COVID-19 and obesity

There is mounting evidence that obesity is a major risk factor for severe illness and mortality from COVID-19. There is an urgent need for research to elucidate the mechanisms by which obesity contributes to the severity of COVID-19 illness, in order to identify potential targets for treatment. In this report, the authors analyse key factors which influence the relationship between COVID-19 and obesity.

From early analyses of coronavirus patients in China, it was quickly established that older adults and people with underlying health conditions, particularly diabetes, hypertension, cardiovascular disease and respiratory diseases, are at greater risk of becoming severely ill with COVID-19.1,2 When the virus later spread to Europe, it quickly became apparent that a disproportionate number of people with overweight and obesity were also being hospitalised and becoming ill or critically ill. This was first noted in Italy, then in the UK, the US and France.3–5

More recent studies have demonstrated that obesity’s association with COVID-19 severity is only partly due to the fact that it is a risk factor for other comorbidities. An analysis of more than 20,000 hospitalised patients in the UK identified obesity as a major independent risk factor for COVID-19 severity and mortality,6 and two recent studies of hospitalised patients in China, the UK and the US and France.3–5 demonstrated that obesity is an independent risk factor, concluding that patients with obesity are three times more likely to develop severe symptoms compared with normal-weight patients.7,8 and each unit increase in body mass index was associated with a 13% increase in the risk of severe COVID-19.7

Given the high prevalence of obesity across the globe, and the fact that the virus is likely to be present in our populations for some time to come, we urgently need to clarify the relationship between obesity and severity of COVID-19, identify the underlying mechanisms and develop strategies to reduce the impact of the disease on people with excess weight. As yet there are more questions than answers, but the impact of obesity on immune function and inflammation is likely to be an important factor.

Obesity and respiratory function

The increased vulnerability of patients with obesity might have been predicted, in view of the research into the 2009 influenza A H1N1 pandemic, which showed they had twice the mortality rate of people with normal weight,9 and the mounting evidence that obesity increases the risk of respiratory diseases and respiratory tract infections, including obesity hypoventilation syndrome, asthma, pulmonary embolism, influenza and community acquired pneumonia.10–13

Obesity negatively impacts respiratory function and resistance to respiratory infections by affecting both lung function and immune function. The presence of large fat deposits around the chest and upper abdomen causes altered lung mechanics such as increased airway resistance, impaired gas exchange, and reduced lung volume and muscle strength, which can predispose to increased risk and severity of respiratory infections.14 However, it is the immunomodulating effects of excess visceral adipose tissue (VAT) in the abdominal cavity which is being increasingly recognised as the most important factor in the link between obesity and respiratory infection, despite the exact mechanisms not being fully understood.10

Adipose tissue

Through the secretion of adipokines, such as adiponectin and leptin, adipose tissue modulates innate and adaptive immune responses. When VAT becomes dysfunctional in obesity, secretion of adiponectin is reduced and leptin increased, resulting in immune dysregulation.15,16 One important outcome of this, in relation to viral infections like COVID-19, is the reduction in Natural Killer (NK) cell activity. NK cells are important in both the initial innate immune response to viral infection and then in clearing the virally infected cells.17

Another result of dysfunctional VAT is increased production of pro-inflammatory cytokines, resulting in low-grade systemic inflammation.18 This inflammatory state is implicated in the cardiometabolic complications and comorbidities associated with obesity, and may also partly explain the severity of COVID-19 in patients with obesity. It has been suggested this chronic activation of the inflammatory response could contribute to the aggressive inflammatory response which is strongly implicated in the respiratory failure that causes the majority of COVID-19 fatalities. It could also underpin the ‘cytokine storm’ and symptoms of sepsis that characterise a significant number of COVID-19 deaths. In these cases, uncontrolled inflammation inflicts multi-organ damage leading to organ failure, especially of the cardiac, hepatic and renal systems.19

It has also been suggested that visceral adipose tissue may act as a ‘reservoir’ for COVID-19. Adipose tissue expresses the protein ACE220 which is the entry point for the SARS-CoV-2 virus into cells, so it is feasible the virus could infect visceral adipose tissue. Adipose tissue has been reported to act as a reservoir for a number of other viruses, including human adenovirus AD36, Influenza A and HIV.21 If this were the case for SARS-CoV-2, adipose tissue would then become a reservoir for more extensive viral spread, increased viral shedding, immune activation, cytokine amplification and systemic tissue damage.22 It is important to state, however, that there is no evidence as yet of direct infection of adipose tissue by SARS-CoV-2 virus.

Vitamin D

Another potential contributor to immune dysregulation in COVID-19 patients is vitamin D deficiency, which is associated not just with obesity, but also diabetes and hypertension.23,24 Vitamin D plays an essential role in glucose homeostasis,
insulin sensitivity and regulation of adipokines and immune function, so deficiency of the vitamin could be involved in mediating inflammation and insulin resistance associated with obesity and type 2 diabetes. What makes vitamin D particularly relevant to COVID-19 is its ability to regulate and suppress the cytokine response of respiratory epithelial cells and macrophages to various pathogens, including respiratory viruses. It could therefore be very important in preventing the excessive cytokine release and subsequent inflammation and respiratory failure that is commonly seen in COVID-19 mortality.

The reason for the strong association between obesity and vitamin D deficiency is unclear, but the leading theory is that dysfunctional adipose tissue in obesity sequesters vitamin D and impairs its release, so it is no longer bio-available. People with obesity therefore need to produce or consume more vitamin D than people of normal weight in order to maintain adequate circulating levels of the vitamin. The primary source of vitamin D is endogenous synthesis under the skin following exposure to UVB radiation from sunlight, so individuals who get insufficient sunlight are at risk of vitamin D deficiency. This is a particular issue during winter in countries further from the equator, when sunlight has insufficient UVB for vitamin D synthesis.

It is therefore interesting to note that the current coronavirus pandemic took hold at the end of winter in the northern hemisphere, the time of year when vitamin D status is at its lowest. What’s more, the European countries most affected by the virus, Spain, Italy and the UK, all have high rates of vitamin D deficiency. It is notable that all have high rates of vitamin D deficiency and disease rates of different ethnic groups. There is mounting evidence that obesity is a major risk factor for severe illness and mortality from COVID-19. Research is urgently needed to elucidate the mechanisms by which obesity contributes to the severity of COVID-19 illness, in order to identify potential targets for treatment. Existing evidence suggests obesity dysregulates innate and adaptive immune function and increases pro-inflammatory cytokine production, which could contribute to the excessive inflammatory response associated with severity and mortality of COVID-19.

Vitamin D deficiency can contribute to immune function dysregulation, so could play a role in COVID-19 severity. People with obesity, of advanced age and of BAME heritage, are all at elevated risk of vitamin D deficiency, so these groups should be advised to get
daily sun exposure in summer months, eat oily fish and supplement 1000 IU vitamin D daily, while this is investigated.

Individuals with obesity, particularly those with other comorbidities or from BAME backgrounds, should be advised to take extra care to avoid infection with SARS-CoV-2. Health and social care workers in these categories should be afforded the protection they merit, as key workers at higher risk from COVID-19, from their employers.

While it is vital we understand as much as possible about this new virus and learn how we might be able to minimise the impact of this and future outbreaks, it is arguably even more important to renew and re-ignite our efforts to tackle obesity. We need to reduce obesity rates, not just to help limit the impact of future pandemics, but also to reduce the devastating effects of cardiovascular disease, type 2 diabetes and other obesity-related illnesses on the health and well-being of the millions of people with obesity, and ease the burden these diseases place on our health care systems.

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KEY POINTS
- Mounting evidence suggests obesity is a major independent risk factor for severe illness and mortality from COVID-19
- Dysfunctional adipose tissue, systemic inflammation and immune system dysregulation may contribute to the aggressive inflammatory response and/or ‘cytokine storm’ associated with COVID-19 fatalities
- Obesity is a risk factor for vitamin D deficiency, as are advanced age and black or Asian heritage
- Research is required to elucidate the mechanisms by which obesity contributes to COVID-19 illness and what part vitamin D deficiency might play in disease severity

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