High prevalence for obesity in severe COVID-19: Possible links and perspectives towards patient stratification

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ABSTRACT

It is becoming obvious that in addition to aging and various hearth pathologies, excess of body weight, especially obesity is a major risk factor for severity of COVID-19 infection. Intriguingly the receptor for SARS-CoV-2 is ACE2, a member of the angiotensin receptor family that has a relatively large tissue distribution. This observation likely explains the multitude of symptoms that have been described from human patients. The adipose tissue also expresses ACE2, suggesting that adipocytes are potentially infected by SARS-CoV-2. Here we discuss some of the potential contribution of the adipose tissue to the severity of the infection and propose some aspects of obese patients metabolic phenotyping to help stratification of individuals with high risk of severe disease.

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1. Introduction

Coronaviruses are a large family of enveloped, positive-sense, single-stranded RNA viruses that infect a broad range of vertebrates, and for which bats are believed to be an important reservoir [1]. In humans, coronaviruses are responsible of mild to moderate upper respiratory tract infections such as the common cold [2,3]. The recent occurrence of variant strains exhibiting stronger virulence and efficient cross contamination in human has been responsible for severe epidemic crisis and these viruses have been called severe acute respiratory syndrome coronavirus (SARS-CoV). Sequencing of the virus responsible for COVID-19 revealed that this novel coronavirus that shared 88% sequence identity with two bat-derived SARS-like COVID, suggesting it had originated in bats [4]. Additionally, it was shown that this coronavirus, which was termed 2019-nCoV or SARS-CoV-2, shared 79.5% sequence identity with SARS-CoV [4,5].

The coronaviral genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein [6]. The S protein gives the typical coronal shape to the virus and is responsible for facilitating its entry into target cells by binding to a specific receptor. In all coronaviruses the S protein presents a short intracellular tail, a transmembrane anchor, and a large ectodomain that consists of a receptor binding S1 subunit and a membrane-fusing S2 subunit [7]. Although the SARS-CoV-2 S protein is only 75% identical to the SARS-CoV S protein, the receptor-binding motif in the S protein is highly conserved, suggesting that the two coronavirus strains use the same host receptor for cell entry [8]. Recently the atomic details at the binding interface obtained from the 3D structure obtained from the co-crystal of the S protein and the receptor demonstrated that key residue substitutions in SARS-CoV-2 S slightly strengthen the interaction and lead to higher affinity for receptor binding than to SARS-CoV S protein [9].

The Angiotensin-Converting-Enzyme 2 (ACE2) was undoubtedly identified as the entry receptor used by SARS-CoV [10]. ACE2 is a

Abbreviations: ACE2, angiotensin-converting enzyme II; AGT, angiotensinogen; AT, angiotensin receptors; BAT, brown adipose tissue; BMI, body mass index; COVID-19, corona virus disease 2019; IL, interleukin; LDL, low-density lipoprotein; MERS, Middle East respiratory syndrome; nAChRs, nicotinic acetylcholine receptors; NLRP3, NOD-like receptor family pyrin domain containing 3; PAI-1, Plasminogen Activator Inhibitor-1; PD-1, programmed cell death receptor 1; PUFA, polyunsaturated fatty acids; RAS, renin angiotensin system; TMPRSS2, transmembrane protease serine 2; TNFα, tumor necrosis factor-alpha; SARS-CoV-2, Severe acute respiratory syndrome coronavirus-2; WAT, white adipose tissue.
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type I transmembrane metallocarboxypeptidase involved in the Renin-Angiotensin system (RAS) and a target for the treatment of hypertension [11]. Vascular endothelial cells, the renal tubular epithelium, and in Leydig cells in the testes were shown to have high expression levels of ACE2, but its expression is also substantial in the lung, kidney, and gastrointestinal tract [12]. Angiotensin II is the major substrate for ACE2 and is cleaved into angiotensin 1-7, thereby, negatively regulating RAS and exerting a protective function in the cardiovascular system and other organs [13]. Several research groups have independently confirmed that ACE2 is also the receptor for SARS-CoV-2, which is further supported by the observation that anti-ACE2 antibodies block cellular entry of vesicular stomatitis virus mutants expressing the SARS-CoV-2 S protein [14]. Finally, the serine protease TMPRSS2 by cleaving the S protein is involved in the priming of SARS-CoV-2 S protein prior to ACE2 binding, suggesting that a TMPRSS2 inhibitor may be used to prevent cellular SARS-CoV-2 entry and might constitute a treatment option [14,15]. The contribution of the RAS in the COVID-19 pandemic and the influence of various factors including endogenous variations due to polymorphism as well as external factors such as air pollution have been recently reviewed [16].

1.1. COVID-19 is a multi-organ disease

It is an understatement to say that COVID-19 is a pathology that differs from what is seen in most other viral respiratory infections. This infection can cause multiple forms of extra-respiratory symptoms, some atypical, such as neurological troubles covering loss of smell (anosmia) and loss of taste (ageusia), or even vascular damage to the extremities manifested by pseudo-frostbite of the fingers and toes [17]. Table 1 lists the different organs that appear to be targets of the virus and the resulting pathological conditions. These various clinical manifestations show that the infectious pathology COVID-19 is also a systemic disease, that is to say characterized by a diffuse attack simultaneously affecting many tissues and organs. Thus, the presence of multiple small blood clots greatly contributes to the diversity of clinical signs. In fact, generalized inflammation promotes the formation of thromboses manifested by venous and arterial occlusions. On top of this a direct vascular attack by the virus of endothelial cells lining inside of blood vessels, expressing ACE2 on their cell surface, may serve as a gateway for the coronavirus. Involvement of the walls of small vessels, arterioles and capillaries, results in some patients with kidney disease, especially as the ACE2 receptor is also present at the level of the proximal tubules, which collect newly formed urine. Kidney damage is observed in approximately 5% in mild forms of COVID-19, a percentage that reaches 30% in patients with intensive care. This microvasculopathy also affects the cardiac, digestive, central and peripheral nervous systems. Hence diffuse attack of small vessels could perhaps explain strange neurological observations, including functional impairment executive.

Although most patients will naturally overcome the disease, around 10% of those, most of which are either over 70 years old and/ or present co-morbidities, and/or obesity-overweight will need hospital care treatments. Among those a subgroup of patients with severe COVID-19 will experience "cytokine storm syndrome" referring to the overproduction of immune cells and cytokines, which are associated with a surge of activated immune cells into the lungs, usually 7—15 days following the onset of symptoms. Cytokines and chemokines play important roles in immunity and immunopathology, and a recent study reported that deregulated and amplified immune responses in patients infected with the SARS-CoV-2 are associated with severe lung damage, respiratory complications and reduced survival rates [18]. Of note this cytokine storm was previously described, but at a lower scale, in SARS-CoV and MERS-CoV pandemics. In these patients, interleukin (IL)-6, IL-10 and tumor necrosis factor-alpha (TNFα) surge coincidental with peak adverse clinical symptoms, rapidly declining during recovery. Patients requiring intensive care unit admission have significantly higher levels of IL-6, IL-10 and TNFα and fewer T cells. This cytokine storm likely dampens innate adaptive immunity against SARS-CoV-2 infection [19]. Around 5% of infected person in the general population will need intensive care treatment largely because of this surge of cytokines. Among those patients overweight and obese people are by far over represented, which prompted us to examine the role of adipose tissue excess in disease outcomes.

Indeed, the crucial importance of body mass index (BMI, defined as the ratio of kg body weight to square height in meter) was first

Table 1
List of organs affected by the COVID-19 and various typical symptoms associated with the infection.

Lung	Difficulty breathing
	Acute respiratory distress syndrome
	Pulmonary embolism
Kidney	Acute renal failure
Liver	Impaired liver function with elevated liver enzymes in the blood
Digestive system	Diarrhea
	Nausea
	Vomiting
	Abdominal pain
Brain	Disorders of consciousness (loss of consciousness, coma)
	Vigilance disorders (drowsiness, listlessness)
	Epilepsy
	Stroke
Nerves	Damage to the peripheral nervous system (Guillain-Barré syndrome)
Eyes	Conjunctivitis (inflammation of the conjunctiva lining the inside of the eyelids)
Nose	Affection of the olfactory nerve nets located behind the nasal cavity
	Anosmia (loss of smell) associated or not with an ageusia (loss of taste)
	Runny nose
Heart and blood vessels	Damage to endothelial cells lining the interior of the vessels
	Myocarditis (inflammation of the heart muscle)
	Severe ventricular rhythm disturbances
	Pericarditis (inflammation of the thin membrane surrounding the heart)
	Decreased contractility of the heart muscle
	Clots in veins and arteries
Skin	Frostbite-like lesions of the fingers and/or toes (acrocyanosis)

noticed in China in a study from 383 patients, reporting that the risk of developing severe pneumonia raised to 140% in obese patients (BMI>30) and 86% in overweight individuals (BMI>25) [20]. From observations worldwide, obesity is now recognized as the second strongest independent predictor for hospitalization after old age. For instance, a French study on 124 patients with severe COVID-19 needing invasive mechanical ventilation recently reported strong association with BMI, independent of other comorbidities [21]. Most recently, this was confirmed in an additional cohort including 340 patients from the Lyon University Hospital, showing that patients with obesity and COVID-19 admitted in the hospital are significantly more frequent than expected (+35%). This is particularly important in intensive care units where patients with obesity are twice as numerous as usual as well as twice as numerous as in other medical departments with COVID-19 patients [22]. Similarly, in New York patients over 60 years old with BMI>30 had more than double morbidity related to COVID-19 [23]. Although most early studies lacked records on body weight and height parameters, needed to calculate BMI, some including small number of patients did suggest that BMI significantly increased severity of COVID-19 infection. More recently, this was confirmed in larger pools of patient [21,23,24]. A yet unpublished study termed OpenSAFELY based on medical records from 17 million UK patient indicated a 27% increase death risk with a 30 < BMI<35 compared to patient with lower BMI [25]. This death risk is further increased at 56% for patient with 35 < BMI<40 and 227% for BMI>40 [25]. As the pandemic hits the USA, a country with one of the highest proportion of obese people (around 40% versus 20% in Europe), the John Hopkins Hospital reported a significant negative correlation between BMI and age in 265 patients admitted to ICU for severe COVID-19, indicating that obesity could shift severe COVID-19 risk to younger ages [26]. The frequent co-occurrence of both obesity and diabetes mellitus, cardiovascular disease and kidney disease can clearly confound or at least make more difficult the identification of the independent role of obesity in the severity of SARS-CoV-2 infection [27,28]. In this regard, poor blood glucose control in diabetic patients was shown as a significant parameter for patient outcome [29].

2. The adipose tissue as target of COVID-19

Body weight excess is a well-established respiratory disease risk factor, especially for sleep apnea [30], and the reported correlation between obesity and severe cases of COVID-19 infection is therefore unsurprising. The underlying pathophysiology is likely multi-stranded, ranging from complement system hyperactivation, increased interleukin-6 and interferon secretion, chronic inflammation, presence of comorbidities such as diabetes and hypertension, and a local mechanical deleterious effect of fat accumulation in the chest. However, understanding the link between obesity and SARS-CoV-2 likely extends beyond the lung, and could aid proper tailoring of immunomodulatory treatments, together with improving stratification among those possibly requiring critical care.

As a multifactorial pathology, obesity is grossly defined by adipose tissue excess. However, not only adipose tissue is overdeveloped in obesity, but it also becomes dysfunctional. Main traits of adipose tissue dysfunction include a state of low-grade chronic inflammation, which further expands systemically as fat tissue secretes inflammatory cytokines. In this regard, adipose dysfunction in obesity is highly dependent on fat tissue distribution across the body as not all adipose tissues depots accumulating in different areas are equivalent: for instance, fat accumulating in the visceral region, close to intra-abdominal organs such as the liver (called omental fat), the kidney (perirenal fat), the intestine (mesenteric

fat), or the heart (pericardial fat) are more susceptible to become inflammatory in obese patients than fat accumulating subcutaneously. In addition, sex hormones highly contribute in body fat distribution, and visceral fat accumulation is a feature of so-called android obesity, whereas premenopausal women more likely develop subcutaneous fat in the limbs and hip region, referred to as gynoid obesity. As men are clearly overrepresented in patients with severe COVID-19, it is probable that total fat ratio (on average higher in women) is not the sole criterion. Rather, the gender difference might reflect android fat distribution, more likely detrimental in the context of viral infection, presumably through its higher inflammatory response, and its close vicinity to vital organs (for instance intestinal ACE2 and adipocyte ACE2 in the abdominal region). From the limited data available, it seems that the male prevalence for severity is also true for patient with BMI bellow 25. However, it is important to have in mind that BMI is not a good estimate of the excess abdominal fat mass more often found in male even if their BMI is considered normal. Hence the requirement for better stratification and documentation of COVID-19 patients is urgently needed.

Another main feature of dysfunctional obese adipose tissue is metabolic inflexibility. This concept refers to the physiological alternation of anabolic and catabolic states controlling either energy storage (post-prandially) or lipid mobilization (during fasting) when energy source to other organs is needed. Obese adipose tissue is no more able to physiologically respond to hormones that govern this cycle, as it is mostly insulin-resistant, and less able to contain lipid mobilization, leading to a steady state leak of fatty acids. This in turns promotes ectopic lipotoxicity due to excessive fatty acid exposure of many organs, as a basis for development of obesity-associated comorbidities, especially type II diabetes, fatty liver and cardiovascular diseases. Of note, lipid mobilization by adipose tissue also physiologically participates in global immune activation, as cytokines are potent lipolytic molecules, a process that is thought to provide the energy source to support immune system responses.

3. How can adipose tissue excess or dysfunction be linked to the severity of SARS-CoV-2 infection?

3.1. Indirect links through altered dynamics at the whole body level

Obese patients often have respiratory dysfunction characterized by alterations in respiratory mechanisms, increased airway resistance, impaired gas exchange and lower lung muscle strength and respiratory volume. Increased BMI was shown to gradually predispose to hypoventilation-associated pneumonia, pulmonary hypertension and cardiac stress. Causality between these parameters and COVID-19 severity will be difficult to achieve but correlation might be established in large longitudinal studies as the number of patient has become excessively large in Europe and the USA. This will, however, require some level of standardized information collection of the patient at the hospital level. Therefore, even in the absence of comorbidities of obesity, excess of adipose tissue might predispose individuals to severe COVID-19 outcome. We list below some possible mechanism that might explain this situation (Fig. 1).

3.2. Reservoir for viral production

The possibility that adipose tissue may serve as a reservoir for viral production is another factor that might contribute to the increased risk from COVID-19 for patients with obesity (Fig. 2). The presence of human adenovirus Ad-36, influenza A virus, Human Immunodeficiency Virus, Cyto-MegaloVirus, Trypanosoma gondii, and Mycobacterium tuberculosis in the adipose tissue has been

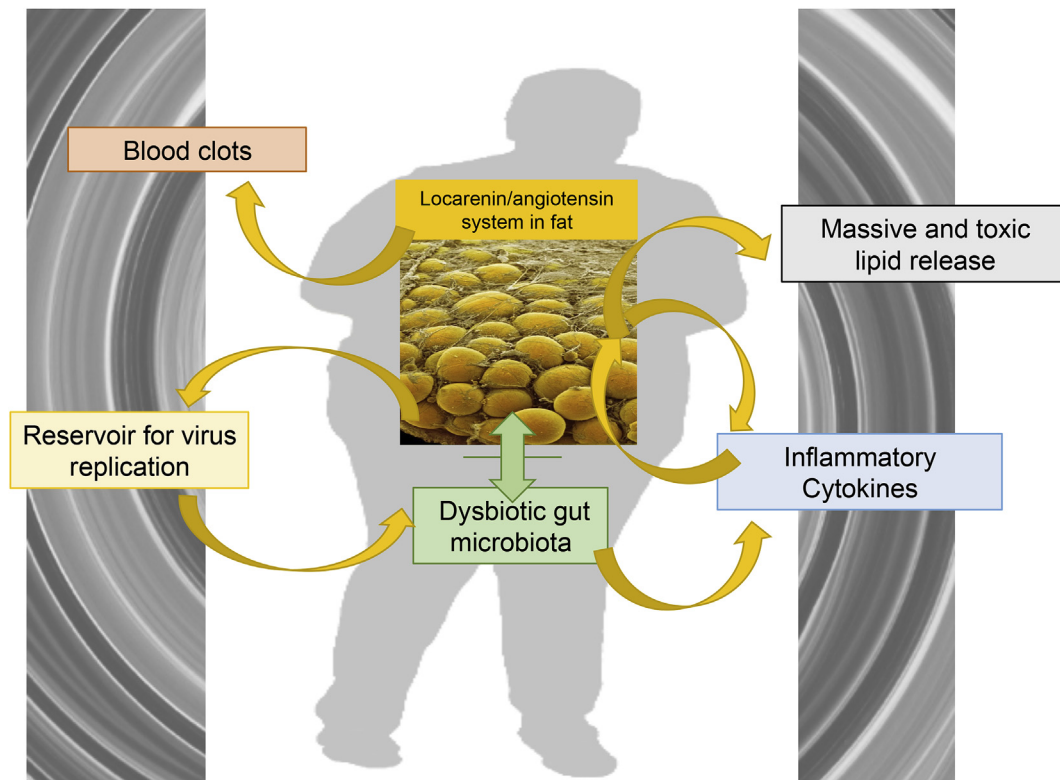An adipocentric view of severe COVID-19 risk in obesity

Fig. 1. An adipocentric view of severe COVID-19 risk in obesity. Schematic representation of possible contributions of adipose tissue excess in disease severity.
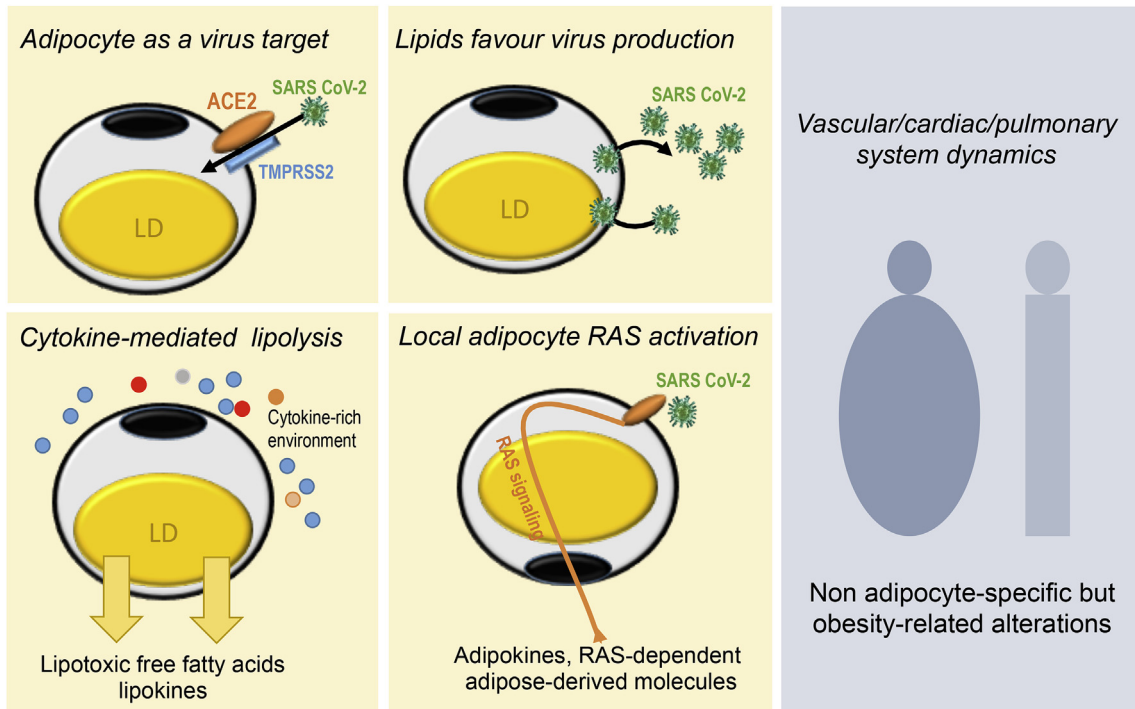

Fig. 2. Overview of possible adipocyte pathways to worsen COVID-19. The left side depicts four scenarios for the possible adipocyte contribution in COVID-19 severity. SARS-CoV-2 virus is shown in green and adipocyte unilocular lipid droplet (LD) in yellow. Pro-inflammatory cytokines released in the blood in response to viral infection are shown as coloured dots. The right side illustrates the importance of non-adipocyte dependent but obesity-related whole body systemic alterations in vascular, cardiac, and pulmonary functions.

reported [31]. Although these observations are poorly documented so far, analogy can be made for COVID-19, but will need to be validated by postmortem analysis. The infection of the adipose tissue by SARS-CoV-2 is supported by observations at the gene expression levels from public databases that adipocytes express ACE2 receptor for SARS-CoV-2 as well as TMPRSS2. The mechanism by which SARS-CoV-2 enters cells is not fully elucidated, but apart from direct fusion of the virus with the plasma membrane, it seems that all different types of endocytosis might be involved [32]. These membrane trafficking events include clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis and phagocytosis. Caveolin-mediated endocytosis is especially interesting to study as caveolae are particularly abundant in adipocytes [33], caveolins participate in adipocyte function [34] and because caveolin was shown to interact with various viral proteins [35]. Further, in obese patients the increased number of adipocytes would increase the pool of infection susceptible cells. Of note, adipose tissue, contains not only adipocytes, but cells of stroma vascular fraction among which adipocyte precursors and macrophages [36]. These latter cells also express ACE2 and represent a potential target of SARS-Cov-2 infection and thus may contribute to increased inflammatory situation. All these aspects of SARS-CoV-2 endocytosis clearly need to be further investigated with modern cell biology approaches such as RNA interference and high-resolution imaging. Further, a still unsolved question relates to how the virus would reach the adipose tissue and be spread from its entry sites, mainly the respiratory and intestinal tracts. In line with the view that adipose tissues located at close vicinity of virus entry sites organs might in turn be infected, a recent study has demonstrated a bacterial signature in mesenteric adipose tissues without apparent blood presence, likely the result of a leak from gut microbiota in diabetic patients [37].

Another possibility is that lipid droplets, which are instrumental in the adipose tissue could provide a platform for virus replication and assembly, as already documented for Hepatitis C Virus which hijacks liver fat for virus production [38]. With regard to the hypothesis that adipose tissue is an infection site for the SARS-CoV-2 virus, it remains to be established if viral loads are indeed proportional to adipose tissue mass in patients. Of interest, it cannot be excluded that during infection, the ACE2 activity decreases leading to increased levels of angiotensin II and thus increased inflammation and pulmonary damage. However, it must be kept in mind that in most cases when the clinical situation rapidly deteriorates the viral load is very low or even undetectable, suggesting that a massive exit from a potential reservoir may not be directly involved.

It is also noteworthy that lipids play a vital role in viral infection and viral life cycle. Indeed, lipids directly contribute to the fusion of the viral membrane to the host cell, to viral replication, and to viral endocytosis and exocytosis [39]. For instance, lipids are key to the formation and function of the viral replication complex, and provide some of the energy required for viral replication. Moreover, specific lipids are required for the formation of double-membrane vesicles needed for viral genome amplification and for the production of viral particles. Viral internalization occurs through endocytosis and viral release from cells occurs through exocytosis both process being tightly regulated by lipids [40]. Of note among these lipids, cholesterol seems to play a particularly important role for numerous viruses. It is therefore possible that lipid availability and lipid metabolism modifications occurring in obese patient also contribute to improve several steps of the virus life cycle and thus to the severity of the disease.

3.3. Chronic inflammatory status generates inappropriate immune response

It is now recognized that obesity and other related metabolic diseases develop in the long term with a state of low-grade chronic inflammation, first limited to the adipose tissue but further extending to many other metabolic organs. A common suggestion to explain overrepresentation of obese patients experiencing a virus induced cytokine storm is that they start with an already challenged immune system, which could explain exaggerated responses (Fig. 2). Immune-related changes in obese adipose tissue have been extensively explored in the last years, because they are thought to be a major origin of insulin resistance in obesity. First recognized was adipose tissue production of pro-inflammatory cytokines [41], followed by studies that discovered more extensive immune changes related to adaptive immunity [42]. In line, the activation of the NLRP3 inflammasome downstream of Toll-like receptors signalling and changes in the proportions and function of lymphocyte subpopulations were reported in many studies [43]. It has been proposed that high fat diet triggers innate immune activation at the expense of adaptive immune response, causing host defence vulnerability towards viral pathogens and chronic excessive cytokine release [44].

Although it is tempting to link the initial state of chronic low-grade inflammation to the severity of COVID-19 in obese patients, some questions remain. Particularly, why other related viruses like SARS-CoV and MERS-CoV, that apparently target very similar cells would not induce aggravation effects in obese patients. Indeed, although low-grade inflammation is a common trait of obesity, to our knowledge, the association between disease severity and obesity is specific to SARS-CoV-2.

The occurrence of a cytokine storm is not restricted to viral infection and can also occur during cancer treatment. In favour of the state of low-grade inflammation in obesity as a factor aggravating cytokine storm outcomes, a study in obese rodent models (ob/ob or diet induced obesity) reported that adiposity could promote lethal cytokine storm after administration of stimulatory immunotherapy regimens in aged mice [45].

3.4. Exaggerated-adipose tissue lipolysis in response to proinflammatory cytokines

Besides the above-mentioned hypothesis that adipose tissue excess could participate in the cytokine storm, the possibility also exists that it could be a site of an inadequate response in face of cytokine afflux (Fig. 2). Indeed, adipocytes respond to cytokines by promoting lipid mobilization, and release large amounts of free fatty acids through activated lipolysis [46]. Although more common lipolytic stimuli are fast or cold stress triggering adrenergic receptors activation, cytokines can also potently stimulate fatty acid release from fat cells [46]. The mechanism of cytokine-mediated lipolysis is likely to involve changes in gene expression, particularly inhibition of the expression of perilipin 1, which is an adipocyte specific lipid droplet coating protein to preserve from lipid degradation by cytoplasmic lipases [47]. Thus, massive cytokine-mediated lipolysis could induce a burst of unbuffered circulating free fatty acids in the blood, with detergent-like properties further aggravating virus-mediated cytolysis. In support of a profound alteration of lipid metabolism in COVID-19 patient a small cohort longitudinal study found that a decrease in low-density lipoprotein (LDL) was positively correlated with the severity of the disease [48]. In agreement with this observation, LDL-cholesterol and total cholesterol levels decreased in a large cohort of patients with

COVID-19 denoting a parallel development of hypolipidemic profile and the severity of COVID-19 [49]. This might reflect metabolic deficiency in liver, the most active lipoprotein producer. Thus more detailed knowledge of blood lipid changes in the course of severe COVID-19 is urgently needed.

3.5. Potential role of adipose-derived products in aggravating COVID-19 infection

The cytokine storm is described as the massive and unrestrained secretion of various cytokines and chemokines by different immune cells such as lymphocytes, monocytes, and macrophages. These cytokines include interferons, IL, growth factors, TNFα and allow cellular communication to boost immune response to fight inflammation. However, the considerable and uncontrolled cytokine secretion may trigger an excessive inflammation leading to extensive damage to vital organs including lung, liver, and kidney. The fact the balance between the different cytokines that are over-secreted varies between patients could explain the heterogeneity of the symptoms seen in severe COVID-19 cases (Fig. 2).

In addition to cytokines, lipokines including the eicosanoid family of inflammatory mediators are also recognized as major player in inflammation and are potentially massively produced by the adipose tissue. Eicosanoids include prostaglandins, thromboxanes, leukotrienes, and hydroxyeicosatetraenoic acids. They are generated from 20-carbon polyunsaturated fatty acids (PUFAs) mostly released from cell-membrane phospholipids by the action of phospholipases, especially phospholipase A_2 [50]. The membrane phospholipids of inflammatory cells and adipose tissue taken from humans consuming Western-type diets typically contain approximately 20% of fatty acids as the omega-6 PUFA arachidonic acid thereby favouring inflammation [44]. On the contrary increased intake of omega-3 fatty acids appears to be anti-inflammatory [51]. The adipose tissue uses lipokines to communicate with distant organs that might play an anti-inflammatory action such as the recently identified 12(13)-diHOME, 12-HEPE and fatty acid—hydroxy—fatty acids (FAHFA) species [52—54]. How these lipids change in severe COVID-19 is presently unknown.

The adipose tissue is largely composed of adipocytes, but is also irrigated and as such it is relatively abundant in blood cells including immune cells that altogether may contribute to an excess of cytokine and lipokine secretion. One possible link between the severity of SARS-CoV-2 infection and the amount of adipose tissue comes from the recent identification that interferon increase ACE2 expression, suggesting the possibility of a positive feedback loop leading to further increased viral production within the adipose tissue [55]. This possibility remains however to be tested.

Apart from the production of proinflammatory molecules, which largely originate from macrophages, and not adipocytes, a diversity of other molecules is derived from fat cells, and the adipose tissue is now recognized an endocrine organ [56]. Among adipose tissue hormones, the potential role of obesity-associated high leptinemia and that of low adiponectinemia in the immune response to SARS-CoV-2 infection is unknown. As abundant producers of Plasminogen Activator Inhibitor-1 (PAI-1) a serine protease inhibitor inactivating urokinase and plasminogen activators, obese adipocytes are also potential players in thrombosis and dysregulated blood coagulation. Interestingly, PAI-1 adipocyte production is higher in visceral adipose depots [57].

Fine-tuning of immune responses is achieved through cohabitation of the host with a community of commensal microbes that participate in the shaping of self-defense to invaders. It is now well established that obesity is associated with gut microbiota dysbiosis, featured by a loss of diversity in bacterial genes, which can be reversed by nutritional intervention [58]. As gut microbes are also active producers of host metabolites, a working hypothesis could be that some of them participate in inappropriate viral responses to SARS-Cov-2 in obesity.

3.6. Adipose tissue contribution through the renin angiotensin system (RAS)

In addition to ACE2, the SARS-Cov-2 virus receptor, several other proteins of the classic RAS are also produced in adipose tissue. These include renin, angiotensinogen (AGT), angiotensin I, angiotensin II, angiotensin receptors type I (AT1) and type 2 (AT2), and angiotensin-converting enzyme 1 [59]. Expression of AGT, ACE, and AT1 receptors is higher in visceral compared with subcutaneous adipose tissue [55]. Thus, the adipose tissue RAS is a potential link between obesity and hypertension (Fig. 2). Whether or not SARS-CoV-2 binding to its ACE2 receptor also modulates angiotensin pathway is presently unclear. Since Angiotensin II can regulate adipose tissue metabolism, particularly by inhibiting lipolysis, a possibility exists that exacerbated response of obese patients might involve local interaction with the adipose tissue RAS system. Furthermore, the adipose tissue RAS regulates the expression of adipose tissue-derived endocrine factors including prostacyclin, nitric oxide, PAI-1, and leptin [60].

More recently, it has been observed in critical care units in charge of patients with COVID-19 that the proportion of smokers were lower that usually observed in the global French population, which led to the hypothesis that nicotine, could decrease susceptibility to viral infection. As a mechanistic basis for this hypothesis, nicotine is known to modulate the RAS system, especially to reduce ACE2 expression through binding to nicotinic acetylcholine receptors or nAChRs [61]. These clinical observations provide further evidence for the importance of the RAS balance, and have raised interest for the prevention of infection by limiting the presence of the cellular receptor for virus entry.

It is also well known that the adipose organ is a reservoir of environmental pollutants known as endocrine disruptors such as persistent organic pollutants, heavy metals, "nonpersistent" phenolic compounds among others. The pollutants exert several dysregulations such as modification of lipid metabolism and increased inflammation. The amount of these pollutants is exacerbated in patients with obesity. Thus one can hypothesize that pollutants might favour virus entry through modifications of membrane fluidity.

Lastly the adipose organ is the largest endocrine organ and links metabolism and immunity [62] and is composed with white and brown adipose tissues that have different functions. White adipose tissue (WAT) is specialized in the storage and release of fatty acids. By contrast, brown adipose tissue (BAT) as well as the beige adipocytes dissipates energy in the form of heat by uncoupling mitochondrial respiratory chain from ATP synthesis. The presence of brown/beige adipose tissue is associated with metabolic health and the amount of brown/beige adipocytes is reduced in obesity and with aging [63,64]. The expression of inflammatory markers is lower in brown than in white adipose tissues, providing further support that brown adipose tissue is generally more resistant to inflammation. It is worth to postulate that overweight and obese patients might be more prone to SARS-CoV-2 infection as they develop low grade infection with adipose tissue macrophages polarized to pro-inflammatory (M1) instead of M2 macrophages (anti-inflammatory) brought by brown and beige adipose tissues.

3.7. Perspectives and avenues for COVID-19 therapies

In addition to the development of an effective vaccine and symptomatic treatments, numerous groups are also working to

develop effective drugs that will target COVID-19 cellular entry, intracellular trafficking and replication. For instance, antibodies such as anti-ACE2 or recombinant soluble ACE2 [65] could be used to block SARS-CoV-2 binding to the receptor. Additionally, TMPRSS2 inhibitors could also be used to prevent SARS-CoV-2 entry into host cells by preventing the priming of the S protein.

These are crucial strategies towards epidemic control in the general population, that require additional time for research before the development of expected treatments and vaccines can be achieved. In the meantime, any approach to reduce intensive care units burden with severe patients is worth considering, and these include identification of high-risk patients among the obese population. This can be permitted by detailed metabolic phenotyping in retrospective studies, to search for traits that can predict disease evolution in face of virus infection. Hopefully some factors have been already identified in recent reports: cytokine levels [66], glycemic control in obese with diabetes [29] that will need to be further defined. In line with the observations reviewed here, identification of an increased severity in influenza infection for obese patient [67], may help identify common or specific features for both cases.

Another aspect that is currently actively looking at is the possibility to train the immune system. In line with this perspective, the BCG vaccine has been postulated to boost immunity against SARS-CoV-2 [68]. Interestingly a recent study reported that polyphenol-rich plant extract prevented macrophage recruitment to adipose tissues and extends the median lifespan of mice models independently of body weight and fat storage [69], suggesting the possibility to improve immunity training through diet. In line with this hypothesis, Mediterranean diet has been proposed to be the base for nutrition to reduce severity of severe COVID-19 [70]. This diet is characterized by a relatively high dietary intake of minimally processed fruit, vegetables, olive oil, whole grains, nuts, and monounsaturated fats, followed by low-to-moderate consumptions of fermented dairy products, fish, poultry, wine, and, lastly, low consumptions of processed and red meats and is generally considered to carry anti-inflammatory properties. Although in the short-term it is difficult to expect important changes in the BMI by switching from Western diet to Mediterranean diet, it may be possible to expect a significant reduction in chronic inflammation. In favour of this possibility is the recent observation that resveratrol may have a protective role by up regulating ACE2, whereas dietary fat may have a detrimental role by down regulating ACE2, arguing for the possible interactions between dietary fat and/or resveratrol and ACE2 gene variations in the modulation of SARS-CoV-2 illness severity [71]. This observation appears rather counter intuitive as ACE2 is necessary for SARS-CoV-2 host cell entry and replication. However knockout of ACE2 or its inactivation in mice after SARS-CoV infection increased acute lung failure severity [72], arguing for a protective effect of ACE2 after its initial permissive action. It is also of note that following SARS-CoV infection, ACE2 expression is down regulated, which may play a causal role in the pathogenesis and disease progression [73].

Other lifestyle interventions, including physical activity, may also prove to be beneficial, not only by improving the general health status of the population, but also indirectly by reducing the deleterious effect of the fat tissue listed in this review. However, the severity of the COVID-19 being also tightly correlated to age, this long-term effect of physical activity may be difficult to reach.

Considering the immunocompromised profile observed during obesity, novel hypotheses are currently tested in a French multi-center clinical trial, which are related to immune stimulation by blocking immune checkpoint. Specific drugs will be tested that target the programmed cell death receptor 1 (PD-1) involved in lymphocyte T exhaustion (see the details on rationale and design of the NIVISCO trial in another article in this issue: Disse et al. submitted to Biochimie 2020).

Lastly, on the basis of the recently published cell protein interaction map with SARS-CoV-2 viral proteins [74], and subsequent identification of novel potentially druggable interactions between cellular and viral components, it is possible that new regulatory pathways in adipose tissue biology engaged in obesity, will be identified. For instance, this large-scale screen pointed out virus interactions with sigma receptors, which are linked to lipid droplet organelles [75,76], but whose function is poorly understood.

4. Conclusion

An important question that clinicians would like to resolve is what are objective factors that influence the severity of the COVID-19 disease. At this moment, we can propose that the initial viral load may play an important role in the capacity of the organism to win the first battle against the COVID-19. The contribution of genetic factors that remain to be identified is also most likely, together with the contribution of prior metabolic health and diabetes conditions. Here we propose that a close investigation of the reason that explain the high prevalence of people with excess of body weight in the severe cases needs to be performed. Another aspect that will be interesting to evaluate is the importance of body weight excess in the recovery of the disease, an increasing number of long-term effects are reported by patients, even after the SARS-CoV-2 cannot be detected. All this is especially important as similar outbreak of viral infection that will target multi-organs including the adipose tissue are likely to occur in the future.

Author contribution

ID, EZA, NV contributed to the conception of the work, collection and analysis of data, writing and editing of the manuscript. All authors have approved the final version of the article.

Declaration of competing interest

None.

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