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Targeting the Adipose Tissue in COVID-19

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The WHO considers non-communicable diseases (NCDs), such as obesity, a major risk factor for becoming seriously ill with 2019 novel coronavirus (COVID-19) (1). A study by the UK Intensive Care National Audit and Research Centre indicates that two thirds of people who developed serious or fatal COVID-19-related complications were overweight or obese (2). The report includes data from all COVID-19 admissions in intensive care units in the UK until midnight, March 19, 2020. The study shows that almost 72 % of those in critical care units are either overweight or with obesity suggesting the impact of obesity in seriously ill COVID-19 patients.

At the outset of the COVID-19 outbreak, the Italian National Institute of Health (Instituto Superiore di Sanità [ISS]) launched a surveillance system to collect information on all people with COVID-19 throughout the country. Data on all COVID-19 cases were obtained from all 19 Italian regions and the 2 autonomous provinces of Trento and Bozen (3). The report from Italy indicates that 99% of deaths occurred in patients with pre-existing non-communicable diseases, such as obesity, hypertension, type 2 diabetes mellitus, heart disease, kidney damage and cancer (3). As of April 2, 2020, 145 out of the 12,250 (1.2%) COVID-19 positive patients under the age of 50 died. In particular, 35 of these were less than 40 years, 94 men and 26 women (age range between 26 and 39 years). For 14 patients under the age of 40 years no clinical information is available; the remaining 18 had serious pre-existing pathologies such as severe obesity and its comorbidities (cardiovascular, renal, diabetes mellitus and psychiatric pathologies) and 3 had no major pathologies (3).

The frequent co-occurrence of both obesity and diabetes can clearly confound or at least make more difficult the identification of the independent role of obesity. The anamnestic collection of the history of diabetes and other active obesity co-morbidities at the time of admission is what is important to separate the risk of obesity from its co-morbid complications on developing serious COVID-19 infection.

Obesity seems to be a risk factor for poor adverse outcomes of the COVID-19 disease, as summarized in *Figure 1*. The propensity of people with obesity to develop more serious complications if exposed to a virus could be attributed to multiple factors such as the chronic inflammatory status and the delayed and ineffective immune response. Nevertheless, so far, the adipose tissue has been not taken in full consideration as major player of the COVID-19 infection

Severe acute respiratory syndrome coronavirus (SARS-CoV) binds with the angiotensin converting enzyme 2 (ACE2) receptor for intracellular invasion, and the mechanism for acute lung injury during infection has been postulated to be mediated through the activation of the renin-angiotensin- system (RAS) (4). RAS blockade has been proposed as a potential treatment for COVID-19 (5). Remarkably, ACE2 is expressed in the human adipose tissue. The overall angiotensin converting enzyme (ACE)/ angiotensin II (Ang II)/type 1 angiotensin 2 receptor (AT1R) RAS axis activation plays an important role in the pathophysiology of obesity and visceral adiposity-related cardiac risk (6). The interaction between ACE2-RAS system, adipose tissue and the 2019 novel coronavirus could, at least partially, explain the higher morbidity and mortality risk of COVID-19 obese patients. However, the role of ACE2-RAS in COVID-19 remains to be elucidated.

Human dipeptidyl peptidase 4 (DPP4) was also identified as a functional receptor for the spike protein of the MERS-Co-V (7). MERS-CoV binds to the receptor-binding domain and interacts with T cells and nuclear factors involved in the pathogenesis of inflammatory disorders. DPP4 a transmembrane protein, has been identified in human adipose tissue and is associated with obesity-related type 2 diabetes. DPP-4 inhibition increases glucagon like peptide -1 (GLP-1) secretion leading to an improved insulin sensitivity and glucose metabolism within the adipocyte. DPP4 inhibition could also play a role in the immune response to COVID-19 by reducing inflammation (8). Inhibition of the DPP4 enzymatic activity suppresses T-cell proliferation and the secretion of pro inflammatory cytokines, such as interleukin 6 (IL6) and 10 (9).

Besides the expression of these enzymes and their possible role, there are multiple mechanisms by which the adipose tissue may contribute to the development and progression of the COVID-19 disease (10). Complex interactions occur between the immune system and the adipose tissue. The overexpression of inflammatory adipokines from visceral fat depots can affect the immune response, impair the chemotaxis and alter the macrophage differentiation. The imbalance between anti and pro-inflammatory adipokines secretion from thoracic visceral fat depots, such as the epicardial and mediastinal, can also play a role in the cytokine storm described in patients with severe SARS-COv2. Interestingly, adiponectin was reported to predict mortality in critically ill patients upon admission to the intensive care unit. The innate inflammatory response of the visceral fat depots can cause an up-regulation and higher release of inflammatory cytokines such as IL-6. Excessive proinflammatory

cytokine release was thought to be the link between visceral obesity and influenza-related severe respiratory complications. As elderly individuals are at higher risk of COVID-19 complications and poorer outcome, it is worth noting that aging can cause visceral fat accumulation, and adipose tissue inflammation and fibrosis. Similar changes have been described also in patients with human immunodeficiency virus.

Hence, the role of the adipose tissue during infectious diseases, like COVID-19, could be important. If obesity represents a predictor of poor prognosis or higher rate complications in SARS-Cov2 patients, it is still a modifiable risk factor. Therapeutic actions targeting the adipose tissue may be considered to reduce the burden of the COVID-19 disease.

Figure 1

This cartoon depicts the imbalance between a person with obesity and a normoweight in developing COVID-19 complications

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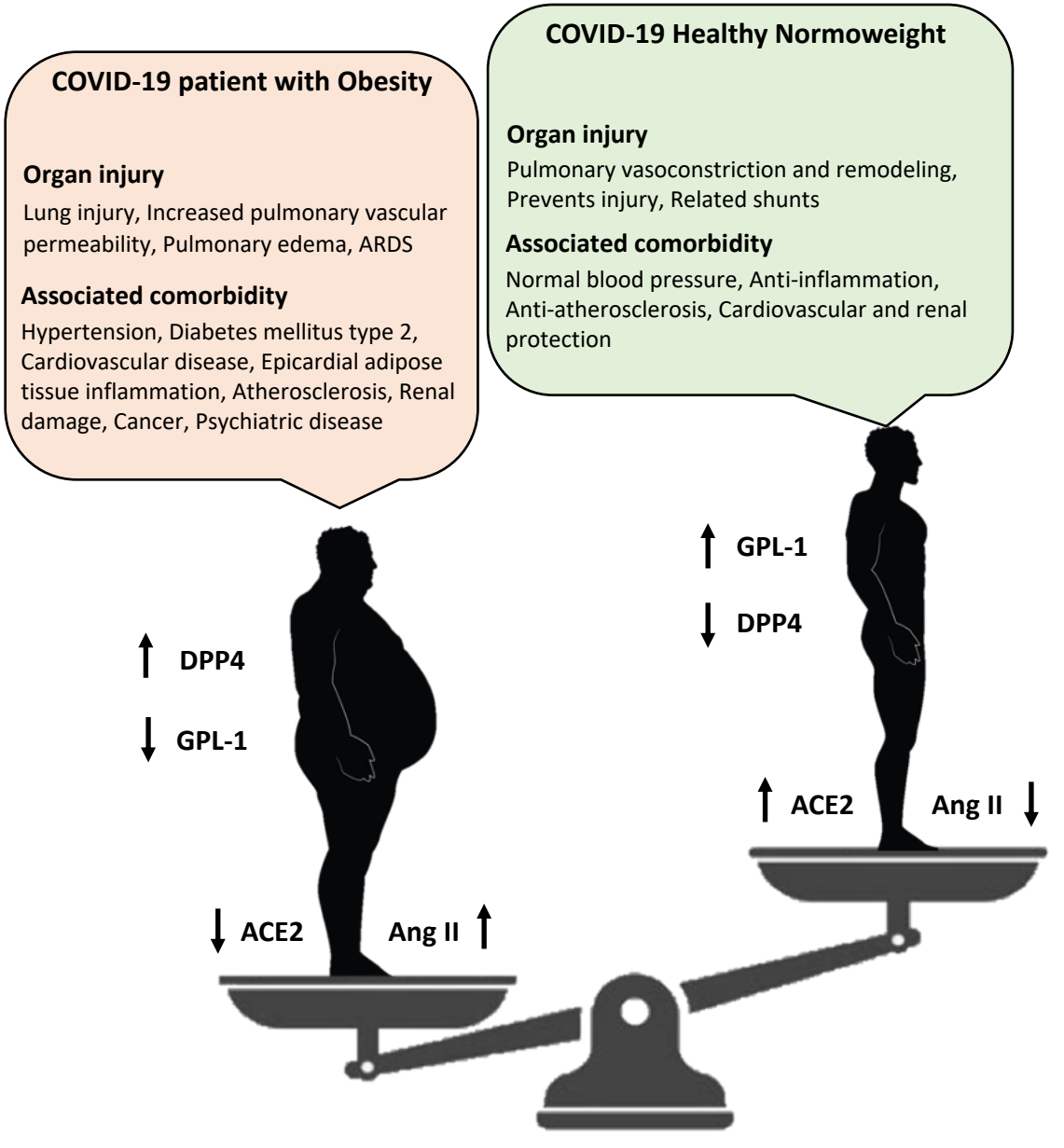
COVID-19 patient with Obesity
Organ injury
Lung injury, Increased pulmonary vascular permeability, Pulmonary edema, ARDS
Associated comorbidity
Hypertension, Diabetes mellitus type 2, Cardiovascular disease, Epicardial adipose tissue inflammation, Atherosclerosis, Renal damage, Cancer, Psychiatric disease
COVID-19 Healthy Normoweight
Organ injury
Pulmonary vasoconstriction and remodeling, Prevents injury, Related shunts
Associated comorbidity
Normal blood pressure, Anti-inflammation, Anti-atherosclerosis, Cardiovascular and renal protection
DPP4
GPL-1
ACE2
Ang II
GPL-1
DPP4
ACE2
Ang II