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 Chinese COVID-19 patients also identified obesity as 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 ACE2[20] 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,[25,26] 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.[25] 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.[26] 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.[27] What's more, the European countries most affected by the virus, Spain, Italy and the UK, all have high rates of vitamin D deficiency.[28] It is notable that Scandinavian countries have lower COVID-19 infection rates, despite being even further north and getting less sunlight. However, these countries are acutely aware of possible vitamin D deficiency and therefore eat foods fortified with the vitamin and have a diet traditionally rich in oily fish, especially herring, which is the richest food source of vitamin D. A cross-sectional analysis of countries in Europe has shown a statistically significant correlation between population vitamin D levels and COVID-19 cases and deaths.[29] Furthermore, researchers at Northwestern University in the US analysed data from hospitals across China, South Korea, Iran, the US and Europe. They found that patients from countries with high mortality rates, such as Italy, Spain and the UK, had lower levels of vitamin D compared to patients in countries that were not as severely affected, and a possible correlation between low vitamin D status and raised C-reactive protein, which they argued is a surrogate marker for hyper-inflammation or 'cytokine storm'.[30] The use of retrospective data and population averages for vitamin D status, and a surrogate marker for cytokine levels means these results must be interpreted with caution, but add more weight to the argument for urgent research into the links between vitamin D and COVID-19.

Routine vitamin D screening could be introduced for hospitalised COVID-19 patients, to establish whether there is a link between vitamin D deficiency and disease severity, and to provide the opportunity to correct any deficiencies as part of treatment and prevention measures.

BAME

Vitamin D deficiency could also partly explain the disproportionate number of people from black, Asian and minority ethnic (BAME) heritage who are succumbing to COVID-19 in the UK. People with darker skin colour who live in northern European countries are at even greater risk of vitamin D deficiency than the white population, because they absorb less UVB radiation.[31]

People from BAME backgrounds constitute 14% of the UK population but, according to a recent analysis, account for 33% of critically ill COVID-19 patients and a similar percentage of all COVID-19 cases.[32] Looking at the COVID-19 statistics for health and social care workers, the picture is quite shocking. Of all staff employed by the NHS, approximately 21% are from BAME backgrounds, including approximately 20% among nursing and support staff and 44% among medical staff,[33] but analysis of 119 fatalities among health and social care workers revealed tht 63% of nurses, 64% of support staff and 95% of medical staff deaths were of BAME heritage.[34]

The recent Public Health England report, on disparities in the risk and outcomes of COVID-19, revealed that deprivation partly accounts for increased BAME deaths, but after adjusting for deprivation the mortality rate for Bangladeshis is still double that of the white British population, and for other ethnic minorities 10–50% higher.[35] The report highlighted the fact that these analyses did not take account of obesity, comorbidities or occupation. The black African/Caribbean populations have the highest rates of obesity and hypertension of all ethnic groups in the UK,[36] while black and Asian populations have three to five times the prevalence of type 2 diabetes compared to the white population, and are diagnosed on average 10–12 years younger.[37] Obesity and comorbidities are therefore likely to have a significant impact on the COVID-19 mortality rates of different ethnic groups.

Conclusion

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,[27] 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-invigorate 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.

Nigel Hinchliffe, BSc (Hons), MSc, Director of Education, College of Contemporary Health, London, UK
Valerie Bullen, BSc (Hons), MSc, FRSM
Professor David Haslam, MB BS, DGM, FRCPEdin, General Practitioner, Bariatric Physician, UK
John Feenie, BSc (Hons), MBA, Founder and CEO, College of Contemporary Health, London, UK

Correspondence to: email: nigel.hinchliffe@contemporaryhealth.co.uk

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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