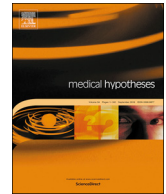




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IL-17A and TNF- α as potential biomarkers for acute respiratory distress syndrome and mortality in patients with obesity and COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was declared a pandemic and international health emergency by the World Health Organization. Patients with obesity with COVID-19 are 7 times more likely to need invasive mechanical ventilation than are patients without obesity (OR 7.36; 95% CI: 1.63–33.14, $p = 0.021$). Acute respiratory distress syndrome (ARDS) is one of the main causes of death related to COVID-19 and is triggered by a cytokine storm that damages the respiratory epithelium. Interleukins that cause the chronic low-grade inflammatory state of obesity, such as interleukin (IL)-1 β , IL-6, monocyte chemoattractant peptide (MCP)-1, and, in particular, IL-17A and tumour necrosis factor alpha (TNF- α), also play very important roles in lung damage in ARDS. Therefore, obesity is associated with an immune state favourable to a cytokine storm. Our hypothesis is that serum concentrations of TNF- α and IL-17A are more elevated in patients with obesity and COVID-19, and consequently, they have a greater probability of developing ARDS and death. The immunobiology of IL-17A and TNF- α opens a new fascinating field of research for COVID-19.

Background

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic and international health emergency by the World Health Organization (WHO) [1]. Notably, the obesity pandemic causes at least 2.8 million deaths each year, and no strategy has proven to be effective in reducing its incidence [2,3]. Finkelstein et al. [4] predict that by 2030, more than 51% of the population worldwide could suffer from obesity.

Obesity causes a chronic low-grade inflammatory state, and this inflammation has been associated with different chronic diseases, such as type 2 diabetes, arterial hypertension, cardiovascular diseases, metabolic syndrome, non-alcoholic liver steatosis, non-allergic asthma, autoimmune diseases and certain types of cancer [5].

Some diseases associated with obesity, such as diabetes, arterial hypertension and cardiovascular diseases, have been well identified as risk factors for death related to COVID-19. Zhou et al. [6] reported that compared with patients with COVID-19 alone, patients with COVID-19

and coronary heart disease have a probability of death 21-fold higher (odds ratio [OR] 21.4; 95% CI: 4.64–98.76, $p < 0.0001$), those with COVID-19 and diabetes have an almost 3-fold higher probability of death (OR 2.85; 95% CI: 1.35–6.05, $p = 0.0062$) and those with arterial hypertension have a 3 times higher chance of dying (OR 3.05; 95% CI: 1.57–5.92, $p = 0.0010$); however, that study, conducted in the city of Wuhan, China, does not specify whether these patients also suffered from obesity.

Petrilli et al. [7] conducted a study in New York City (US) with 4,103 patients with COVID-19 and found that compared with patients with a body mass index (BMI) < 30 kg/m², patients with a body mass index (BMI) of 30–40 kg/m² were 4.26 times more likely to be hospitalized (OR 4.26; 95% CI: 3.5–5.2, $p < 0.001$) and those with a BMI > 40 kg/m² were 6.2 times more likely to be hospitalized (OR 6.2; 95% CI: 4.21–9.25, $p < 0.001$). In that study, the ORs were adjusted for age, sex, race, chronic diseases and smoking, and it was found that obesity was an independent predictor for hospitalization due to COVID-19.

Recent data from New York City [8] have shown that patients under

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60 years of age with a BMI between 30–34 kg/m² were almost twice as likely to be admitted to the intensive care unit (ICU) (OR 1.8; 95% CI: 1.20–2.7, $p = 0.006$) than were patients with a BMI < 30 kg/m². It was also observed that the higher the BMI, the higher the probability was: patients with a BMI > 35 kg/m² were 3.6 times more likely to be admitted to the ICU (OR 3.6; 95% CI: 2.5–5.3, $p < 0.0001$).

A study conducted in France [9] showed that the odds may be even higher, as patients with a BMI > 35 kg/m² were 7 times more likely to require invasive mechanical ventilation (IMV) than were patients with a BMI < 25 kg/m² (OR 7.36; 95% CI: 1.63–33.14, $p = 0.021$). Interestingly the OR was adjusted for age, sex, diabetes, hypertension and dyslipidaemias, indicating that obesity itself was an independent risk factor for IMV.

A study by Zheng et al. [10] showed that patients with metabolic associated fatty liver disease with obesity were 6 times more likely to present with severe COVID-19 than were patients with metabolic associated fatty liver disease without obesity (OR 6.32; 95% CI: 1.16–34.54, $p = 0.033$). The OR was adjusted for age, sex, smoking, type 2 diabetes, hypertension and dyslipidaemia. The most interesting finding of that study was that obesity was a predictor of COVID-19 severity, regardless of the presence of metabolic associated fatty liver disease.

These epidemiological data are very alarming and are a concern for public health, particularly in countries where there is a high rate of obesity. Patients with obesity and COVID-19 could overwhelm ICU capacity, consequently collapsing the health system.

It is well documented that acute respiratory distress syndrome (ARDS) is one of the main causes of death related to COVID-19 and that ARDS is triggered by a cytokine storm that directly damages the respiratory epithelium, liver, heart and kidney [6,11].

It is important to highlight that interleukins that cause the chronic low-grade inflammatory state of obesity, such as interleukin (IL)-1 β , IL-6, IL-17A, tumour necrosis factor alpha (TNF- α) and monocyte chemoattractant peptide (MCP)-1, also play very important roles in ARDS-related lung damage in patients with COVID-19. Additionally, the interleukins that cause lung damage in a model of obesity and asthma, such as TNF- α , IL-6, IL-8, IL-17A, regulated on activation, normal T cell expressed and secreted (RANTES), granulocyte macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), vascular cell adhesion molecule-1 (VCAM-1) and vascular endothelial growth factor (VEGF), are the same that cause lung damage associated with COVID-19. Therefore, it is assumed that obesity is associated with an immune state favourable to a cytokine storm, ARDS, multiple organ failure and death [5,12,13].

Huang et al. [13] showed that the levels of cytokines such as IL-1 β , IL-6, IL-8, IL-17, G-CSF, GM-CSF, interferon γ (IFN- γ), MCP-1, TNF- α and VEGF are higher in patients with COVID-19 than in healthy adults. In that same study, it was observed that plasma concentrations of MCP-1 and TNF- α were high in patients with COVID-19 who were admitted to the ICU. Similarly, Chen et al. [14] reported that patients with severe COVID-19 have high concentrations of IL-6 and TNF- α . As we can see, the cytokine profile in COVID-19 is predominantly Th1-Th17, similar to obesity.

Obesity is associated with an immune state favourable to a cytokine storm caused by COVID-19

The main source of IL-17A in obesity is Th17 lymphocytes and group 3 innate lymphoid cells (ILC3), and the main source of IL-1 β , IL-6, IL-15 and TNF- α in obesity is type 1 macrophages (M1) located in visceral adipose tissue. IL-1 β , IL-6 and IL-15 are essential for naïve CD4⁺ T cells to differentiate into Th17 lymphocytes and become activated [15–17]. (Fig. 1).

IL-6 is elevated in obese patients, and its main source is M1 macrophages. Moreover, IL-6 plays an important role in the differentiation of Th17 lymphocytes; it binds to signal transducer and activator of

transcription 3 (STAT3), and this signal activator binds directly to the chromatin of Th17 lymphocytes and activates the gene expression of retinoid-related orphan receptor C (RORC). RORC forms a complex with histone acetyltransferase p300 coactivator; this complex binds to the chromatin of Th17 lymphocytes and stimulates the expression of IL-17A [18,19] (Fig. 1).

Apart from this, IL-17A stimulates M1 macrophages, which respond with the increased synthesis of IL-1 β , IL-6, IL-15 and TNF- α , which subsequently activate more Th17 lymphocytes. Therefore, there is a positive immunological feedback loop between M1 macrophages and Th17 lymphocytes; for this reason, a Th1-Th17 immune profile predominates in obesity with an increase in serum concentrations of IL-17A and TNF- α [5,17] (Fig. 1).

However, IL-6 is not the only pathway through which Th17 lymphocytes are activated. Endo et al. [20] described a metabolic pathway mediated by acetyl-CoA carboxylase 1 (ACC1), a key enzyme for the synthesis of monounsaturated fatty acids, which directly activate RORC as a dependent ligand and consequently stimulate the gene expression of IL17A. In patients with obesity, the expression of ACC1 is upregulated; therefore, the synthesis and serum concentrations of monounsaturated fatty acids will be higher, and as a result, the concentrations of IL-17A will be higher as well (Fig. 1).

The N protein of SARS-CoV is a potent inducer of IL-6. SARS-CoV-2 is captured and processed by macrophages, dendritic cells and monocytes in the respiratory and intestinal epithelia. These cells, when processing and presenting antigen to naïve CD4⁺ T lymphocytes, produce large amounts of IL-1 β , IL-6, MCP-1 and TNF- α and, as a result, activate more Th17 lymphocytes. This may explain why patients with ARDS from COVID-19 have a greater number of Th17 lymphocytes in peripheral blood and therefore higher concentrations of IL-17A and TNF- α [11–13,21,22]. As we can see, there is a positive feedback loop between the low-grade inflammation of obesity and the immunology of COVID-19. Finally, all these immunological events culminate in higher concentrations of IL-17A and TNF- α and, consequently, greater lung damage and death. (Fig. 1).

How may IL-17A and TNF- α cause damage to the respiratory epithelium in patients with COVID-19 and obesity?

TNF- α causes bronchial hyperreactivity, a decrease in the calibre of the airway and significant neutrophilia in the respiratory epithelium [23]. Additionally, TNF- α directly damages the respiratory epithelium, which responds by producing mucin and releasing inflammatory cytokines such as IL-8, GM-CSF, RANTES and intercellular adhesion molecules (ICAMs) [24].

Moreover, TNF- α induces the release of matrix metalloproteinase-9 (MMP-9) by neutrophils and, as a result, stimulates the production of glycosaminoglycans by pulmonary fibroblasts [25]. Apart from this, TNF- α directly stimulates the synthesis of collagen by myofibroblasts and fibroblasts; all these events end in irreversible damage via pulmonary fibrosis [25–28].

IL-17A acts directly on smooth muscle and on the respiratory epithelium, causing bronchial hyperreactivity. Its main role is the recruitment of neutrophils via IL-8, IL-6, IL-11, GM-CSF and G-CSF induction. These inflammatory cytokines are released by the respiratory epithelium, smooth muscle cells and fibroblasts. Likewise, IL-17A increases the elastases and myeloperoxidases contained in the granules of neutrophils [29,30].

Neutrophilia in COVID-19 is associated with poor prognosis. Chen et al. [14] reported that patients with severe COVID-19 had a greater number of neutrophils in peripheral blood than did patients with moderate disease (6.9 (interquartile range [IQR]: 4.9–9.1) vs 2.7 (IQR: 2.1–3.7) $\times 10^9/L$ $p = 0.002$). Remarkably, Huang et al. [13] found similar data; patients who required admission to the ICU had a greater number of neutrophils in peripheral blood than did patients not admitted to the ICU (10.6 (IQR: 5.0–11.8) vs 4.4 (IQR: 2.0–6.1) $\times 10^9/L$

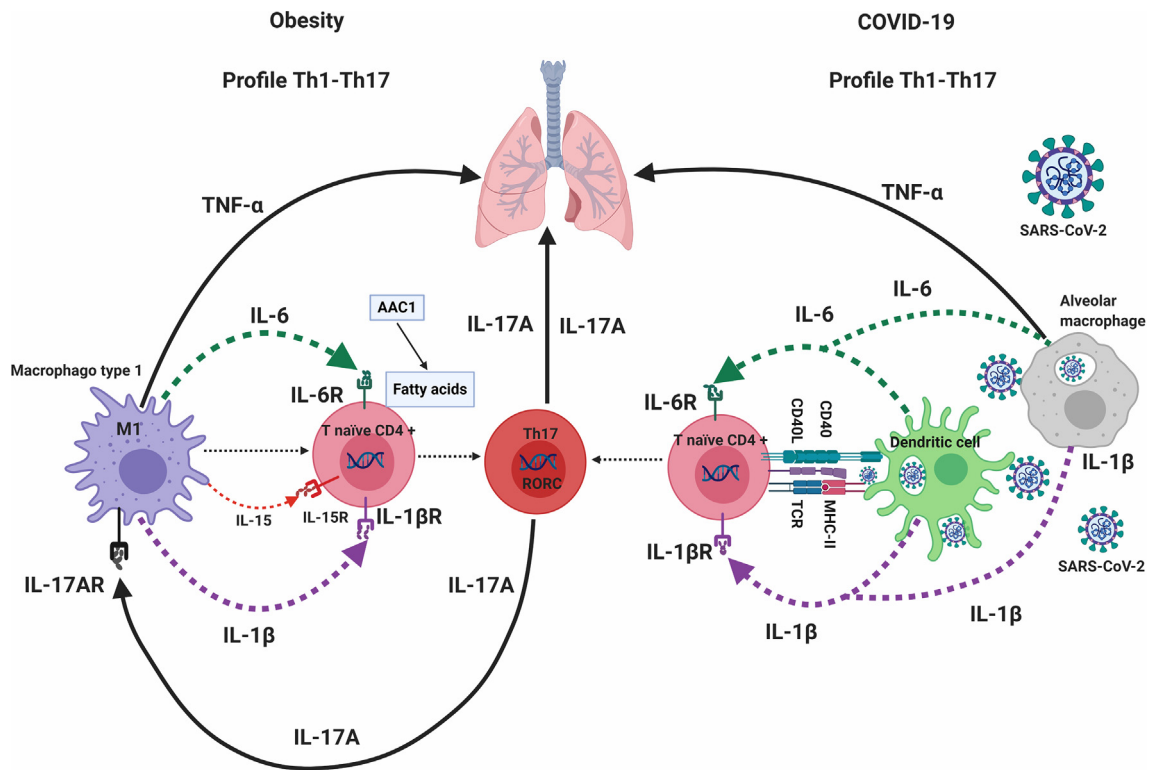


Fig. 1. Obesity is associated with an immune state favourable to a cytokine storm caused by COVID-19. Obesity causes chronic low-grade inflammation with increased tumour necrosis factor alpha (TNF- α), interleukin (IL)-1 β , IL-6 and IL-15 levels. IL-1 β , IL-6 and IL-15 are essential for naïve CD4⁺ T cells to differentiate into Th17 lymphocytes. IL-6 stimulates retinoid-related orphan receptor C (*RORC*) gene expression and consequently *IL17A* gene expression. IL-17A stimulates type 1 macrophage (M1), which in turn responds with the increased synthesis of IL-1 β , IL-6 and IL-15, and these cytokines activate more Th17 lymphocytes. There is positive feedback between M1 macrophages and Th17 cells. Moreover, acetyl-CoA carboxylase 1 (ACC1), a key enzyme for the synthesis of fatty acids, is upregulated in obesity, and fatty acids directly activate RORC and, as a result, *IL17A* gene expression. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is captured and processed by macrophages, dendritic cells and monocytes; these cells, when processing and presenting the antigen to naïve CD4⁺ T lymphocytes, produce large amounts of IL-1 β , IL-6 and TNF- α , which activate more Th17 lymphocytes. Thus, there is a positive feedback loop between the low-grade inflammation of obesity and the immunology of COVID-19. Finally, all these immunological events culminate in higher concentrations of IL-17A and TNF- α and, consequently, greater lung damage and death.

p = 0.00069).

TNF- α and IL-17A stimulate the synthesis of IL-8 by the respiratory epithelium; this interleukin is a potent chemotactic of neutrophils in the lung [31]. Neutrophilia in the respiratory epithelium is associated with severity and death in respiratory diseases such as asthma [32–35] and severe lung damage in influenza pneumonitis [36].

An in vitro study by Laan et al. [37] showed that IL-17A induced the release of IL-8 by the respiratory epithelium. Pelletier et al. [38] reported that neutrophils induced chemotaxis of Th17 lymphocytes via the CCL2 and CCL20 chemokines.

Laan et al. [39] showed in in vitro experiments that TNF- α and IL-17 potentiated the release of higher concentrations of IL-8 from the respiratory epithelium than did IL-17 or TNF- α individually. In an in vitro experiment, Jones et al. [40] incubated respiratory epithelial cells with IL-17 for 48 h and demonstrated the synthesis and stimulation of IL-8 and G-CSF gene expression. Another important finding was that IL-17 synergistically improved the release of IL-8 and G-CSF induced by TNF- α in respiratory epithelial cells.

Neutrophilia in sputum is associated with obesity. Scott et al. [41] found that in women with obesity and asthma, the percentage of neutrophils in sputum was positively associated with BMI (β = 1.015, 95% CI 0.258–1.772; p = 0.009) and that the proportion of neutrophilia in sputum (neutrophils \geq 61%) was higher in women with obesity and asthma than in women with asthma without obesity (42.9% vs 16.2%, p = 0.017).

Marijse et al. [42] reported similar findings. They showed that adults with asthma and obesity had a higher proportion of neutrophils

in sputum than did adults with asthma without obesity (66.2% vs 25%, p = 0.02).

Given the above, it can be inferred that the inflammatory pathway of TNF- α and IL-17 is a common pathway for both obesity and COVID-19, as both interleukins are associated with neutrophilia in the respiratory epithelium and, consequently, severe lung damage and death.

Analysis

Imagine the scenario of a patient with obesity, whose biological characteristics include elevated levels of proinflammatory cytokines such as IL-1 β , IL-6, IL-15, IL-17A and TNF- α and who unfortunately became infected with SARS-CoV-2. It is logical to assume that this patient will have a greater probability of presenting with a cytokine storm due to both inflammatory conditions and, consequently, severe lung damage, multiple organ failure and a poor survival prognosis.

IL-6 is a good prognostic indicator for mortality in patients with COVID-19. Zhou et al. [6] showed that plasma concentrations of IL-6 were higher in patients who died from COVID-19 than those in survivors (11.0 pg/ml (IQR: 7.5–14.4) vs. 6.3 pg/ml (IQR: 5.0–7.9) p < 0.0001). Interestingly, Ruan et al. [43] also reported very similar findings (11.4 \pm 8.5 pg/ml vs 6.8 \pm 3.61 pg/ml, p < 0.001).

A situation that worries doctors in the emergency room and ICU is a cytokine storm as a cause of ARDS, lung damage and death. What immunological characteristics prior to COVID-19 are present in patients with obesity who develop cytokine storms and consequently ARDS, multiple organ failure and death, and what immunological

characteristics are present in patients with obesity with COVID-19 who do not develop ARDS and have milder disease? Given the need to make the best clinical decisions for this vulnerable group of patients, we formulated the following hypothesis.

Hypothesis

The serum concentrations of TNF- α and IL-17A are more elevated in patients with COVID-19 and obesity than in patients with COVID-19 without obesity, and the former, consequently, are more likely to develop ARDS and death.

Patients with COVID-19 and obesity who develop ARDS will have higher serum concentrations of TNF- α and IL-17A than those in patients without ARDS. Last, patients with COVID-19 and obesity who died will have higher serum concentrations of TNF- α and IL-17A than those in survivors.

The best design to test our hypothesis is an incipient cohort study, initiating all patients at the same early COVID-19 disease stage, confirmed by a diagnostic RT-PCR test. Serum concentrations of TNF- α and IL-17A will be measured at the beginning of the study and at each established time point. Patients will be followed over time to determine who develops ARDS and who die. A careful analysis of the dynamics of TNF- α and IL-17A concentrations at each time point and for each group of patients will be performed; this analysis will include Kaplan-Meier survival analysis, a Cox's proportional hazards regression model adjusted for confounding variables and, last, a receiver-operating characteristic analysis to evaluate accuracy and establish a cut-off point for each cytokine.

Discussion and future perspectives

Although IL-6 is a good prognostic indicator of COVID-19 severity and COVID-19-related death and seems to be a good therapeutic target for this disease, there is no suitable biomarker for ARDS and mortality or to serve as a therapeutic target for patients with COVID-19 and obesity [6,43].

It is important to emphasize that the synthesis of IL-17A does not depend solely on IL-6. There is another mechanism mediated by ACC1 and monounsaturated acid acids, which are increased in obesity, and for this reason, this vulnerable group of patients should be considered individually [20].

At present, approximately 15 therapeutic interventions for COVID-19 have been reported, but none has focused on TNF- α and IL-17A. Blocking the biology of TNF- α and IL-17A in their target organs would be a good option as an anti-inflammatory treatment [44,45].

Wu et al. [46] showed in a murine model that fedratinib, a JAK2 inhibitor, may be a potential therapeutic option for inhibiting IL-17A synthesis in patients with COVID-19. The immunobiology of IL-17A and TNF- α opens a fascinating new field of research for COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authorship contributions

All the authors conducted the literature search and worked together to construct the hypothesis and theory. The authors accept responsibility for the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.109935>.

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