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STATE-OF-THE-ART REVIEW

The role of T-cell immunity in COVID-19 severity amongst people living with type II diabetes

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The COVID-19 pandemic has highlighted the vulnerability of people with diabetes mellitus (DM) to respiratory viral infections. Despite the short history of COVID-19, various studies have shown that patients with DM are more likely to have increased hospitalisation and mortality rates as compared to patients without. At present, the mechanisms underlying this susceptibility are unclear. However, prior studies show that the course of COVID-19 disease is linked to the efficacy of the host's T-cell responses. Healthy individuals who can elicit a robust T-cell response are more likely to limit the severity of COVID-19. Here, we investigate the hypothesis that an impaired T-cell response in patients with type 2 diabetes mellitus (T2DM) drives the severity of COVID-19 in this patient population. While there is currently a limited amount of information that specifically addresses T-cell responses in COVID-19 patients with T2DM, there is a wealth of evidence from other infectious diseases that T-cell immunity is impaired in patients with T2DM. The reasons for this are likely multifactorial, including the presence of hyperglycaemia, glycaemic variability and metformin use. This review emphasises the need for further research into T-cell responses of COVID-19 patients with T2DM in order to better inform our response to COVID-19 and future disease outbreaks.

Introduction

To date, the COVID-19 pandemic has infected at least 117 million people resulting in approximately 2.6 million deaths worldwide [1]. Consistently throughout the course of the pandemic, patients with diabetes mellitus (DM) have been identified as being at risk of severe COVID-19 morbidity and mortality [2]. At present, the reason for this increased susceptibility is unclear. However, there is a large body of evidence that DM is associated with an impaired antiviral T-cell response. Here, we seek to highlight the role that T-cell immunity plays in the increased severity of COVID-19 in people living with type 2 diabetes.

Abbreviations
CXCL10, C-X-C motif chemokine ligand 10; M, Matrix; N, Nucleocapsid; S, Spike; T2DM, type 2 diabetes mellitus; TRAIL, TNF-related apoptosis-inducing ligand.

SARS-CoV-2

SARS-CoV-2 is a highly infectious respiratory pathogen (with an average R_0 of ~ 3.28) and is primarily transmitted through respiratory droplets [3], although aerosol transmission may play a more significant role than previously suggested [4,5]. ACE2 and TMPRSS2 are crucial in determining SARS-CoV-2 recognition and infection of host cells and are ubiquitously coexpressed throughout the body [6]. Importantly, ACE2 and TMPRSS2 are highly expressed in epithelial cells in the nasopharynx and oral mucosa, where the virus first binds after respiratory droplet exposure [6,7]. The median incubation period for this virus is 5.1 days post-exposure, although a proportion of individuals will never develop symptoms [8]. For ~ 80% of symptomatic individuals, the disease presents as mild flu-like symptoms (such as fever and cough) and viral infection is confined to the upper respiratory tract. However, for the remaining 20% of people, SARS-CoV-2 may spread to the lower respiratory tract, which leads to severe disease including pneumonia and acute respiratory distress syndrome [8]. A determinant for disease progression in patients is age and sex, where men over 65 years old are more likely to develop severe disease. Additionally, comorbidities can be linked with increased COVID-19 severity, including cardiovascular disease, obesity, respiratory disease and diabetes [9]. Accumulating evidence suggests that severe COVID-19 disease is also determined by a 'cytokine storm' [10]. The cytokine profile during COVID-19 infection can include and is not limited to the upregulation of interleukins IL-6, IL-10, IL-1β, IL-18, tumour necrosis factor α (TNF-α), interferons (IFN-α/β, IFN-γ) and C-X-C motif chemokine ligand 10 (CXCL10) [11,12]. Although there are many different SARS-CoV-2 vaccines currently approved for clinical use, there are limited treatments available for patients infected with SARS-CoV-2. Two of the most used therapeutics are monoclonal antibodies (such as bamlanivimab) and dexamethasone [13]. More recently, there has also been an increased interest in using the IL-6 receptor antagonist tocilizumab in combination with dexamethasone [14].

Diabetes mellitus

Diabetes mellitus (DM) is highly prevalent in today's society [15]. Globally, 463 million adults were estimated to have DM in 2019, of which one in two were undiagnosed [16]. This figure is projected to increase to 700 million by 2045. DM is defined by chronically elevated blood glucose levels (hyperglycaemia). DM can be broadly classified into two types: type 1 DM (T1DM) and type 2 DM (T2DM). T2DM is the most common type of diabetes, accounting for approximately 85–90% of diabetes cases, while T1DM accounts for 10–15% of diabetes cases [16]. A third type of diabetes has been proposed – type 3 diabetes – which refers to Alzheimer's disease as a result of insulin resistance in the brain. However, this is not yet a medical term or a recognised condition [17]. T2DM is characterised by insulin resistance, that is an impaired response to circulating insulin and an unmatched compensatory increase in insulin production [18,19]. Insulin production can be affected by numerous conditions including obesity. Obesity is defined by an individual's body mass index (BMI), where 25.0 to 29.9 $kg{\cdot}m^{-2}$ is generally regarded as overweight and ≥ 30.0 $kg{\cdot}m^{-2}$ is generally regarded as obese [20]. It is estimated that by 2030, 38% of the worldwide adult population will be overweight, and another 20% obese [20]. Obesity is known to facilitate the onset of T2DM [18-20], due to the role of adipose in insulin resistance [19,21]. Importantly, obesity does not directly cause T2DM, but indirectly predisposes the individual by increasing insulin resistance in peripheral tissue [19]. In contrast, T1DM is characterised by a deficiency in insulin production that is usually immune-mediated. In a healthy individual, insulin is produced and released by pancreatic β-cells in response to elevations in blood glucose levels, such as after a meal. Insulin then targets a range of tissues, including skeletal muscle to enhance glucose uptake, which consequently lowers blood glucose levels [22].

DM and viral infections

Patients with DM experience increased COVID-19 severity [23,24], increased ICU admission rates [25,26] and increased mortality rates [27,28]. For example, in an international multicentre study of more than 7000 patients with COVID-19, DM was independently associated with increased risk of both noninvasive and invasive ventilation after adjusting for BMI, age, sex and other comorbidities. A prospective cohort study, which included approximately 500 000 study participants, showed similar findings, with an increased risk of fatal COVID-19 observed in patients aged 40–69 with DM [29]. Similarly, in China, a study of > 72 000 patients with COVID-19 showed that individuals with DM had a higher mortality rate compared to those without (7.3 vs. 2.3%) [30]. The majority of COVID-19 studies to date have not differentiated between patients with T1DM and T2DM [23,27,29]. It is therefore still unclear whether susceptibility to severe

COVID-19 is more relevant to T1DM or T2DM [28,31,32]. Recent studies showed higher unadjusted odds ratios of COVID-19 mortality and disease severity in T2D patients as compared to those with T1D [33]. However, a higher adjusted odds ratio of mortality was observed in T1D patients after adjusting for host conditions such as age, sex and BMI, and pre-existing conditions such as hypertension [31,33]. In a Scottish study of ~ 4200 COVID-19 patients, T1DM was associated with a higher adjusted and nonadjusted odds ratio of severe disease compared to T2DM [34]. Nevertheless, as the global prevalence of T2DM is considerably higher than that of T1DM [16], this review will focus on T2DM and the various factors in these patients that could contribute to an impaired immune response to SARS-CoV-2.

Increased severity of viral disease in patients with T2DM is not restricted to COVID-19. For example, from 1986 to 1989, people with diabetes were more likely to have pneumonia and influenza recorded on their death certificate than people without diabetes [35]. This relationship between diabetes and severe respiratory disease became even more well established during the 2009 H1N1 pandemic, when patients with pre-existing T2DM were four times more likely to be admitted into the ICU with influenza (adjusted odds ratio 4.29 [1.29–14.3]) [36]. Additionally, a longer course of hospital admission and increased influenza mortality rates were observed in patients with DM compared to patients without DM [37,38]. Similar observations have been made in the context of Middle East respiratory syndrome coronavirus (MERS-CoV), West Nile virus and dengue virus infections, where patients with DM were also more likely to suffer an increased disease severity and a higher mortality rate compared to patients without DM [39-43]. A growing body of evidence has shown that T2DM impairs T-cell function, which is essential to the resolution of viral infections such as SARS-CoV-2 and influenza virus [44,45]. These observations raise the intriguing question as to whether increased COVID-19 severity in patients with T2DM is related to defects in T-cell immunity.

COVID-19 and T-cell immunity

T cells are vital in the control and clearance of viral infections, including respiratory viruses, such as influenza virus [46-50]. Therefore, it is no real surprise that numerous studies have now demonstrated that the magnitude of the T-cell response inversely correlates with COVID-19 disease severity [51-56] As such, there is much interest in further understanding T-cell responses in SARS-CoV-2 immunity. Indeed, many groups are working towards this common goal, investigating the role of both innate and adaptive immune responses during SARS-CoV-2 infection. To collate the enormous amount of research being published, Sette *et al* [57] have proposed a working model, which suggests that the innate, and subsequently the adaptive, immune response is delayed during SARS-CoV-2 infection. This delayed adaptive immune response, which includes T cells, is simply too little too late in individuals with severe COVID-19.

T cells can be subdivided on the basis of the expression of a CD4 or CD8 coreceptor. $CD4^+$ T cells are known as the helpers of the immune system [50]. Their traditional roles involve the secretion of cytokines to attract immune cells to the site of infection, providing help to B cells for the production of high affinity antibodies [58] and licencing of dendritic cells (DCs), which in turn activate $CD8^+$ T cells [59]. Conversely, $CD8^+$ T cells are known as the killers of the immune system. Following activation, they can directly kill virally infected cells using a range of effector mechanisms. These include the release of cytotoxic cytokines such as TNF-related apoptosis-inducing ligand (TRAIL) [60], the secretion of cytolytic molecules perforin and granzymes [61] or the binding of $CD8^+$ FASL to FAS expressed on the surface of virally infected cells, initiating the of death-receptor pathway [61].

Both $CD4^+$ and $CD8^+$ T cells are important in the protection against viral infections [46,47,49]. Antigen-specific $CD4^+$ and $CD8^+$ T cells have been detected in individuals following SARS-CoV-2 infection [55,56,62,63,64], indicating their importance in the control of COVID-19. Despite the logistical challenges of obtaining samples from individuals with acute SARS-CoV-2 infection, some studies have assessed the $CD4^+$ and $CD8^+$ T-cell response during the acute disease phase. Rydyznski Moderbacher *et al* [55] demonstrated that $CD4^+$ and $CD8^+$ T cells could be detected in around half of individuals with acute SARS-CoV-2 infection [55]. Interestingly, $CD4^+$ and $CD8^+$ T cells have been detected as early as four–five days post-symptom onset in some individuals [55,65]. As expected, the majority of studies to date have assessed the T-cell response in convalescent samples following viral clearance [55,56,62,63]. $CD4^+$ and $CD8^+$ T cells target numerous proteins of the SARS-CoV-2 virus, with the majority of responses observed towards the spike (S), matrix (M), nucleocapsid (N) and ORF3 proteins [56,62,66], while $CD4^+$ T cells also often target NSP3, NSP4 and ORF8 [62].

Interestingly, SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cell responses have been detected in individuals

unexposed to SARS-CoV-2 [45,57,62,66,67] showing that some individuals have pre-existing immunity. SARS-CoV-2 is a coronavirus and is related to SARS-CoV-1 (the causative agent of the SARS outbreak in 2003), as well as other circulating common cold-causing coronaviruses [68,69]. This pre-existing T-cell response is likely due to memory T cells, activated by previous exposure to one of these other coronaviruses, which can cross-react towards SARS-CoV-2 epitopes [66,67,70].

Broadly speaking, compared to neutralising antibodies which can recognise viruses before they enter their host cells, T cells only recognise viral peptide fragments presented following infection of the host cell. As such, memory or pre-existing T cells have limited capacity to prevent viral re-infection. they do, however, activate quickly and effectively work to clear the infection, thereby limiting the viral load, lessening disease symptoms and enhancing recovery. Therefore, it is important to understand the longevity of the T-cell response following viral clearance. Since SARS-CoV-2 is a novel virus, there is understandably a paucity of data on the frequency at which re-infection occurs. Following viral resolution, $CD4^+$ and $CD8^+$ T-cell populations contract to form a stable pool of long-lived memory T cells, capable of re-activating in the face of re-infection. At present, it is unclear how long memory $CD4^+$ and $CD8^+$ T-cell responses will last. However, looking at T-cell responses towards other viral vaccinations or infections may give us a glimpse of their potential longevity. Epitope-specific $CD8^+$ T cells have been detected up to 50 years following vaccination [71,72] and as many as 13 years following natural influenza virus infection [73]. Perhaps more relevant, SARS-CoV-1-specific T cells have been observed 17 years post-SARS-CoV-1 infection [67] and these could cross-react with SARS-CoV-2 peptides [67]. This demonstrates that long-lived T cells can be established following infection with coronaviruses. Short-term longitudinal studies have thus far identified SARS-CoV-2-specific T cells up to 6–8 months post-infection [74-76]. Only time will tell how long-lasting SARS-CoV-2-specific T cells will be.

T2DM and the T-cell response to viral infections

There are few studies that specifically examine the antiviral T-cell response to COVID-19 in patients with T2DM (Table 1). Looking at global T-cell populations in COVID-19 patients, Gupta and colleagues found that individuals with T2DM had significantly fewer $CD4^+$ and $CD8^+$ T cells than patients without T2DM, which may contribute to the observed increased viral severity [77]. Other studies reported decreased $CD8^+$ T cells in COVID-19 patients with T2DM but an increase in the $CD4^+$ population [78]. In a broader sense, patients with comorbidities had reduced T-cell responses [44] and an increased senescent T-cell population [79], both markers of severe COVID-19 disease. However, there is an urgent need for studies that specifically address the effects of DM on the T-cell response to SARS-CoV-2.

While there is a lack of studies specifically investigating the T-cell response to SARS-CoV-2 in patients

Table 1. The effects of T2D on T-cell immunity during SARS-CoV-2 infection.

Pathogen	Study Subject[a]	Findings	References
SARS-CoV-2	Humans 22/201 patients with DM (10.9%)	Significantly lower CD8 T cells in patients with DM Lymphocytopenia (lowered CD3 and CD4 counts) in patients with DM Patients with ARDS had a higher proportion of comorbidities, including DM	[127]
SARS-CoV-2	Humans 14/71 patients with DM (19.72%)	Significantly higher $CD4^+$ T-cell percentages in patients with DM Significantly lower $CD8^+$ T-cell percentages in patients with DM Patients with DM had significantly higher serum levels of IL-6, IL-2, IL-10 and IFN-γ Patients with impaired fasting glucose had significantly lower levels of IL-10 and IFN-γ compared to patients with DM	[78]
SARS-CoV-2	Humans 129/306 patients with T2D (42.16%)	On admission, lower $CD4^+$ T cells and $CD8^+$ T cells in patients with T2D During the first week of hospital admission, all patients with T2DM showed a significant decrease in total T lymphocyte counts and $CD8^+$ T-cell counts During the first week of hospital admission 7 out of 9 patients with DM showed obvious broad decrease in all lymphocyte subsets, including total B cell count and $CD4^+$ T-cell count Elevated cytokine levels (IL-2R, IL-1β, TNF-α, IL-6, IL-8, IL-10) in patients with T2D	[128]

[a]Comparisons performed between patients living with DM suffering from COVID-19 and healthy patients without comorbidities suffering from COVID-19.

with T2DM, there is some evidence from other viral infections that lower cytokine expression after stimulation and a suboptimal T-cell response are associated with T2DM [80,81] (Table 2). For example, impaired migration of $CD8^+$ T cells has been implicated in the increased susceptibility of T2DM patients to West Nile virus encephalitis [82]. Impaired migration of $CD4^+$ T cells and subsequent increased disease severity was also observed in diet-induced diabetic mice following MERS-CoV infection [83]. In the context of influenza, Diepersloot and colleagues showed that $CD8^+$ T cells from patients with DM showed reduced capacity to lyse target cells relative to healthy controls [84]. There is also evidence to suggest that patients with T2DM accumulate higher numbers of senescent T cells [85], suggesting a reduced protective T-cell response against viral pathogens during an infection. However, the mechanisms of this impaired cellular function remain poorly defined (Fig. 1).

A role for hyperglycaemia in impaired antiviral immunity?

Hyperglycaemia has been heavily implicated in the severity of both influenza and COVID-19 with DM. Specifically, hyperglycaemia was associated with higher disease severity and mortality rates in COVID-19 patients with pre-existing DM [86-89]. Similarly, a study in China showed that COVID-19 patients with T2DM and blood glucose levels that ranged from 3.9 to 10 $mmol{\cdot}L^{-1}$ had significantly lower mortality compared to patients with elevated blood glucose levels (> 10 $mmol{\cdot}L^{-1}$) [90]. Elevated glucose levels are also associated with increased influenza-associated damage to the pulmonary epithelial–endothelial barrier *in vitro* and *in vivo* [91]. However, the effect of hyperglycaemia per se on T-cell function remains both scant and controversial [92,93].

Hyperglycaemia may impair adaptive immune responses via the induction of oxidative stress. Specifically, increased intracellular glucose concentration increases the mitochondrial proton gradient, releasing reactive oxidative species (ROS) via different sources [94]. Oxidative stress has a clear, detrimental effect on $CD8^+$ T-cell responses [95]. Specifically, oxidative stress reduces the production of key effector cytokines TNFα and IFNγ from peripheral blood T cells following stimulation with a MHCI-specific influenza virus peptide [95]. This effect is most pronounced with memory T cells [95,96]. Uncontrolled oxidative stress drives T-cell signalling and activation, potentially leading to dysfunctional immunity via T cells [97,98]. Oxidative

Table 2. The effects of T2D on T-cell immunity.

Pathogen	Study Subject[a]	Findings	References
West Nile virus	C57BL/6 J-Lepr ^{db} /Lepr ^{db} (db/db) mice (a murine model of T2DM)	Reduced leucocyte infiltration in the brains of *db/db* mice after infection Significantly increased levels of IL-1β, TNF-α, IL-6, IFN-γ and IL-1α in brain tissue at 8d.p.i in *db/db* mice Increased WNV-induced neuronal death in *db/db* mice.	[82]
	Humans 246/1521 patients with DM (16.2%)	Patients living with T2D have a significantly reduced naïve and increased senescent $CD4^+$ and $CD8^+$ populations Increased effector memory $CD4^+$ populations in patients with DM Increased central memory $CD8^+$ populations in patients with DM Increased CXCR2 chemokine receptor in T-cell subsets in patients with DM Impaired T-cell migration in patients with DM	[85]
MERS-CoV	hDPP4-expressing C57BL/6 mice (diet-induced T2D)	Diabetic male mice show delayed and prolonged severe disease following viral infection No differences in viral replication and clearance between mice with and without T2DM T2DM mice have decreased $CD4^+$ T-cell and inflammatory monocyte/macrophage responses after viral infection	[83]
	Humans 9/19 patients with T2D and stage 2 obesity (47.37%)	PBMCs from subjects with stage 2 obesity produced significantly less IL-2, IL-6 and TNF-α after PHA stimulation than cells from subjects with stage 0 obesity Higher proportion of cytotoxic T cells ($CD3^+CD8^+$) and activated Th cells ($CD4^+CD278^+$) in patients with stage 2 obesity when compared with subjects with stage 0 obesity	[81]

[a]Clinical studies compared the immune response of patients living with DM and healthy patients.

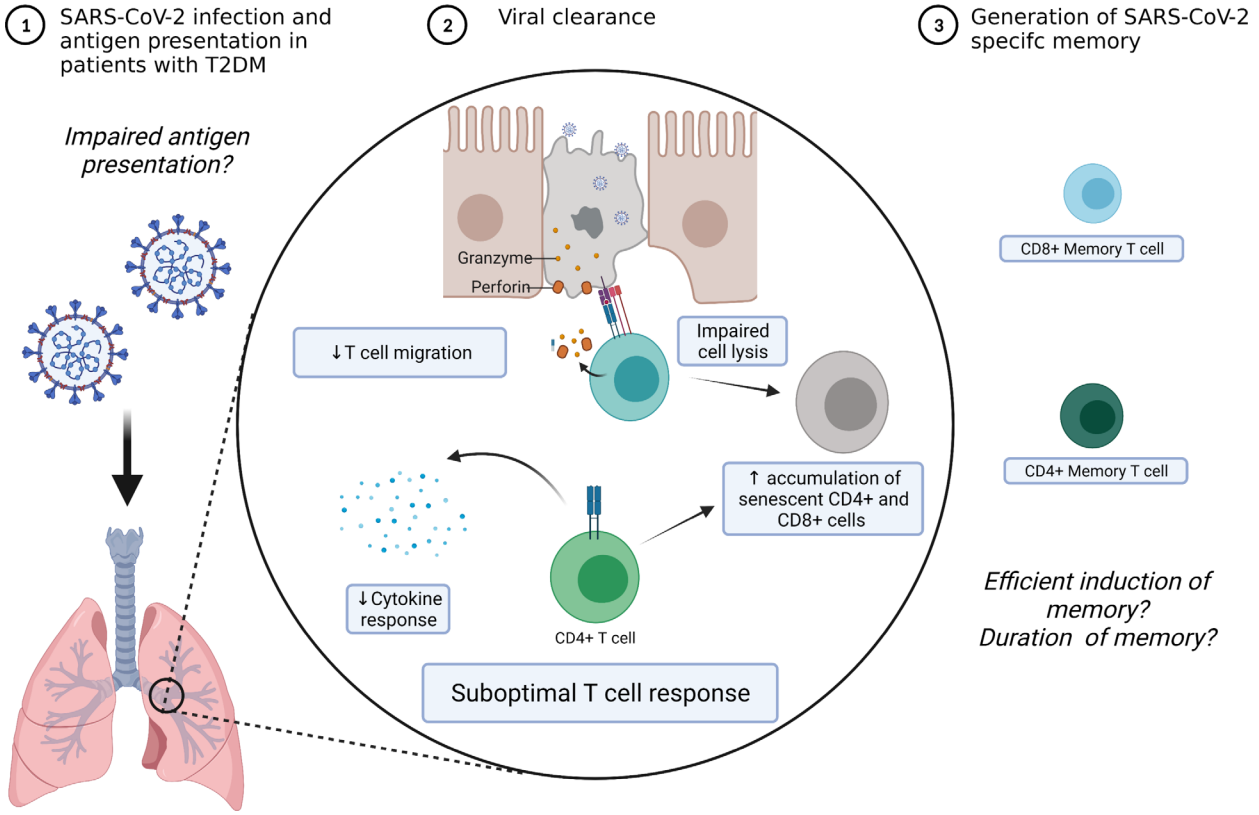

Fig. 1. Possible mechanisms of T-cell dysfunction in patients with T2DM. The impact of T2DM on antigen presentation to T cells remains unclear (1). T2DM may reduce viral clearance in the lung by reducing T-cell migration to the site of infection [82], decreasing the cytokine response of $CD4^+$ T cells [83], impaired cell lysis [84] and increasing the number of senescent T cells [85] (2). The effect of T2DM on the generation of T-cell memory remains undefined but may include effects on both memory induction and duration (3). Figure created with biorender.com.

stress via ROS also potentially causes structural modifications to T-cell receptor signalling proteins, reducing immune response in T cells via CD3 signalling [99]. However, at present, the association between hyperglycaemia, impaired adaptive immunity and oxidative stress remains speculative.

A role for glycaemic variability in impaired antiviral immunity?

Healthy blood glucose levels are kept within a narrow range of 4.4–6.7 $mmol{\cdot}L^{-1}$, including small and short-lived postprandial peaks. In patients with untreated or poorly managed T2DM, these postprandial glucose excursions are generally higher and more frequent [100]. There is no precise definition of blood glucose variability, and it may refer to hour-to-hour, intra-day, day-to-day, month-to-month or even year-to-year variations in blood glucose levels [101]. In routine clinical practice, diagnostic tests such as HbA1c blood tests are used to monitor T2DM management. However, these tests estimate the effects of average blood glucose levels over the preceding three months and provide no information on glycaemic variability. It is clear from research studies using continuous glucose monitors that people with T2DM experience significant glucose fluctuations over a 24-h period [102].

Recent studies have suggested that glycaemic variability in the context of T2DM increases the deleterious effects of influenza virus infection [100,103]. Using a novel murine model of glycaemic variability, we have shown a more severe influenza infection, including increased weight loss and pro-inflammatory responses, compared to mice with steady high blood glucose levels [100]. This increased disease severity was also observed in the context of influenza virus re-infection where it was speculated that $CD8^+$ T-cell function was impaired in mice with glycaemic variability [100]. A similar phenomenon may occur with COVID-19. An exploratory study in Wuhan monitored 35 patients with COVID-19 and pre-existing DM with a continuous glucose monitor over ten days during their

hospital stay [104]. In these patients, high glycaemic variability, but not mean glucose levels, was significantly associated with an adverse outcome of COVID-19 [104]. In addition, the odds ratio of an adverse outcome was correlated with the degree of glycaemic variability observed in these patients [104], suggesting the importance for glucose control in COVID-19. In a retrospective study of hospitalised COVID-19 patients, 21 out of 107 patients were newly diagnosed with T2DM during admission and it was these individuals who had more severe COVID-19. Consistent with these findings, undiagnosed DM in men is associated with a 3.5-fold excess risk of fatal COVID-19 disease after infection [29], potentially due to a history of poor blood glucose control and increased glycaemic variability [105]. A growing body of evidence suggests that glycaemic variability observed in DM patients causes oxidative stress via ROS, over and above levels produced by hyperglycaemia alone [106-108]. It is therefore tempting to speculate that glycaemic variability drives oxidative stress, causing impaired T-cell responses (as described above) and thus severe COVID-19.

A role for obesity in impaired antiviral immunity?

T2DM is frequently co-associated with obesity, which may have directly deleterious effects on T-cell function. Indeed, obese COVID-19 patients have a significantly higher risk of hospitalisation, ICU admission and mortality rates than non-obese patients [109], indicating the importance of evaluating BMI as a confounding risk factor. Obesity is associated with an impaired T-cell response to influenza virus infection, with chronic T-cell activation causing T-cell dysregulation [110,111]. Specifically, increased adipose tissue in obese individuals impairs T-cell and macrophage function, inducing chronic inflammation as well as reducing the antiviral response [21]. A study observed impairment of dendritic cells in obese individuals, indicating lower T-cell responses to influenza antigens [112]. Obesity was also correlated with an accelerated deterioration of T cells and other immune cells [113].

A role for medication in impaired antiviral immunity?

Finally, it is important to recognise that many people with T2DM are using multiple pharmacological agents [114]. Metformin is prescribed to nearly 120 million people worldwide for the management of high blood glucose levels [115]. In various reports, the prescription of metformin to people with obesity and/or T2DM was associated with reduced COVID-19 mortality rates [116-119]. Whether this is a direct result of metformin or indirect evidence of the importance of glucose control in the resolution of COVID-19 remains to be determined. Interestingly, the effects of metformin in reducing the occurrences of severe COVID-19 were more pronounced in females than in males [116,119].

The benefits of metformin are also observed in terms of the $CD8^+$ T-cell response. For instance, pre-existing T2DM increases the risk of *Mycobacterium tuberculosis* infection progression into active tuberculosis due to dysfunctional $CD8^+$ T-cell responses [120,121]. In PBMCs from patients with T2DM, metformin treatment augments $CD8^+$ T-cell metabolic circuits and expands $CD8^+CXCR3^+$ memory-like T cells, indicative of effector T-cell phenotypes to control progression into tuberculosis disease [121]. The multifunctionality of $CD8^+$ T cells was also recognised as a marker for healthy immune responses. Improved multifunctionality of $CD8^+$ T cells in both mice and PBMCs of patients with T2DM has been reported with metformin treatment [122]. In addition, metformin was found to decrease $CD4^+$ T-cell exhaustion in patients infected with human immunodeficiency virus (HIV) [123]. These studies suggest that metformin has beneficial effects on both $CD4^+$ and $CD8^+$ T-cell responses.

However, other studies show a detrimental effect of metformin on the host immune response. Interferons such as IFNα are essential in priming the T-cell response against viral pathogens such as SARS-CoV-2 [124]. A study by Saenwongsa and colleagues reported that metformin treatment in patients with T2DM inhibits the expression of IFNα in human PBMCs via the mTORC1 pathway [114]. In the same study, patients with T2DM prescribed with metformin or glibenclamide had a delayed and reduced humoral immune longevity to influenza viruses after vaccination [114]. Similarly, metformin reduces type I interferon-stimulated genes in $CD4^+$ T cells from human PBMCs after *IFN-α* stimulation [125]. Impaired type I interferons from metformin treatments could contribute the hyperinflammatory response in COVID-19 patients with pre-existing T2DM [126].

In summary, the current evidence on metformin clearly shows that it is able to modulate the host immune response; however, whether this has a beneficial or detrimental effect in terms of SARS-CoV-2 infection remains to be fully elucidated. Moreover, the immunomodulatory properties of metformin in individuals undergoing combination therapy (e.g. metformin and sulfonylurea or metformin and insulin) is thus far undefined.

Conclusion

Patients with DM are at risk of severe COVID-19. Many different mechanisms underlie this susceptibility, one of which may include impaired T-cell function. At present, while there are a limited number of specific studies investigating the T-cell response in COVID-19 patients with T2DM, evidence from other viral infections suggests that DM increases the number of senescent T cells, impairs T-cell migration and reduces T-cell lysis. These T-cell impairments may be the result of hyperglycaemia, glycaemic variability, obesity and/or medication use. It is essential that the mechanisms of T-cell dysfunction in patients with DM is better elucidated in order to advise clinical care and reduce the severity of COVID-19 in patients living with T2DM.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceived, wrote and approved the manuscript: ZWMT, EG, SG, MW, CS, HLB, LAG, KRS.

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