $30.8 \text{ kg/m}^2$ ). The incidence of DM and mortality were similar among different age groups. In this cohort, 30.8% of patients who died and 16.7% of those who remained hospitalized in the ICUs were diabetics while none of the patients who were discharged had DM ( $p = 0.074$ ). Additionally, obesity

was more common in patients who died (46.2%), rather than in survivors (26.7%) ( $p=0.077$ )<sup>17</sup>.

## PATHOPHYSIOLOGY

The pathophysiologic mechanisms that contribute to increased incidence of severe COVID 19 and worse prognosis for obese and diabetic patients are not fully understood. DM predisposes to infections due to immune system disorder and especially alterations of innate immunity. The higher frequency of DM in the older patients and the common coexistence with cardiovascular disease and other comorbidities may interpret the worse prognosis of these patients<sup>18</sup>. Also, angiotensin converting enzyme 2 (ACE2) may be implicated in the increased severity of COVID 19 in diabetics. The virus SARS CoV-2 (COVID-19), like SARS CoV-1, enters host cells after binding to ACE2. ACE2 receptors are expressed in epithelial cells of lung, upper respiratory system, intestine, kidneys, heart, vessels and pancreas<sup>3</sup>. ACE2 decreases the levels of angiotensin II and interleukin 6 (IL-6) and increases angiotensin 1-7 which has anti-inflammatory effect and causes vasodilation<sup>12</sup>. After its connection with SARS CoV-2, ACE 2 is decreased, losing its protective role<sup>3</sup>. DM and hypertension are characterized by activation of the renin-angiotensin system in different tissues, while the increased expression of ACE2 that is observed in diabetic patients may predispose to COVID 19<sup>3</sup>. Also, diabetic patients are often treated with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) which increase the levels of ACE2 facilitating possibly the entry of SARS-CoV-2 in alveolar cells<sup>12</sup>. Additionally, increased levels of proinflammatory cytokines and especially of interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor -  $\alpha$  (TNF- $\alpha$ ) in diabetic patients contribute to cytokine "storm" that characterizes severe COVID 19 and leads to rapid deterioration<sup>12</sup>. Patients with uncontrolled DM and COVID 19 have higher values of inflammation markers (polymorphonuclear neutrophils, CRP, d-dimers, ferritin, Erythrocyte Sedimentation Rate [ESR], IL-6 and fibrinogen) compared with patients with well controlled DM that exhibit a milder inflammatory response<sup>19,20</sup>. Respectively, obesity is related to chronic, low-grade, subclinical inflammation due to cytokines and hormones released from adipose tissue, while often is accompanied by decreased physical activity leading to insulin resistance and immunological disorder<sup>7,18</sup>. Finally, the decreased vital capacity and compliance of

the respiratory system, seen in obese patients, raises further the risk of respiratory failure and complications of mechanical ventilation<sup>21</sup>.

In critically ill patients with COVID 19 and DM, the optimal glycemic control with continuous intravenous insulin infusion is necessary and seems to improve the outcome<sup>18</sup>. In a study with 7337 patients from China, lower mortality was reported for patients with adequate glycemic control (glucose levels 70–180 mg/dL) compared with those with insufficient regulation of blood glucose levels (>180 mg/dL)<sup>19,20</sup>. In ICU COVID 19 patients, a higher risk of diabetic ketoacidosis and hyperosmolar hyperglycemic state has been observed, while greater amounts of insulin are required due to insulin resistance<sup>18</sup>. Patients with COVID 19 and especially those with high risk of metabolic disease, should be tested for new onset diabetes, as the pancreatic beta-cells insult by the virus may result in derangement of insulin secretion and contribute to the deterioration of pre-existing DM or the emergence of new DM. In the past, the development of new onset DM was attributed to the coronavirus SARS (SARS-CoV-1) and the direct damage to pancreatic islet cells<sup>22-24</sup>. Regarding

the use of ACEI/ARB in patients with COVID 19, DM and hypertension the findings are conflicting. The European Society of Cardiology, the European Society of Hypertension and the American Heart Association do not recommend the discontinuation of ACEI/ARB in patients with DM and COVID 19, as currently there are no sufficient data that ACEI/ARB increase the risk of severe disease or the susceptibility to the infection. On the contrary in experimental models, ARB exhibit a possible protective effect on the lung and losartan is currently being evaluated for the treatment of COVID 19<sup>3,18</sup>.

In conclusion, both DM and obesity are related to severe COVID 19 (ARDS, ICU hospitalization, mechanical ventilation) and increased mortality. Possible responsible pathophysiologic mechanisms include the severe inflammatory response in diabetics and obese patients, the over expression of ACE2 and the immune system dysfunction. The optimal glycemic control and the monitoring for new onset DM are essential in critically ill COVID 19 patients.

#### CONFLICT OF INTEREST

None.

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### ΠΕΡΙΛΗΨΗ

#### Ο ρόλος του Σακχαρώδη Διαβήτη και της Παχυσαρκίας σε ασθενείς με COVID-19

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<sup>1</sup>Παθολόγος-Εντατικολόγος, Επιμελήτρια ΕΣΥ, Τμήμα Επειγόντων Περιστατικών, Π.Γ.Ν.Α «Αττικόν», Ιατρική Σχολή Ε.Κ.Π.Α., <sup>2</sup>Καθηγητής Εντατικής Θεραπείας, <sup>2</sup>Κλινική Εντατικής Θεραπείας, Π.Γ.Ν.Α «Αττικόν», Ιατρική Σχολή Ε.Κ.Π.Α., <sup>3</sup>Αναπληρωτής Καθηγητής Παθολογίας, Β' Προπαιδευτική Παθολογική Κλινική, Π.Γ.Ν.Α «Αττικόν», Ιατρική Σχολή Ε.Κ.Π.Α.

*Πολλοί παράγοντες κινδύνου (μεγαλύτερη ηλικία, υπέρταση, καρδιαγγειακή νόσος, ανοσοκαταστολή) έχουν συσχετιστεί με τη νόσο COVID 19. Ο Σακχαρώδης Διαβήτης (ΣΔ) και η παχυσαρκία φαίνεται ότι αυξάνουν την ευαισθησία στη λοίμωξη και τη βαρύτητα. Η πιο σημαντική φλεγμονώδης απάντηση που παρατηρείται σε αυτούς τους ασθενείς, η δυσλειτουργία του ανοσοποιητικού συστήματος και η αυξημένη έκφραση του μετατρεπτικού ενζύμου της αγγιοτενσίνης-2 (ACE-2), που αποτελεί στόχο για τον ιό SARS-CoV-2 πιθανά να συμβάλουν στη χειρότερη έκβαση των διαβητικών και των παχύσαρκων ασθενών. Η επαρκής ρύθμιση των επιπέδων της γλυκόζης αίματος μπορεί να βελτιώσει την πρόγνωση, ενώ βαρέως πάσχοντες ασθενείς με COVID 19 και υψηλό μεταβολικό κίνδυνο θα πρέπει να ελέγχονται για την εμφάνιση νέου ΣΔ.*

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**Λέξεις - Κλειδιά:** COVID 19, Σακχαρώδης διαβήτης, Παχυσαρκία

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