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Letter to the Editor

Obesity and COVID-19: renin–angiotensin as a mediator of morbidity and mortality

The strong link between visceral adipose tissues and both cardiovascular deaths and cancer is well known. It is also known that obesity both increases the risk of acute respiratory distress syndrome, the main cause of COVID-19 mortality[1], and mortality from influenza, another virus with severe respiratory manifestations[2], possibly through impairments in innate and adaptive immune responses[3] among other potential pathways[4]. Recently, Popkin *et al.* found that individuals with obesity had a significantly higher rate of death (48 % increase (OR = 1·48, 95 % CI 1·22, 1·8, $P < 0·001$)), amongst other increased severe morbidity risk in COVID-19[5].

Considering both the exponential rise in the number of cases of COVID-19 globally and the rise in the prevalence of individuals with obesity, understanding the mechanism of obesity and COVID-19 mortality is essential to ensure that appropriate therapeutic options are available to treat this disease.

Mechanistically, there are a series of fundamental pathophysiological issues associated with COVID-19 that are worse with obesity. At its core, SARs-CoV-2 targets a key element of the renin–angiotensin system (RAS) to gain human entry and in doing so dysregulates inflammation hemostasis. Over 30 years ago, Cassis *et al.* demonstrated the presence of expression of angiotensinogen in adipose tissue[6]; subsequently, the expression of the angiotensin (Ang)-converting enzyme in human adipose tissue was established[7]. Of fundamental importance is the observation that the expression of ACE2, the target for SARs-CoV-2 has a high expression in subcutaneous adipose tissue and may be the driver of greater infection severity with excess adiposity[8].

In addition to the heightened activity of the RAS in obesity, recent discussion has included analysis of the effect of obesity and the resultant cluster of interrelated plasma lipid and lipoprotein abnormalities, including reduced HDL-cholesterol, a predominance of small dense LDL particles and elevated tracylglycerols (TAGs). That combination generally is pro-atherogenic, pro-inflammatory and induces vascular complications. This process is compounded by infection with SARs-CoV-2 which is vasculopathic and immunogenic *per se*. Statins are known to inhibit macrophage release of pro-inflammatory cytokines, a key pathologic event in COVID-19 disease progression, via binding to TL4 receptor, and also inhibit IgE binding to mast cells preventing mast cell degranulation[9], another key pathological pathway in severe COVID-19. These facts may not only explain some of the contribution of obesity to poor outcome with COVID-19 but also explain the observed mortality and morbidity benefit with statin use in COVID-19[10–12].

A further possibility for the observed increased mortality in obesity is that human adipose tissue is a reservoir for SARs-CoV-2, a site for significant inflammatory generation as a complex venue for viral eradication in COVID-19 should be explored.

Dyett[13] addresses the growing evidence suggesting that obesity may be the second most important risk factor after age for developing serious COVID-19 disease. This outcome is entirely consistent with the pattern described previously with different viruses where for example a critical consideration of the HIV includes viral persistence in cellular sites that preclude eradication, with the possibility that adipose tissue is a viral reservoir[14] both for the SARS-COV2 virus[15] as with HIV[16]. However evidence on the role of obesity as a lipid reservoir on 'long COVID' is currently sparse.

Specifically, chronic inflammation and immune modulation in adipose tissue in HIV infection has also been described[17]. Additionally, and as summarised by Honce *et al.*[3], obesity was identified as a risk factor for enhanced mortality and severity in the 2009 H1N1 influenza A pandemic with focus on the link between obesity and the meta-inflammatory state. We have summarised previously the fact that dysregulated control of inflammation is the hallmark of COVID-19[18]; the increased generation and reduced clearance of Ang II and increased inflammation due to COVID-19 are both processes that are also higher in obesity and result in unpredictable and context-specific effects on innate and adaptive immunity[19]. Further, the *severity* of COVID-19 disease correlates with an excessive pro-inflammatory immune response and profound lymphopenia, factors in common with the heightened pro-inflammatory state induced by obesity[20]. Obesity and related inflammation, and yet paradoxical suppression of the innate immune response within the pulmonary compartment are important determinants in the host response to a novel viral pathogen[21].

In this context, it is very clear that overweight and obesity are an easily modifiable risk factor for this disease, treatment of which could significantly reduce mortality. It remains unclear

Abbreviation: RAS, renin–angiotensin system.

however whether the kinetics of reversing obesity would be sufficient after COVID-19 diagnosis to significantly alter the pathogenesis in time to reduce mortality. Preventing obesity is the key public health message as once people are obese, the tissue based 'meta-flammation'[21] and RAS is switched on.

Preventative weight reduction also has additional potentially non-RAS benefits for clinicians managing severe COVID such as improved ability to intubate, mobilising in the bed and ventilating on safe ventilatory pressures in ICU.

Overall from a prevention perspective, this observation of additional adverse effects of obesity on COVID adds to the existing portfolio of benefits of preventing obesity. Mechanistically, many of the pathophysiological contribution of obesity on worsened organ function are due to inflammation on top of an activated RAS system. It would seem that the combination of such lifestyle modifications together with 'treating the host' principles with repurposed drugs to reduce the activity of the RAS[18] and statins[16] to inhibit inflammation would appear to be key elements of strategy for COVID-19 treatment.

Jennifer H. Martin[1] and Richard E. Head[2]

[1]*Centre for Drug Repurposing and Medicines Research, Clinical Pharmacology, University of Newcastle, NSW 2305, Australia*
email jen.martin@newcastle.edu.au

[2]*University of South Australia, Adelaide, SA 5002, Australia*

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