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COVID-19 severity and obesity: are MAIT cells a factor?

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People with obesity have an increased risk of severe COVID-19: a meta-analysis by Popkin and colleagues[1] found that the odds ratio of people with obesity being hospitalised with COVID-19 was 2·13 when compared with those without obesity, and mortality was 48% higher in patients with obesity than in those without. This increased risk of severe disease is linked to higher rates of metabolic and cardiovascular complications.[2] Another major contributing factor is the presence of substantial immune dysregulation and chronic systemic inflammation. Obesity is associated with increased levels of numerous inflammatory mediators, including interleukin (IL)-1, IL-6, IL-17, and tumour necrosis factor α.[3] These cytokines are also implicated in the pathogenesis of COVID-19.[4] In addition to inflammation, obesity is associated with important defects in immune cells tasked with host protection, including natural killer cells and mucosal associated invariant T (MAIT) cells.[5,6]

Several publications have highlighted MAIT cells as potentially having a crucial role in the host response to SARS-CoV-2.[7,8,9,10] In each of these studies, reduced peripheral serum MAIT-cell frequencies were observed in a COVID-19 severity-dependent manner (ie, with lower frequency associated with more severe COVID-19). Conversely, increased numbers of MAIT cells were noted in the lungs of patients with COVID-19 together with higher expression of MAIT-cell chemoattractants,[7,8] and increased levels of activated MAIT cells producing granzyme B were noted in patients with COVID-19.[9,10] Furthermore, importantly, after co-culturing MAIT cells with SARS-CoV-2-infected macrophages, increased activity of the MAIT cells producing granzyme B was observed, suggesting a possible ability of MAIT cells to respond to or directly kill infected cells.[9,10]

A striking observation across these studies is the COVID-19 severity-dependent increase in the activation marker CD69.[7,9,10] MAIT-cell activation (via CD69) was associated with prolonged hospitalisation, reduced PaO_2/FiO_2 ratio, and increased Simplified Acute Physiology Score (SAPS II), a measure of mortality risk for patients in the intensive care unit. These associations with COVID-19 severity might be due to altered MAIT-cell activity driving a proinflammatory response in patients with COVID-19. Pulmonary MAIT cells increase their expression of IL-17A,[7,9] a cytokine implicated in the pathogenesis of COVID-19 and the development of acute respiratory distress syndrome (ARDS; figure A, B).[11,12] Moreover, analysis of an alveolar lavage single-cell dataset by Parrot and colleagues[9] showed that MAIT cells were the predominant T-cell source of IL-17A.[8]

A study by Provine and colleagues[13] highlighted MAIT cells as an important mediator for adenovirus-vectored vaccine immunogenicity to COVID-19. The authors found that, after administration of the ChAdOx1 nCoV-19 vaccine, MAIT cells in both mice and humans had increased levels of the activation marker CD69. These ChAdOx1-activated MAIT cells also produced increased levels of the antiviral molecules interferon (IFN)-γ and granzyme B (figure C). Furthermore, MAIT cells, in response to IFN-α and IL-18, were shown to support vaccine-induced $CD8^+$ T-cell immunity, providing an important link between innate and adaptive immunity.[13]

These studies highlight a potentially crucial role for MAIT cells in the pathogenesis of COVID-19. In addition, the COVID-19-associated alterations in MAIT cells closely reflect those changes in MAIT cells observed in people with obesity.[6,14,15] We and others have reported reduced MAIT-cell frequencies

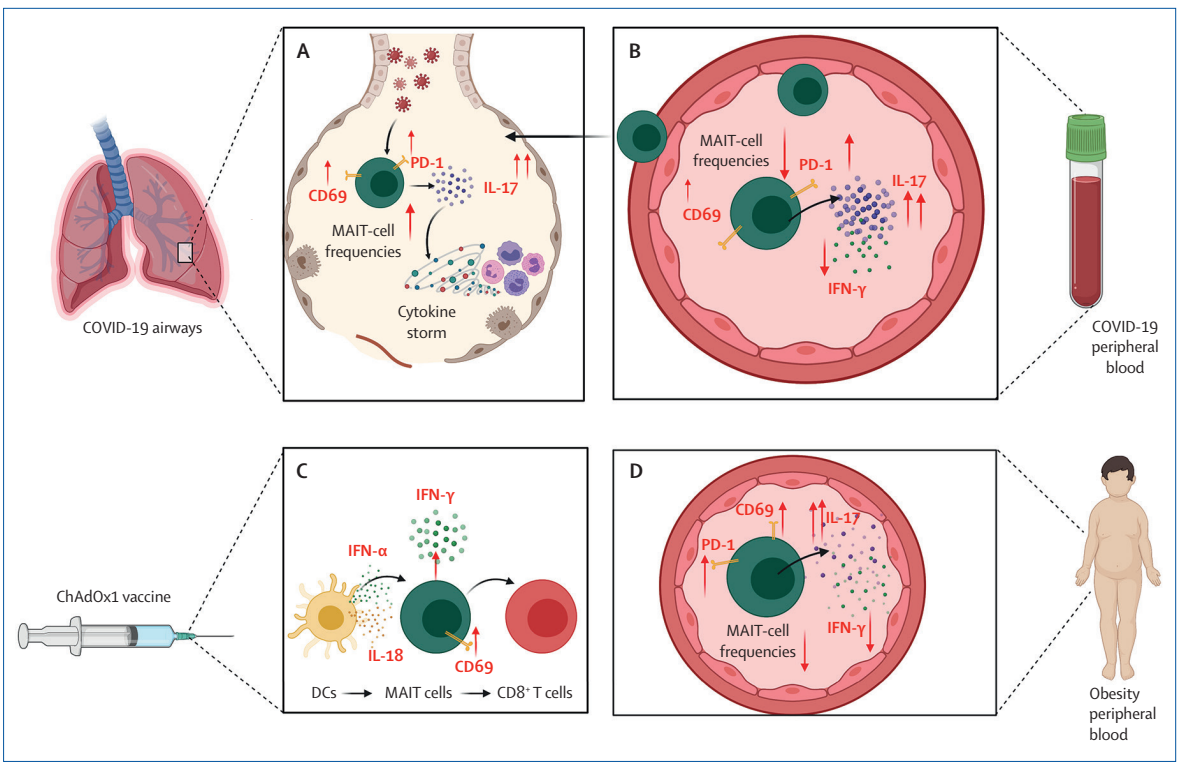

Figure: **Role of MAIT cells in COVID-19 and obesity**
MAIT cells in (A) the lungs and (B) the peripheral blood of patients with COVID-19. (C) MAIT-cell response to adenovirus-vectored SARS-CoV-2 vaccine. (D) MAIT cells in the peripheral blood of people with obesity. CD=cluster of differentiation. DC=dendritic cell. IFN=interferon. IL=interleukin. MAIT cell=mucosal associated invariant T cell. PD-1=programmed cell death protein 1.

and an activated phenotype (increased CD69 and PD-1 expression) in people with obesity.[6] MAIT cells from people with obesity also display a loss of IFN-γ, a cytokine that is key for antiviral responses, and elevated levels of the inflammatory cytokine IL-17, an established driver of ARDS (figure D).[6,15] We propose two open questions. First, could the poor outcome in people with obesity and COVID-19 be the result of a second hit from SARS-CoV-2 on the already compromised, proinflammatory MAIT-cell population? Second, could the obesity-related defects in MAIT cells affect the immune bridge proposed by Provine and colleagues and lead to diminished vaccine efficacy? In addressing these questions, clinicians and scientists will need to consider the contribution of this novel population of T cells to the prevention, pathogenesis, and treatment of COVID-19. Only then will we be able to harness fully the potential of MAIT cells or their cytokine products as targets for modifying the course of disease caused by SARS-CoV-2.

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*Cormac McCarthy, Cliona P O'Donnell†, Neil E Wrigley Kelly†, Donal O'Shea, Andrew E Hogan
cormac.mccarthy@ucd.ie
†Contributed equally.

School of Medicine (CMC) and Obesity Immunology Group, Education and Research Centre (NEWK, DOS, AEH), University College Dublin, Dublin T04 T6F4, Ireland; Department of Respiratory Medicine, St Vincent's University Hospital, Dublin, Ireland (CMC, CPOD); Institute of Immunology, Department of Biology, Maynooth University, Maynooth, Ireland (AEH)

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Could a good night's sleep improve COVID-19 vaccine efficacy?

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More than 2 million people have died from COVID-19, caused by SARS-CoV-2.[1] In an unprecedented effort to develop vaccines to control the COVID-19 pandemic, mRNA, protein subunit, and viral vector-based vaccines have been developed within an extraordinarily swift timeframe. However, the efficacy of these vaccines (ie, their ability to reduce the incidence of severe disease and death from COVID-19) can vary considerably. For example, among 43 448 adults, the efficacy of the mRNA-based COVID-19 vaccine produced by Pfizer and BioNTech ranged between 29·5% and 68·4% against symptomatic COVID-19 after the first dose, and between 90·3 and 97·6% after the second dose.[2] By comparison, in an interim analysis of ongoing clinical trials (involving 23 484 participants), the corresponding efficacy of two standard doses of the ChAdOx1 nCoV-19 adenovirus vector vaccine produced by AstraZeneca ranged between 41·0% and 75·2%.[3]

Although data from phase 3 trials indicate that factors such as age and biological sex might not be as prominent in modulating the efficacy of certain COVID-19 vaccines (eg, in case of the mRNA-based COVID-19 vaccine produced by Pfizer and BioNTech),[2] the role of sleep in this context is unclear. As suggested by previous studies, sleep duration at the time of vaccination against viral infections can affect the immune response (figure). For instance, 10 days after vaccination against the seasonal influenza virus (1996–97), IgG antibody titres in individuals who were immunised after four consecutive nights of sleep restricted to 4 h were less than half of those measured in individuals without such sleep deficits.[4] Similarly, shorter actigraphy-based sleep duration was associated with a lower secondary antibody response to hepatitis B vaccination.[5] Sleep might also boost aspects of virus-specific adaptive cellular immunity. Compared to wakefulness, sleep in the night following vaccination against hepatitis A doubled the relative proportion of virus-specific T helper cells, which are known to play a prominent role in host-protective immune responses.[6] Interestingly, in individuals who slept the night after the first vaccination, the increase in the fraction of interferon-γ (IFN-γ)-positive immune cells at weeks 0–8 was significantly more pronounced than in those who had stayed awake on that night.[6] IFN-γ directly inhibits viral replication and activates immune responses to eliminate viruses, thus protecting the host against virus-induced pathogenesis and lethality.[7] Further emphasising the importance of sleep in the fight against viral pandemics, lack of sleep in the night after vaccination against the 2009 H1N1 influenza virus was found to reduce the early-phase production of H1N1-specific antibodies in men but not women.[8] Finally, nocturnal sleep has been shown to promote a cytokine milieu supporting adaptive cellular immune responses, such as decreased activity of the anti-inflammatory cytokine interleukin-10 and

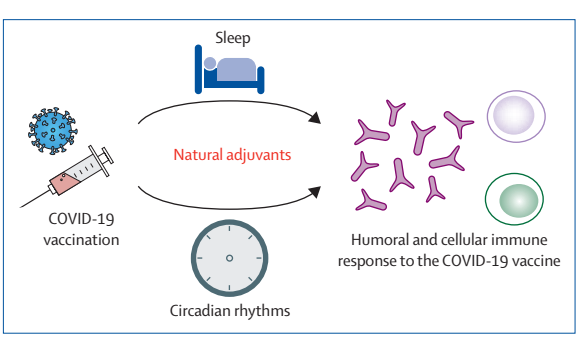

***Figure*: Post-vaccination sleep and morning timing of vaccination as possible immune adjuvants for COVID-19 vaccination**