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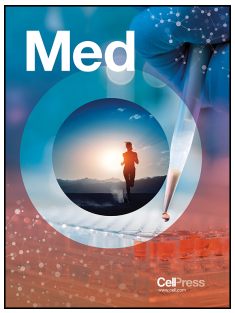

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When two pandemics meet: Why is obesity associated with increased COVID-19 mortality?

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Abstract

A growing body of evidence indicates that obesity is strongly and independently associated with adverse outcomes of COVID-19 including death. By combining emerging knowledge of the pathological processes involved in COVID-19 with insights into the mechanisms underlying the adverse health consequences of obesity, we present some hypotheses regarding the deleterious impact of obesity on the course of COVID-19. These hypotheses are testable and could guide therapeutic and preventive interventions. As obesity is now almost ubiquitous and no vaccine for COVID-19 is currently available, even a modest reduction in the impact of obesity on mortality and morbidity from this viral infection could have profound consequences for public health.

Introduction

Emerging evidence suggests that people with obesity are at increased risk of mortality from Coronavirus Disease 2019 (COVID-19) but the mechanisms underlying this are poorly understood. An improved understanding of the pathophysiological intersection of COVID-19 and obesity should help guide preventive and therapeutic strategies for this vulnerable group. Here we summarise existing knowledge regarding the pathophysiology of COVID-19 and consider how its various components might be exacerbated by the presence of obesity. We end by suggesting some experiments which could inform public health interventions and/or approaches to therapy.

The strong association of obesity with adverse outcomes in COVID-19 is real and relatively specific to a subset of viral pneumonias.

Soon after the emergence of COVID-19 there was a flurry of reports from hospitals around the world drawing attention to an apparent excess of obese patients among those ventilated [5, 10, 12, 45, 62]. More recently, preprints have appeared which report much larger and more rigorous epidemiological investigations. OpenSAFELY examined 5683 COVID-19 deaths in the UK and related these to pre-existing potential risk factors documented in over 17 million electronic health records [72]. As in all studies to date, age was the most important pre-existing risk factor, but the effect of obesity was highly significant and graded according to the severity of the obesity. The hazard ratio (adjusted for ethnicity) for death for those with Class III obesity (Body Mass Index (BMI) >40kg/m2) was as high as 2.28 (1.96-2.65). The ISARIC study of 16,749 COVID-19 related admissions to Intensive Care Units in the UK reported a lower hazard ratio of 1.37 (1.16-1.63) associated with clinician-reported obesity [19]. It should be noted, however, that BMI was not reported in this study and reliance on clinical diagnosis is known to seriously underdiagnose obesity [53].

In an analysis of COVID-19 mortality in over 300,000 patients with diabetes, obesity was associated with mortality in both type 1 (T1D) and type 2 diabetes (T2D) [36]. Taken together with myriad smaller studies it seems increasingly clear that obesity does indeed increase the risk of mortality and of requiring admission to Intensive Care in people infected with SARS-CoV-2. In contrast to worse outcomes once an obese person is infected, there is currently no evidence that obesity has a significant impact on the risk of becoming infected by the virus in the first place.

Is there something about infection with the SARS-CoV-2 virus that interacts so adversely with the obese state, or does being obese have a similar impact on other forms of viral pneumonia? Although obesity has been associated with an increased risk of hospitalisation in seasonal influenza, a study of almost 10,000 cases of seasonal influenza in the USA did not find any evidence of obesity as a risk factor for requiring mechanical ventilation or death [6]. In contrast, it seems clear that during the 2009 H1N1 influenza pandemic, which largely spared the partly immune elderly, obesity was a strong risk factor for adverse outcomes [51]. The role of obesity in severity of SARS-CoV-1 and MERS-CoV, other pandemic coronavirus infections with poor outcomes, has not been thoroughly examined. The Acute Respiratory Distress Syndrome (ARDS) has some pathophysiological similarities to COVID-19 pneumonia. While obesity has been reported to increase the risk of developing ARDS of a variety of aetiologies [32], it has been reported to be associated with increased survival rates, something that has come to be known as the ARDS obesity paradox [67]. Thus, the association of obesity with worse outcomes in acute lung infection or widespread alveolar damage of other types, appears to be strongest and most consistent with COVID-19 and pandemic H1N1 influenza.

What are obese patients with COVID-19 dying from?

The majority of COVID-19 patients die having required artificial ventilation for hypoxemic respiratory failure due to COVID-19 pneumonia [59]. Emerging post-mortem histopathology of the COVID 19 lung offers insights into the underlying pathophysiology. Briefly, there is evidence of diffuse alveolar damage, as in other forms of viral pneumonia, but sometimes this is patchy [2, 48]. What is striking, and shared to a degree with the pathology of pandemic H1N1 influenza [2], is the extent of pulmonary capillary microangiopathy which is considerable and near universal, at least in some series [9]. Complement deposition has also been observed in the endothelium in association with the formation of microthrombi [44]. This suggests that COVID-19 may lead to a state of alveolar hypoperfusion due to a microthrombotic pulmonary angiopathy. The frequent finding of elevated levels of fibrin D-dimers in a large proportion of hospitalised patients is consistent with a thrombotic process, as is the frequent occurrence of venous thrombosis and pulmonary emboli during the course of the illness [16, 35]. The clinical characteristics of COVID-19 pneumonia are still being defined but in early reports from European centres a substantial proportion of ventilated patients were reported to have preserved pulmonary compliance with well aerated lungs, suggesting that hypoxia is being driven by microvascular dysfunction [29, 30]. Reports of CT based lung perfusion imaging supports this [40]. However, a subsequent larger study from the USA described a cohort of patients with respiratory mechanics more in keeping with classical ARDS [24]. Finally, patients who are seriously ill with COVID-19 have evidence of high levels of inflammation with high CRP and circulating pro-inflammatory cytokines [11]. Indeed, it has been suggested that a hyperinflammatory response, occurring downstream of a vigorous activation of either adaptive or innate immunity, or both, may drive the underlying pathophysiological process [47] and IL-6 antagonists are being trialled in severely ill patients [65].

Pathophysiological mechanisms mediating the adverse effects of obesity

Obesity is associated with a wide range of adverse health outcomes with diverse underlying pathogenic processes. For some, e.g. sleep apnoea and reflux oesophagitis, the expanded mass of adipose tissue itself is directly and mechanically contributing to the disease. T2D is one of the commonest sequelae of obesity. An increase in circulating insulin levels in both fasting and post-prandial state is one of the earliest metabolic disturbances associated with obesity and it is due to impaired insulin action, principally in liver and skeletal muscle [57]. This “insulin resistance” clearly predisposes to developing T2D, which ensues when beta cell compensation fails.

The mechanism whereby chronic over-nutrition leads to insulin resistance appears to primarily involve not the expanded adipose tissue itself, but the additional excess nutrient that is stored ectopically in the major insulin responsive tissues, muscle and fat [41]. An alternative hypothesis suggests that adipose tissue inflammation contributes directly to insulin resistance in obesity. Inflammation undoubtedly occurs in obesity however it has less compelling underpinning support from human genetics or human pharmacology [52].

How might the metabolic state of obesity intersect with and exacerbate pathological mechanisms in COVID-19?

Enhanced production of cytokines. A corollary of storing excess fat in non-adipose tissue is that the adipose tissue has reached or is reaching the limits of its ability to store fat safely. Thus, in adipose tissue biopsies from obese, insulin resistant people, one frequently sees an excess of dead and dying adipocytes, often accompanied by an excess of infiltrating macrophages, usually arranged in crown-like structures [13]. These macrophages are activated and contribute to the production of a systemic

pro-inflammatory state, characterised by increases in circulating levels of cytokines such as TNFα, IL6 and IL1β [46, 66]. Lipotoxic damage to other cells such as hepatocytes can also contribute to the enhanced inflammatory state. If increased inflammation contributes to alveolar damage, then this provides an obvious potential route whereby the metabolic risk factors could drive increased mortality.

Altered adipose tissue hormones Adipose tissue expansion not only results in elaboration of inflammatory cytokines, but also changes the profile of secreted hormones. A key signature of insulin resistance is an increase in the ratio of circulating leptin and adiponectin [24]. Obesity is associated with higher circulating leptin and lower circulating adiponectin. There is some literature associating high leptin levels with pulmonary inflammation but this is not, as yet, compelling (24, 25). There is, however, a growing body of evidence more securely implicating adiponectin as an anti-inflammatory agent [61]. Notably, adiponectin-deficient mice develop inflammation of the pulmonary vasculature [63] and are predisposed to experimental acute lung injury [39] suggesting that the hypoadiponectinemia frequently seen in obesity could facilitate an exaggerated inflammatory response directed to pulmonary capillaries. In addition to being lower in obesity and most insulin resistant states it is worth noting that adiponectin levels have been reported to be significantly lower in many of the COVID-19 "at risk" groups e.g. Male < Females [20] and South Asians < White Europeans [1, 20]. Perhaps most interesting is the finding that, at equivalent levels of body fat, black people also tend to have lower levels of adiponectin than white people despite having no more insulin resistance and a lower propensity to store fat ectopically [8]. However, it should be noted adiponectin levels tend to rise after the age of 70 [3, 14], and old age is by far the biggest risk factor for COVID-19 mortality. However, it is possible that different causal pathways may mediate the risk of age vs obesity on COVID-19 severity.

Complement components Gralinski et al. [33] recently reported that mice lacking C3, the central component of the complement system, were protected against severe disease when infected with a mouse adapted SARS-CoV-1 virus. The role of complement in human COVID-19 has not yet been well studied but immunohistological examination of lungs and skin lesions from affected patients show deposition of components of the alternative and lectin complement pathways [44]. Moreover, the N-protein of SARS-CoV-2 can activate the lectin pathway [28] and aberrant activation of complement is clearly implicated in a subgroup of thrombotic microangiopathies suggesting complement could play a causal role in the microthrombosis observed in COVID-19 [7].

Adipocytes are a major source of several of the components of the complement system complement proteins [71]. Levels of some of these (e.g. C3, C3a, CFD and Properdin) are increased with increasing adiposity [74]. Circulating levels of C3 are positively associated with insulin resistance, independent of adiposity [73]. Given the existence of amplification loops in the complement pathway it is conceivable that modest elevations of complement components in obesity could serve as a nidus for microthrombosis and/or pathological inflammation and mediate poor outcomes in obesity, as has been suggested by others [31].

Thrombosis Venous thromboembolism rates are much higher in patients with severe COVID-19 than historical critically ill controls and there is growing evidence of high rates of thrombotic microangiopathy in severe COVID-19 [16, 35]. Obesity is an established risk factor for arterial and venous thrombosis and dysfunction of the endothelium, platelets, fibrinolytic system and the clotting cascade have all been implicated [70]. For example, Plasminogen Activation Inhibitor-1 (PAI-1) is secreted from adipose tissue, associated with insulin resistance and likely contributes to thrombotic risk in obesity by impairing fibrinolysis [23]. In addition, obesity is associated with increased thromboxane metabolites and mean platelet volume (both validated indices of platelet activation)

that normalise with weight loss [15, 18]. Notably, obesity is a robust risk factor for the development of thrombocytopenic thrombogenic purpura [69] with one group suggesting increased circulating antibodies to ADAMTS13 in the obese [42, 76].

Vasculature The role of the vasculature, particularly the endothelium, in the pathogenesis of COVID-19 has recently been highlighted [34, 64]. In a comprehensive analysis of ACE2 (the SARS-CoV-2 receptor) expression in the human vasculature the highest expression was found in the pericytes of heart and brain (but not the lung) with little in endothelial cells [34]. It was proposed that microvascular dysfunction associated with obesity or type 2 diabetes could permit viral passage across the endothelium to infect pericytes, with their dysfunction promoting subsequent endothelial activation and microthrombosis [34]. The effects of diabetes on endothelial barrier function is well established [56] and there is evidence from studies of large animals that endothelial permeability is increased in obesity [27].

Dysfunction of the systemic microcirculation is well described in obesity and the metabolic syndrome [68]. While the effects of obesity on the pulmonary circulation are less studied, there is emerging evidence of a pulmonary vascular dysfunction associated with obesity. In a rodent model of obesity pulmonary resistance vessels were resistant to agonist and hypoxia induced vasoconstriction *ex vivo* compared to lean controls [50]. If the vasoconstrictive response to hypoxia is impaired in the human pulmonary vasculature then this could potentially exacerbate shunting in COVID19 pneumonia, thus contributing to hypoxia.

Alveolus The key functional unit of the lung is the alveolar-capillary unit. Key cells include type 1 pneumocytes (AT1) separated from capillary endothelial cells by a fused basement membrane and the less numerous type 2 pneumocytes (AT2) that produce surfactant and serve as alveolar progenitors. ACE2 is the proposed receptor for SARS-CoV-2 and in the alveolus it is expressed predominantly (if not solely) by AT2 [34]. Critical to gas exchange and pulmonary function, the alveolar capillary unit is the primary site of injury in COVID-19. Understanding how obesity interacts with pre-morbid alveolar function and injury may guide pre-emptive therapeutic intervention.

Circulating Surfactant proteins A and D have been shown to be increased in patients with obesity and Type 2 Diabetes [21, 43], assuming these proteins are expressed only in the lung and secreted to the apical membrane, and this suggests that obesity may affect the integrity of the alveolus. The science of ectopic fat has largely focused on the liver, muscle and heart, where a large body of evidence clearly describes the adverse consequences to these tissues of a chronic excess of intracellular lipid. More recently, however, work is emerging suggesting that, in states of over-nutrition, ectopic lipid can appear in cells of the pulmonary alveolus resulting in ultrastructural abnormalities and altered surfactant production [25]. Genetic enhancement of endogenous lipid synthesis specifically in mouse AT2 cells results in alveolar inflammation [54]. Remarkably, AT2 cells of aged mice were noted to demonstrate similar gene expression changes to these mice and also exhibited increased lipid content [4] suggesting that “fatty lung” could potentially be a common causal pathway whereby both obesity and age worsen COVID-19 pathology. Similarly, genetic deletion of the lipid sensor Liver X Receptor (LXR) resulted in accumulation of lipid in type 2 pneumocytes and, subsequently, pulmonary inflammation and foam cell accumulation [17].

Some testable hypotheses and their potential implications for interventions

Insulin Resistance, not fat mass, is key to the link between Obesity and poor COVID Outcomes

If true, this is important, as even short-term low calorie diets can improve insulin sensitivity within days [38]. Human genetics should ultimately come to our aid here as meta-analysis of Genome Wide

SNP data from COVID victims throughout the world can be undertaken to examine whether the genetic risk scores for insulin resistance are better predictors of outcome than those for obesity *per se*. In the meantime, animal models of SARS infection might be able to provide some early information through the examination of effects of insulin-lowering and insulin-sensitising medications. Some commentators have argued that as it is difficult for obese patients to attain normal weight then there is not much that can be done given the rapid spread of the COVID-19 pandemic. However, if improving insulin sensitivity reduces risk then even a modest amount of caloric restriction, combined with physical activity and perhaps an insulin sensitising/lowering drug such as metformin, may provide a way of reducing risk of death for the large number of at risk obese people

Low circulating levels of adiponectin predispose to aggressive pulmonary inflammation and explain why obese people fare worse with COVID-19

Again, human genetics will be able to help us test this hypothesis as there are genetic instruments which explain quite a high proportion of the variance in serum adiponectin [58]. Agonists of the nuclear receptor PPARγ, such as the thiazolidinedione class of drugs rapidly and markedly increase circulating levels of adiponectin. Examination of the effects of PPARγ agonists on disease outcome in obese animal models of COVID-19 could provide helpful insights. Pioglitazone is licensed for us in T2D worldwide and cheap generic formulations are now available for large scale clinical trials.

Ectopic lipid in alveolar Type 2 cells influences the extent of alveolar damage due to COVID-19

SARS-CoV-2 causes pneumonia by first entering the AT2 through ACE2 which is abundantly expressed on their surface. These cells are lipid rich, storing polar lipids in lamellar bodies, and their structure, and possibly function, are influenced by diet and obesity, at least in animal models [25, 55, 75]. Experiments should be undertaken to examine the effects of lipid content of cells on ACE2 expression, viral uptake, replication and release. Some viruses e.g. Hepatitis C seems entirely reliant on intracellular fat droplets to facilitate its movement around a cell [49]. Viral infections of cells frequently lead to a rapid switch from oxidative phosphorylation to aerobic glycolysis, the so called Warburg effect [60]. Ectopic lipid in cells elsewhere is known to be associated with metabolic inflexibility [26], the inability to shift rapidly between fat and carbohydrate metabolism. Might AT2 cells that have excess lipid be less able to switch to aerobic glycolysis and thus be more prone to cell death during viral infection? Indeed, in mice, diet-induced obesity is associated with downregulation of fatty acid synthase (*Fasn)* in lung and genetic deletion of *Fasn* in AT2 cells impairs induction of glycolysis in response to hyperoxic stress *in vitro* and predisposes to acute lung injury in mice [55]. Though unproven, it is likely that ectopic lipid in lung will start to reduce quickly after people go into negative energy balance, so that modest changes in diet and exercise may be have benefit.

Conclusion

In summary, we have applied insights into the pathophysiology of the adverse consequences of obesity and emerging evidence regarding the pathological mechanisms in COVID-19 to suggest possible routes whereby obesity can exacerbate the tissue damage associated with infection by the SARS-CoV-2 virus. These hypotheses suggest several tractable experiments in cells, animals and humans, some of which we are undertaking and which we encourage others to pursue. Obesity is a notoriously difficult condition to "cure" and this may explain why widespread public health messaging about weight loss in the obese as a preventive measure to reduce COVID-19 mortality has not been vigorously pursued. If obesity is exerting its effects on COVID-19 outcome through its metabolic sequelae, such as insulin resistance, then those abnormalities start to improve very

rapidly when energy intake drops below energy expenditure. In addition to its effects on energy expenditure, regular physical activity, even of moderate intensity and duration can also improve insulin sensitivity and lower circulating insulin levels [37]. The potential implications for unintended adverse consequences of intense COVID-19 "lockdown" strategies that limit opportunities for exercise are obvious.

Given how rapidly large trials of a wide variety of pharmacological agents in COVID-19 are currently being undertaken (some with a rather tenuous rationale [22]) it should be possible to consider undertaking trials of simple interventions in people with obesity either before or immediately after the onset of COVID-19 symptoms. These could involve diet and exercise intentions that do not aim for unrealistic amounts of weight loss but would be designed to ameliorate insulin resistance. These interventions could be supplemented by drugs that assist in modest weight loss and lower circulating insulin, such as metformin or SGLT2 inhibitors, or agents that improve insulin sensitivity, reduce ectopic lipid and increase circulating adiponectin, such as pioglitazone. Such approaches would also be applicable to T2D, another condition which predisposes to increased mortality from COVID-19 [19, 36, 72]. In the majority of T2D cases, obesity precedes and contributes to the development of diabetes through inducing compensatory hyperinsulinemia, necessitated by insulin resistance, which eventually exhausts the ability of genetically vulnerable pancreatic beta cells to maintain insulin production. There is evidence that, in both T1D and T2D, the level of glycaemia is related to COVID-19 outcomes [36, 77]. We urgently need to know if the intensification of glycaemic control using an approach which sensitises patients to insulin would provide benefits to the COVID-19 infected T2D patient that are greater than those achieve by approaches that increase levels of circulating insulin, either through exogenous injection or the stimulation of endogenous secretion.

Obesity affects a very large proportion of the population of most developed and developing countries. Understanding the nature of the link between chronic positive caloric imbalance and COVID-19 pathology could provide novel avenues to reduce the death toll produced by this dangerous new viral infection. Funding agencies will need to foster the interdisciplinary approaches that will be required to respond to this new biomedical challenge which lies at the intersection between traditional disciplines.

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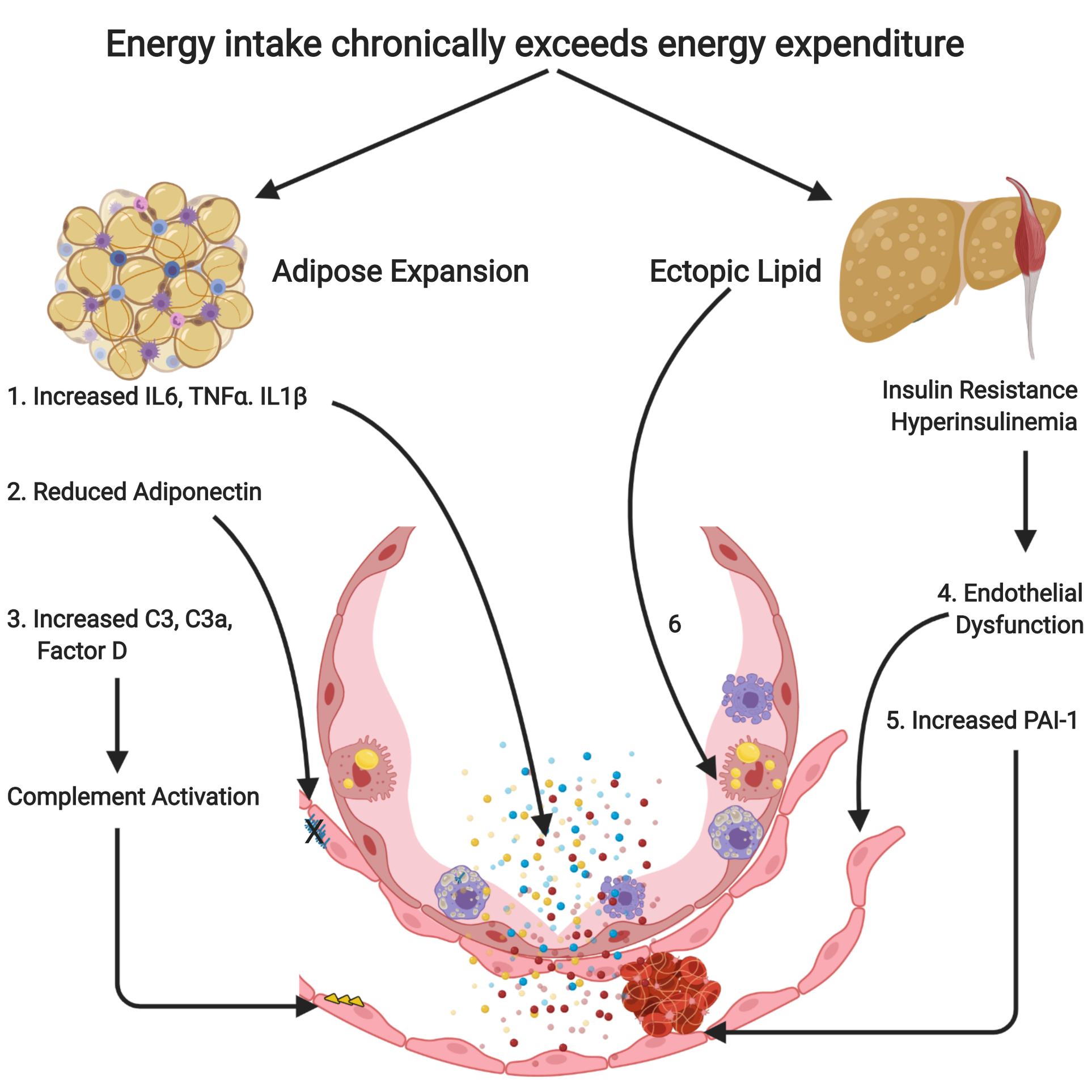
Figure Legend

Obesity exacerbates COVID-19: Potential Mechanisms

Obesity is a disorder of energy balance that ensues when energy intake exceeds expenditure. Adipose tissue expansion occurs to safely store excess energy safely in triglyceride rich lipid droplets. This process is associated with adipose tissue inflammation and elaboration of pro-inflammatory cytokines, increased components of the complement system and altered adipose tissue hormones. 1) Increased inflammatory cytokines are secreted into the systemic circulation and can act on the alveolar capillary unit to potentiate the inflammatory response to SARS-CoV-2 infection. 2) Adipose tissue expansion is associated with a reduction in Adiponectin secretion from the adipose tissue that is that at least partly driven by systemic insulin resistance. Mouse studies suggest adiponectin is abundant in the pulmonary endothelium in the healthy lung and adiponectin deficiency results in pulmonary vascular inflammation and pre-disposes to experimental lung injury. 3) Increases in circulating complement components elaborated from adipose tissue occur in expanded adipose and in association with insulin resistance and could pre-dispose to complement activation and subsequent thrombotic microangiopathy. When the capacity for adipose tissue to expand is exceeded lipid is deposited in other organs. Lipid deposition in skeletal muscle and liver likely plays a causal role in the development of insulin resistance and hyperinsulinemia. 4) Systemic insulin resistance is associated with endothelial dysfunction that may pre-dispose to thrombosis and contribute to lung injury via vascular inflammation and enhanced endothelial permeability. 5) Insulin resistance is robustly associated with increased plasminogen activator inhibitor-1 (PAI-1) which impairs fibrinolysis and may contribute to risk of thrombosis in COVID-19. 6). Finally, ectopic lipid may actually be directly deposited in type 2 pneumocytes pre-disposing to lung injury in SARS-CoV-2 infection.

eTOC Blurb

Obesity is associated with increased COVID-19 related mortality. Lockhart and O'Rahilly review the pathophysiological mechanisms that may underlie this link and converge on a set of testable hypotheses to guide investigation of the effects of obesity on COVID-19.


Energy intake chronically exceeds energy expenditure
Adipose Expansion
Ectopic Lipid
Insulin Resistance
Hyperinsulinemia
1. Increased IL6, TNFα. IL1β
2. Reduced Adiponectin
3. Increased C3, C3a,
Factor D
Complement Activation
6
4. Endothelial
Dysfunction
5. Increased PAI-1