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COVID-19 and Diabetes Mellitus: implications for prognosis and clinical management

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Abstract

Introduction: COVID-19 is a novel coronavirus that emerged from Wuhan, China in December 2019, and within 3-months became a global pandemic.

Areas Covered*:* PubMed search of published data on COVID-19, respiratory infections and Diabetes Mellitus (DM). DM associates with impairments of both cellular and humoral immunity. Early emergent global data reveal that severity of clinical outcome from COVID-19 infection (including hospitalization and admission to Intensive Care Unit [ICU]), associate with co-morbidities, prominently DM. The key principles of management of COVID-19 in patients with DM include ongoing focused outpatient management (remotely where necessary) and maintenance of good glycaemic control.

Expert Opinion: We will remember the dawn of the third decade of the 21st Century as a time when the world changed, the true scale and impact of which is hard for us to imagine. Like a phoenix from the ashes though, COVID-19 provides us with a great learning opportunity to renew insights into ourselves as individuals, our clinical teams and the optimized provision of care for our patients. COVID-19 has re-shaped and re-focused our collective societal values, with a sea-changed shift from materialistic to human-centric, from self-centredness to altruism, ultimately for the betterment of patient care and the whole of society.

Keywords: COVID-19, Diabetes Mellitus, Respiratory Infection, Immunity, Glycaemia

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Article highlights

- The first description of COVID-19 was amongst a cluster of patients suffering from pneumonia in Wuhan, China [1]. Within 3-months, COVID-19 became a global pandemic. In the early stages of the global pandemic, the numbers of new reported cases of COVID-19 doubled every 7.4 days, with a basic reproductive number estimated at 2.2 (95% CI 1.4 to 3.9) [2].

- Diabetes Mellitus (DM) increases risk of both susceptibility to, and severity of respiratory infections generally, including gram-negative bacteria, Staphylococcus aureus, fungi (an example being candidiasis) [3] and Mycobacterium tuberculosis (TB).

- DM is a known risk factor for adverse outcomes from coronavirus-related infections causing respiratory disease, including Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) that occurred in 2002 [4-6], and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) that emerged in Saudi Arabia in 2012 [6,7]. Epidemiological data reveal DM as the primary comorbidity that associated with severe or lethal MERS-CoV infection [8].

- Much compelling evidence from the literature from both human- and rodent-based studies, support the notion that DM associates with impairment of both cellular- and humoral-based immunity. Severity of

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hyperglycaemia is commensurate with some measures of immune dysfunction, such as humoral immunity [9].

- Global data (including from China, Italy and the US) reveal DM as an important and predominant risk factor for COVID-19.

- Based on the experiences of SARS-CoV in Taiwan [4], by maintaining close attention to outpatient preventive management of DM we may limit hospital admissions of our patients with DM, even at a time that post-dates the current pandemic. To optimize outpatient management, we should develop alternate means of healthcare administration, such as telehealth, wearable technologies and remote patient monitoring [10]. We should also strive for good glycaemic control and stability in our patients with DM, both as a preventive measure and in the management of patients with DM who are already infected with COVID-19 (especially during insulin infusions), to optimize clinical outcome.

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1. Introduction

The first description of COVID-19 was amongst a cluster of patients suffering from pneumonia in Wuhan, China [1]. Within 3-months, COVID-19 became a global pandemic. The sheer rapidity of the spread of COVID-19 around the globe is testament to three main factors:

1.1 Viral novelty

COVID-19 is a novel and previously unrecognized virus, and therefore lacks any associated herd immunity within the global human population. This is important as herd immunity directly affects infectivity within any given population. With a complete lack of herd immunity (or history of any vaccination program), a pathogen has the potential to spread

unimpeded within populations, like wildfire. It is helpful here to make a comparison with Seasonal Influenza (SI). Every year, millions of people globally are infected with SI, but this accounts for only a relatively low proportion of the global population (between 5% and 15%) [11] due to a combination of herd immunity and vaccination for SI across the world.

1.2. High infectivity

COVID-19 has a high infectivity. In the early phase of the epidemic, data emerged on the first 425 confirmed cases of COVID-19 associated pneumonia from Wuhan, China [2]. During December 2019, there was linkage of the majority of these cases (55%) to the Huanan Seafood Wholesale Market in Wuhan, China, compared to only 8.6% of the new cases reported in January 2020. In these early stages of the global pandemic, the numbers of new reported cases of COVID-19 doubled every 7.4 days, with a basic reproductive number estimated at 2.2 (95% CI 1.4 to 3.9) [2].

1.3 Global mobility

During medieval times, the plague travelled around the globe via rats that had found themselves onto boats. Global transport back then was, of course, far slower and far less frequent than our modern day global transport infrastructure allows. In medieval times, a boat with a human crew would have taken many weeks or even months to travel between continents, and its arrival at port would have been an event in itself. Nowadays, it is possible to travel to virtually any global destination within 24-hours, and between Europe and the US in around 5-hours. It has been estimated that at any one time (at least in the pre-COVID-19 era), there are >1 million people in the air on flights around the world. Over recent decades, our species has become globally mobile in a way that is unprecedented for hominids, or any other species in Earth's history.

These three factors, viral novelty, high infectivity and global mobility have created a perfect storm for the spread of COVID-19 around the world. The resultant global pandemic has become manifest over an alarmingly short timeframe, that seems to have taken everyone by surprise. The analogy with wildfire is apt. This wildfire, however is not one confined to one region or even one country, but one that affects the whole planet. In this grim analogy with all its attendant pathos, it is perhaps ironic that in this Olympic year, it is not just the Olympic flame of hope, unity and human solidarity that has been passed around countries, but the COVID-19 'flame' that has ignited epidemics in each individual country.

Although infection with COVID-19 appears indiscriminate, the impact of infection on each individual encompasses the entire spectrum from asymptomatic, to death. Guan and

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colleagues reported on the clinical outcomes from COVID-19 infection in a nationwide analysis from China, on >1,500 confirmed cases of COVID-19 between 11th December 2019 and the end of January 2020 [12]. This analysis revealed that severity of COVID-19 infection associates heavily with underlying co-morbidities. Overall, severe cases accounted for 16%, and co-morbidities occurred in around a quarter of the population studied [12]. Regarding risk of serious adverse outcome (including admission to intensive care unit, need for invasive ventilation or death), among those with at least one co-morbidity the HR was 1.79 (95% CI 1.16-2.77). For those with at least two co-morbidities, the HR was 2.59 (95% CI 1.61-4.17) [12]. Regarding Diabetes Mellitus (DM) as a co-morbidity, the HR was 1.59 (95% CI 1.03-2.45) [12].

DM is a highly prevalent condition, with a rapid increase in the numbers affected over recent decades [13]. Currently the global prevalence of DM exceeds 382 million [14,15]. Furthermore, DM is a major cause of premature mortality, primarily from cardiovascular disease [13]. Indeed, between 1990 and 2010, there was a doubling in the absolute number of deaths attributed to DM [15,16]. Given the global prevalence of DM, and its broad implications for morbidity, mortality, overall wellbeing and the global healthcare economy, it is important to provide special attention to COVID-19 infection in the context of the patient with DM during this uncertain and unprecedented period.

We are still in the early stages of this global pandemic. There remain many unanswered questions particularly regarding optimal management of COVID-19 in the context of co-morbidities such as DM. Increased clarity will emerge over time in what is a rapidly developing and dynamic field. In this review, there is consideration of COVID-19 infection from the perspective of the patient with DM, based on the current published data. This includes implications of DM for prognosis (including both respiratory infections in general, and specifically COVID-19 infection), mechanisms that underlie susceptibility to and severity of respiratory infections (including COVID-19) in DM and key strategies for optimized clinical management of patients with DM during the COVID-19 pandemic.

2. Diabetes Mellitus and respiratory infections: implications for prognosis

DM increases risk of both susceptibility to, and severity of respiratory infections. This includes susceptibility to many kinds of respiratory infections such as gram-negative bacteria, Staphylococcus aureus, fungi (such as candidiasis) [3] and Mycobacterium tuberculosis (TB). In one study on patients with TB >20 years old from clinics in Texas and Mexico, the prevalence of DM was 39% and 36% respectively [17], and the incidence of TB in patients with DM demonstrated to be 4-5 times greater than among the non-diabetic population [3,17]. DM also associates with a worse clinical outcome (both morbidity and

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mortality) for respiratory infections with Streptococcus pneumonia and SI [3]. In one study from Hong Kong, in those with DM who were also aged 75 years and over, mortality rates from pneumonia actually exceeded those from cardiovascular disease and cancer [6,18]. Every year, SI causes between 300,000 and 600,000 excess respiratory deaths globally [19]. DM is a known risk factor for adverse outcome of SI [15]. The severity of SI (A or B viruses) depends on the immune and health status of the infected individual [15]. Most patients infected with SI experience mild and self-limiting respiratory symptoms, with more severe cases associated with older age and/or co-morbidities [11,15]. In one reported meta-analysis, it was demonstrated that DM associated with a higher risk of hospital admission for SI A-H3N2 infection, and with increased risk of mortality for the pandemic SI strain, A-H1N1 in 2009 [15,20]. Overall, hospitalization rates of patients with DM suffering from SI was up to six times more likely, compared to those in healthy individuals suffering from SI [3,21]. The data outlined here provide a rationale for recommendation of annual SI vaccination in patients with DM (and other co-morbidities) by the World Health Organization, and numerous other esteemed and learned associations [15,22].

Existing evidence also supports DM as a risk factor for adverse outcome of coronavirus-related infections causing respiratory disease. Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) occurred in 2002, and affected >8,000 people, mainly from Asia [4-6]. Huang and colleagues reported on >120,000 hospitalizations in Taiwan, during the SARS-CoV epidemic itself, and during other key time periods that included pre-, early post- and late post-SARS-CoV epidemic [4]. During the early post-SARS-CoV period, there was a >10% increase in hospitalizations for patients with DM and hypertension, and this remained significant for DM in the later post-SARS-CoV period. The Middle East Respiratory Syndrome coronavirus (MERS-CoV) is a more recent example of coronavirus-related respiratory infection that emerged in Saudi Arabia in 2012, affected >2,400 people mainly from Saudi Arabia, and caused >800 deaths [6,7]. Epidemiological data reveal DM as a primary comorbidity that associated with severe or lethal MERS-CoV infection [8]. One retrospective study from Saudi Arabia reported on >440 patients with confirmed viral pneumonia, including MERS-CoV and SI, hospitalized between January 2012 and December 2015 [23]. In this study, predictors of mortality included age >65 years and male gender, but also included co-morbidies, especially DM, hypertension and Chronic Kidney Diseases. Indeed, number of co-morbidities correlated directly with increased mortality [23].

Interestingly, there is some controversy in the literature regarding clinical outcome of pneumonia in patients with DM. Hespanhol and colleagues reported on a large (n>40,000)

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retrospective cohort study from Portugal, on adult patients hospitalized for pneumonia during 2015 [24]. In this study, mortality associated with older age. However, although many co-morbidities associated with risk of mortality from hospitalized pneumonia, DM and obesity did not appear to worsen mortality outcome [24]. In other studies, however there is a clear association between pneumonia and DM. In one recent study, Isturiz and colleagues reported on the rates of community-acquired pneumonia (including infections caused by the PCV13 serotypes of pneumococcus), on >12,000 hospitalized adults from the US [25]. Amongst those with community-acquired pneumonia, notable co-morbidities included DM and Chronic Obstructive Pulmonary Disease (COPD) in 28.6% and 43% of the cohort respectively [25]. In yet another large multicentre observational cohort study on >20,000 patients admitted to Intensive Care Unit with invasive pneumococcal infection and pneumonia, DM was revealed to be one of only four factors related to mortality (HR 1.91, 95% CI 1.23-3.03, P=0.006) [26].

Based on current data, severity of respiratory infections (including gram-negative, staphylococcus-based and fungal infections, TB, SI, community-acquired pneumonias and recent coronavirus-related epidemics such as SARS-CoV and MERS-CoV) is influenced by DM as an important risk factor, comparable with respiratory co-morbidities including COPD. It is important to explore the underlying mechanisms that mediate the adverse effects of DM on the susceptibility to and severity of respiratory infections.

2.1 Mechanisms that mediate Diabetes Mellitus as a risk factor for respiratory infections

In addition to hyperglycaemia, DM also associates with chronic inflammation [15]. Furthermore, Type 2 Diabetes Mellitus (T2D) also associates with obesity and metabolic syndrome. Indeed, obesity *per se* increases the risk of severe SI [15,27]. Therefore, some of the association of T2D with severe SI probably mediates through obesity-related effects. In one study reported for the SI pandemic of 2009, obesity was shown to associate with increased risk of mortality, and need for hospitalization and ICU admission and ventilator support [15,27]. However, it is also clear that DM *per se* increases mortality from infections generally, with one study showing the HR for infection-related death in DM (excluding pneumonia) to be 1.9-2.9, and the HR for pneumonia-related death in DM to be 1.4-1.9 [15,28]. Hyperglycaemia and glycaemic oscillations may underlie association of DM with increased severity of SI [15,29].

Risk for infections (including respiratory infections) in DM and associated obesity, may stem from the association of DM with deficiencies in immune functioning and immune surveillance that include cellular and humoral innate immunity. Such deficits in immune

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functioning may have contributed towards adverse outcomes and increased mortality from SI in patients with DM [15]. There is compelling evidence to support association of DM with a defective immune response to infections. DM is known to associate with a lower production of interferon (IFN)-α from dendritic cells [15,30], and diminished defence capacity from antibodies, and monocyte malfunction [3]. A lower Cluster of Differentiation 4 (CD4) cell count in patients with DM may contribute towards a dysfunctional neutrophil response to infection, and a diminished response to cytokines [3]. Furthermore, DM associates with a diminished release of interleukin 1 (IL-1) and interleukin-6 (IL-6) [31].

Glycaemic effects may mediate the association between DM and diminished immune response. Glycation appears to inhibit release of interleukin-10 (IL-10) and tumour necrosis factor α (TNF- α) from lymphocytes and macrophages, and release of interferon gamma (IFN-γ) from T-cells and Natural Killer (NK) cells [3]. Glycation may impair cell-mediated immunity through suppressed expression of major histocompatibility class 1 on myeloid cells [31]. Hyperglycaemia also impairs the process of phagocytosis, including mobilization of polymorphonuclear leukocytes and chemotaxis [3]. Other mechanisms that link hyperglycaemia with impaired immune function include enhanced apoptosis of leukocytes, and depletion of cellular Nicotinamide Adenine Dinucleotide Phosphate (NADPH), with increased tissue sensitivity to oxidative stress [3]. To compound the multiple deficiencies of cell-based immunity in DM as outlined here, DM also associates with deficient humoral immunity. In DM, glycation of immunoglobulins is commensurate with HbA1C [9]. Such a process may impair biological functioning of antibodies, and thereby contribute towards impaired humoral immunity [3,9].

To complement human-based studies, much of the existing data to support an association between DM and immune dysfunction originates from rodent-based studies. Kulcsar and colleagues developed a mouse model of enhanced susceptibility to MERS-CoV, and compared wild-type mice with mice that had had induction of T2D through a high-fat diet. Following infection with MERS-CoV, the T2D-induced mice had a prolonged duration of severe disease, and delayed recovery from MERS-CoV [8]. In the same study, T2D-induced mice had fewer inflammatory monocytes, macrophages and $CD4^+$ T-cells. The authors hypothesized that in patients with DM, MERS-CoV-related severe and prolonged lung pathology (including pulmonary infiltration with macrophages), results from a dysregulated immune response [6,8]. In a separate rodent-based model of diet-induced obesity, a defective antiviral and pro-inflammatory cytokine response associated with increased mortality from SI viral infection [15,32].

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In summary, the current literature provides much compelling evidence from both human- and rodent-based studies, to support the notion that DM associates with impairment of both cellular- and humoral-based immunity. Whilst the mechanisms linking DM with impaired immunity are likely to be multiple and complex, data from some of the studies outlined here show that severity of *hyperglycaemia* (based on HbA1C measurements) are commensurate with some measures of immune dysfunction (such as humoral immunity [9]). Consistent with an important role for glycaemia in the mediation of immune dysfunction in DM, reported data show association of poor glycaemic control in DM with propensity for infections, including a meta-analysis on >17,000 adult patients with DM who underwent cardiac surgery. Those patients with a pre-operative HbA1C >6-7% had a substantially increased risk of sternal wound infection [33]. Although poor glycaemic control in patients with DM increases risk of infection through *non*-immune related mechanisms (including encouragement of bacterial growth from a sugary local environment), dysfunction of both cellular- and humoral-based immunity in DM (itself influenced by prevailing glycaemic control) is likely an important contributor to the association between DM and infections (including respiratory infections). In addition to hyperglycaemia, ageing also adversely affects the immune system in multiple ways, including age-related dysregulation of haematopoiesis (required to replenish immune cells throughout life), thymic involution that limits output of naïve T-cells, and age-related changes in the regulation of innate and adaptive immunity [34]. Therefore, older patients with DM, especially those with impaired glycaemic control, are at a particularly high risk from respiratory infections.

3. Diabetes Mellitus and COVID-19: implications for prognosis

COVID-19 is a recent novel infective agent within the human population that did not exist as a human-based pathogen prior to December 2019. However, even at this early stage of the pandemic, existing data on mortality and adverse clinical outcome from COVID-19 does indeed reveal DM as an important risk factor. Yang and colleagues reported on a single-centre, retrospective, observational study from Wuhan, China, on a group of patients on ICU (n=52) with COVID-19 [35,36]. Amongst the non-survivors (n=32), 22% had confirmed DM. A similar proportion (22%) of the non-survivors also had cerebrovascular disease [35,36]. In another study on patients from China with a confirmed diagnosis of COVID-19 (n=1099), amongst those with severe disease (n=173), 16.2% had confirmed DM. Other comorbidities amongst the severe cases included hypertension (23.7%), coronary heart disease (5.8%) and cerebrovascular disease (2.3%) [35,37]. In a further study of hospitalized patients (n=140) with COVID-19 in Wuhan, China it was shown that 12% had a confirmed diagnosis of DM and 30% had hypertension [35,38]. Data from the Chinese

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Centre for Disease Control on >44,600 confirmed COVID-19 cases show an overall mortality rate of 2.3%, but a disproportionately high mortality rate of 7.3% in the subgroup with DM. Not surprisingly, mortality rates were also high (10.5%) in those with cardiovascular disease, and particularly high (49%) in those critically ill patients [39].

To corroborate these data from China, data from other countries have also revealed DM as an important risk factor for COVID-19. Data from Italy revealed DM as the second most common co-morbidity to associate with COVID-19, affecting 33.9% of confirmed infected cases [40]. Preliminary data from the US also show that those with underlying health conditions such as DM, chronic lung disease and cardiovascular disease, are at a higher risk for severe disease from COVID-19 [41]. Amongst the >7,000 cases of COVID-19 in the US where co-morbidities were also reported, 37.6% had one or more underlying health condition, such as DM. Amongst those cases of COVID-19 in the US requiring ICU admission and those requiring hospitalization without ICU admission, the proportions of cases with at least one underlying health condition were 78% and 71% respectively [41].

3.1 Mechanisms that mediate Diabetes Mellitus as a risk factor for COVID-19

As with other respiratory infections, it is clear from the current literature that DM represents an important risk factor for COVID-19 infection. However, given the association of DM with multiple other co-morbidities such as cardiovascular disease, obesity and hypertension, it is currently unknown whether DM *independently* contributes towards increased risk from COVID-19 [10]. It seems reasonable though, based on the evidence outlined in this review, to posit that DM probably does play an important independent role as a risk factor for COVID-19 infection, and that prevailing glycaemic control contributes to this risk. To corroborate this perspective, data from a multi-centre study on >7,300 cases of COVID-19 in Hubei Province, China, demonstrated that amongst the subgroup (n=952) with pre-existing T2D, those hospitalized cases with well-controlled glycaemia had markedly lower mortality rates than cases with poor glycaemia (defined by upper limit of glycaemic variability exceeding 10mmol/l), with HR 0.14 [42]. Furthermore, there was a significantly greater mortality from COVID-19 in those cases with T2D compared with non-diabetic individuals (7.8% vs 2.7% respectively; adjusted HR 1.49) [42].

It has been suggested by Muniyappa *et al.* that there are five main possible mechanisms that may underlie increased susceptibility to COVID-19 in patients with DM: i) greater affinity of COVID-19 for cellular binding and entry; ii) reduced viral clearance; iii) reduced T-cell function; iv) co-existent cardiovascular disease, and; v) susceptibility to cytokine storm and hyper-inflammation [10]. The cellular receptor for COVID-19 is angiotensin-converting enzyme 2 (ACE2) [10]. Rodent models of DM have shown augmented expression

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of ACE2 in the lung, kidney, heart and pancreas [43], thereby providing a possible (but speculative) mechanism for enhanced cellular entry of the COVID-19 virus in DM. As outlined earlier, immune dysfunction in DM (both humoral and cell-based) may result in reduced viral clearance. DM associates with low-grade chronic inflammation that may contribute towards a hyper-inflammatory response to viral infections, although this remains speculative and should form a focus for future research.

To summarize, multiple mechanisms mediate DM as a risk factor for COVID-19, including both diabetes-*related* (such as impaired glycaemia) and diabetes-*associated* (such as immune dysfunction, obesity and hypertension) components, summarized in *figure 1*. Insights from ongoing research into these underlying mechanisms will enable development of novel therapeutic and management strategies, to optimize healthcare provision for patients with DM and COVID-19.

4. Diabetes Mellitus and COVID-19: implications for clinical management

Having explored DM as an important risk factor for COVID-19 infection, it is important to consider how best to optimise the clinical management of such patients. Unfortunately, given the recentness of the current global pandemic, we cannot rely upon randomized controlled trials to inform clinical practice. In such a scenario, it is useful to gain insight from learning points derived from prior epidemics. A detailed exposition of the entire management spectrum of DM is beyond the scope of this review. Rather, in this section, there is discussion of some key principles of effective management of DM during the COVID-19 pandemic.

4.1 Preventive considerations in patients with Diabetes Mellitus

Advice from the Centres for Disease Control and Prevention regarding prevention of COVID-19 in patients with DM does not differ from that provided for the general population [44]. However, as outlined in this review, DM associates with a greater risk for severity of infections generally. Therefore, healthcare professionals should be more vigilant in their assessment of patients with DM who present with symptoms suggestive of COVID-19 infection, such as dyspnoea and fever [44,45].

4.2 Outpatient management of Diabetes Mellitus

It is important for us to learn lessons from the past regarding the current COVID-19 global pandemic. In the study from Taiwan outlined above, the authors hypothesized that one explanation for the increased rate of hospitalization of patients with DM post-SARS-CoV epidemic, was the reduced usage of regular effective care by patients with DM during the

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SARS-CoV epidemic. For example, outpatient utilization dropped by >12% during the SARS-CoV period [4]. The data outlined does not prove the hypothesis that reduced utilization of outpatient care by patients with DM during the SARS-CoV epidemic contributed towards subsequent increased rates of admission to hospital for patients with DM. However, this hypothesis is entirely plausible. DM is a chronic condition that, perhaps more than many other chronic conditions, demands close and meticulous management, usually in an outpatient (or community-based) setting. Glycaemic control influences prognosis in patients with DM in many ways, including susceptibility to and severity of infections [33].

It is important that during the current global COVID-19 pandemic, we do not lose sight of the importance of ongoing close management of our patients with DM, even if current restrictions necessitate remote management. Indeed, the current pandemic demands us to administer a level of ongoing DM management to our patients that *supersedes that during normal times*. To focus our entire attention on acute and reactionary care of the acutely unwell to the detriment of ongoing preventive management strategies (including to patients with DM *who may yet contract COVID-19*), would likely heighten the future risk of severe infections, hospitalizations and adverse outcomes in our patients with DM. We should maintain close attention to outpatient preventive management of DM to limit hospital admissions of patients with DM during and following the current pandemic, based on the experiences of SARS-CoV in Taiwan [4]. Furthermore, we could use this time as an opportunity to develop alternate means of healthcare provision, such as telehealth, wearable technologies and remote patient monitoring [10]. That is not to diminish in any way the need for acute reactionary care at this time of unprecedented need, which of course is crucial. Simply, let us not lose sight of the bigger picture. Let us maintain a sense of wider perspective for our patients with DM, regardless of their current COVID-19 infective status. Accordingly, we can hope to improve overall clinical outcomes and demand in the future, through optimized care and preparedness in the present.

4.3 Maintenance of good glycaemic control

Patients with DM and COVID-19 who also have inadequate glycaemic control have a higher risk of infection and increased likelihood of poor clinical outcome, compared to patients with DM who have good glycaemic control [40,42,46,47]. Plasma glucose level in patients with DM who have SARS-CoV is also an independent predictor of mortality and morbidity [10,48]. Furthermore, as discussed there are adverse effects of glycation on immune functioning [3,9]. Based on such evidence, we should be striving for good glycaemic control in our patients with DM, both as a preventive measure, but also in those patients with DM and COVID-19 as a means of optimizing clinical outcome.

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4.4 Conversion onto insulin infusions in hospitalized patients with Diabetes Mellitus

In patients with DM, any infection can worsen glycaemic control through stress, mediated through mechanisms such as enhancement of cortisol release. This would be exacerbated through any usage of exogenous glucocorticoid therapies [40]. Switch to continuous intravenous insulin-based therapies often occurs in hospitalized patients with DM and acute infections. Unfortunately, sub-optimal management of continuous intravenous insulin-based therapy conversions occurs frequently in hospital-based settings [49,50], and glycaemic variability (including exposure to hypoglycaemia) is common [51]. Exposure to both hypoglycaemia (through mobilization of pro-inflammatory monocytes [52]), and hyperglycaemia (through build-up of toxic by-products of the glycolytic pathway [53] and up-regulation of glucose transporters [54]), during such insulin transitioning may potentially worsen clinical outcome in patients with DM [40]. Glycaemic variability in patients with SI may worsen respiratory function through cytokine release and extravasation of leukocytes into the alveolus [55,56]. Indeed, large glycaemic variability is even predictive of ICU mortality [57].

Effective management of glycaemia in hospitalized patients with DM who are acutely unwell, particularly when suffering from acute infections, is often challenging. Such management is particularly challenging during a global pandemic, with an influx of patients who are acutely unwell. Furthermore, many healthcare professionals are currently stepping outside of their usual working practices, and some may be less familiar with the logistics and practicalities of conversion to, and ongoing management of intravenous insulin-based therapies. There is worsening of such a scenario by a need for personal protective equipment by healthcare staff that may further hamper effective glycaemic management. However, despite these multiple and unprecedented challenges, it is important that healthcare professionals strive for glycaemic stability in patients with DM and COVID-19, and particularly those who have been converted to intravenous insulin-based therapies. Close monitoring of glycaemia is required, and an appreciation that in acutely unwell patients with DM, multiple factors conspire to destabilize glycaemic control. In such a scenario, optimal glycaemic management often requires frequent adjustments to insulin-based therapies, informed by continuous and meticulous observations of prevailing glycaemic status.

4.5 Usage of angiotensin converting enzyme (ACE) inhibitor and angiotensin II type-1 receptor blocker (ARB) drug therapies

It is known that human pathogenic coronaviruses require angiotensin-converting enzyme 2 (ACE2) to bind to target cells [35,58]. Expression of ACE2 occurs within the epithelial

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lining cells of the lung, intestine, blood vessels and kidney [35,58]. ACE2 expression is known to be increased in patients with DM [40]. Furthermore, treatment with ACE Inhibitor and ARB therapies associates with *increased* expression of ACE2 in patients with DM [35,58]. Patients with hypertension treated with ACE Inhibitor and ARB therapies also have upregulation of ACE2 [59]. It has been hypothesized by Fang and colleagues that use of ACE Inhibitor and ARB therapies in patients with DM and hypertension, through enhancement of expression of ACE2 and facilitation of COVID-19 viral cellular entry, may increase the risk of development of severe and fatal COVID-19 infection [35]. It has also been proposed that certain polymorphisms within the ACE2 protein resulting from underlying genetic anomalies, may increase the risk of severe COVID-19 infection in some patients [35]. Such ACE2 polymorphisms may associate with DM, hypertension and stroke, particularly in Asian populations [35].

Despite these credible hypotheses, it is important to exercise caution regarding theoretical risks of ACE Inhibitor and ARB drug therapies in COVID-19, in the absence of any clear supportive evidence. We can perhaps learn from the lessons of SARS-CoV, when a similar hypothesis was proposed regarding ACE2 polymorphisms linked to DM and other co-morbidities, that may confer genetic predisposition to SARS-CoV infection [40]. At the time, this hypothesis caused global anxiety and alarm regarding ongoing usage of ACE Inhibitor and ARB therapies. In response, advice from most relevant international scientific societies was to follow evidence-based medicine demonstrating the well-established cardiovascular benefits of these classes of drug therapies [40,60]. Indeed, the cardiovascular implications of inappropriate discontinuation of these classes of therapies on a large scale could have been catastrophic. Optimization of modern-day medical practice occurs through adoption of an evidence-based approach. Hypotheses are important as a stimulus and rationale for experimentation and data generation. By definition though, hypotheses lack evidence. We should therefore not sway our medical practice by hypotheses without supportive evidence. It may seem logical to discontinue ACE Inhibitor and ARB therapies in patients with DM, based on a theoretical reduction in the risk of susceptibility to COVID-19. However, at this stage without any supportive evidence, this approach would be incorrect [44], and indeed would likely result in a future worsening of cardiovascular profile and events in patients with DM. Evidence-based medicine, by its nature, is a dynamic entity and our future practice may need to change accordingly. Based on current evidence though (or lack of it), there is no indication to discontinue ACE Inhibitor or ARB therapies in patients with DM.

4.6 Usage of Metformin

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Metformin is a first-line therapy for T2D in many patients, often in combination with other therapies (both oral and injectable). However, metformin has a potential side effect of lactic acidosis, with heightened risk in the context of renal, cardiac and liver impairment, hypotension and acute illness [61]. Therefore, current NICE guidance recommends temporary discontinuation of metformin therapy during any acute illness, (including COVID-19 infection). In such a scenario, alternate therapies may be required to maintain good glycaemic control.

4.7 Usage of dipeptidyl peptidase 4 (DPP-4) Inhibitor therapies

As outlined, ACE2 is the cellular receptor for COVID-19 and for SARS-CoV [62]. Conversely, MERS-CoV utilizes DPP-4 as its cellular receptor [10,63]. Accordingly, in the transgenic mouse model outlined earlier, expression of DPP-4 receptors on pulmonary alveolar cells was used to study the effects of MERS-CoV [8]. There is currently a lack of published human-based data on DPP-4 and COVID-19 [40]. However, given that cellular entry of COVID-19 appears independent from the DPP-4 receptor, there does not appear to be any theoretical rationale for modifying DPP-4 Inhibitor therapies in patients with DM.

4.8 Usage of sodium-glucose like-transporter 2 (SGLT2) inhibitor therapies

The SGLT2 inhibitor class of therapies has risen to prominence in recent years, as an efficacious therapeutic option for glycaemic control, with secondary benefits of weight loss and systolic blood pressure reduction. Furthermore, recent randomized control studies have revealed reduced risk for cardiovascular events and renal protection [64]. However, SGLT2 inhibitor therapies can also increase risk of Diabetic Ketoacidosis (DKA), especially in older patients and with longer-term usage [65]. Current NICE guidance recommends temporary discontinuation of SGLT2 inhibitor therapies during any acute illness (including COVID-19 acute infection) as a precautionary measure. In such scenarios, it is important to ensure maintenance of good glycaemic control with alternate therapies if necessary, especially given that glycaemic control is likely to worsen during acute illness. Dapagliflozin is currently being assessed in hospitalized patients with COVID-19 and risk factors (such as hypertension, T2D, heart failure, chronic kidney disease stages 3 or 4, and atherosclerotic cardiovascular disease) for developing serious complications. The Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) study will explore the effects of Dapagliflozin versus placebo on time to first event of all-cause death or morbid disease complications (including respiratory, cardiovascular and renal), during a 30-day follow-up period (https://clinicaltrials.gov/ct2/show/NCT04350593).

4.9 Usage of glucagon-like peptide 1 (GLP1) therapies

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GLP1 therapies are widely used in the management of T2D. Although heterogeneity exists amongst the class, glycaemic efficacy with GLP1 therapies is generally excellent. This class also provides secondary benefits of systolic blood pressure reduction and weight loss. Furthermore, some of the GLP1 therapies also provide cardiovascular protection, with reduced occurrence of cardiovascular events [66,67]. Unlike metformin and SGLT2-Inhibitors, there is no equivalent guidance from NICE regarding discontinuation of GLP1 therapies during acute illness. Therefore, in patients with T2D managed with GLP1 therapies, COVID-19 infection *per se* should not be a reason to discontinue this therapeutic class: indeed maintenance of GLP1 therapies in such a scenario is likely to contribute towards glycaemic stability. Of course, temporary withdrawal of GLP1 therapies may be required in certain clinic scenarios, such as in severely ill patients with deterioration of renal function below licensing threshold.

5. Concluding remarks

The COVID-19 global pandemic has spread around the world in an alarmingly short time-frame. Although the COVID-19 pandemic is a rapidly evolving phenomenon, it has already changed the world in ways that would have been unimaginable just a few months ago. In these unprecedented and most challenging of times, all of us in society have an important role to play, particularly healthcare professionals. Many of us are working in unfamiliar and stressful circumstances, and often outside of our comfort zones. Tragically, some healthcare professionals have lost their lives from COVID-19. Our entire profession, and indeed the whole of society, owe a huge debt of gratitude to these courageous and altruistic colleagues who worked selflessly for their patients: a titanic loss to colleagues, patients, friends, family and loved ones.

Given the novelty of COVID-19 and the complete absence of herd immunity, the entire population is at risk. Any one of us could suffer from the severe and even fatal consequences of COVID-19. However, it is also clear that certain subgroups of the population are at particularly high risk. Data from around the world have consistently demonstrated that certain co-morbidities are risk factors for COVID-19, and that DM is a particularly prominent risk factor. It is important, therefore, to consider patients with DM as a special group of patients that require and deserve our focused attention. In these unprecedented and challenging times, it would be easy to focus entirely on acutely ill patients. Whilst this is clearly important, it would be a mistake to allow this focus to detract from ongoing outpatient care of patients with DM. Indeed, we should prioritize care of patients with DM, with a particular focus on improved and optimized glycaemic control, in the hope that this strategy will reduce the likelihood of future infection with

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COVID-19 and the severity of such infection. The COVID-19 pandemic has provided healthcare professionals with an opportunity to explore novel means of executing outpatient and community-based care through remote technologies, including for example telehealth. Much of outpatient management of DM lends itself well to such technology. Perhaps following this pandemic, some of these remote technologies will persist for some of our patients who find it difficult to leave the house, or visit hospital. This would be a positive learning outcome from the current pandemic.

We will remember the COVID-19 pandemic for decades and centuries to come as a landmark event, on a par with the Spanish Flu pandemic of 1918, and even the great plagues from medieval times. The current COVID-19 pandemic will eventually end. Whether the concluding scenes will emanate from an effective vaccine, from the establishment of herd immunity, or even from adaptation to a new way of living through social distancing, is impossible to predict. Perhaps a combination of all three of these scenarios will pertain. However, what is easier to predict is that following our emergence from this dreadful chapter of world history, the world will have changed in many ways. Economic, political and psychosocial landscapes will be re-written. As healthcare professionals, we will need to adapt to these changes. It is important that we use this unique experience to our advantage, and for each of us to reflect individually on key learning points. These may include new insights into our own capacities and capabilities as humans, or novel means of managing our patients for example. As clinical teams, we will have an opportunity to look back on these times as a great learning experience too, perhaps to adopt new and effective ways of working, and to appreciate the importance of comradery and collegiality amongst colleagues. As healthcare professionals, we will emerge from the COVID-19 pandemic stronger, and ultimately this will be to the betterment of patient care.

Florence Nightingale said, '*How very little can be done under the spirit of fear*'. Let us therefore proceed in a spirit of confidence, and manage this pandemic together, socially distanced, but united and resolute.

6. Expert opinion

COVID-19 has punctuated all of our lives in a way that will leave an indelible imprint in our collective memories. We will remember the year 2020 for years, decades, even centuries to come as a year that changed the world. The future will determine exactly how the world will change following COVID-19, but change it will. We can compare the magnitude of COVID-19 with historical global events such as the Spanish Flu pandemic of 1918, and even the great plague pandemics of medieval times. Throughout human history, we have

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always lived with the threat of infections. Indeed, up until relatively recently, infections (along with famine and the effects of war) were a major cause of premature mortality amongst the entire global population. Thankfully, we live in an era of modern healthcare systems and infrastructure, modern therapies such as antibiotics to treat pathogens, modern lifestyles with an emphasis on sanitation, clean water supplies and effective preventive measures to limit the spread of infections. Vast healthcare inequalities still exist around the globe, and we can only hope that such inequalities diminish through global efforts over time. A notable exemplar in this enterprise includes the Bill Gates philanthropic fund for people living in sub-Saharan Africa, covering the cost of potentially life-saving treatments for Human Immunodeficiency Virus (HIV) and Mycobacterium tuberculosis (TB) to a vast population in which many live below the poverty line.

Over centuries, there has been transformation of our knowledge and understanding of infections and their spread encompassing humoral and germ-based theories. Facilitation of such insights has occurred through application of epidemiological data, powerful statistical tools, and cell-based studies on the cellular entry and effects of pathogens, and the resultant host immune response. Put simply, our species has become adept in the prevention and effective management of pathogens. Nothing epitomizes this adeptness better than the global eradication of smallpox, which remains one of the greatest medical achievements of all time.

It is in this modern era that COVID-19 has emerged, and one reason why the devastating impact of this pandemic is so shocking and humbling. In one single event we are compelled to a collective realization that despite our advanced knowledge, understanding and insights into pathogens, our modern-day healthcare infrastructures and therapies, lifestyles, hand-washing routines, sanitation and clean drinking water, infections still have the potential to devastate our world. This is a wake-up call to politicians and governments around the globe to take infections seriously, and to invest in appropriate preparedness for future pandemics, that will certainly occur. There is no room for complacency.

COVID-19 has resulted in much pain, suffering, loss, misery, anxiety and distress across the globe, and will continue to do so. It is important though, that despite such immense human suffering, we embrace hope. With a common viral enemy, COVID-19 is uniting the world in a way that we have never experienced. Using an analogy of national unity in response to a common enemy during times of war, COVID-19 evinces as a common enemy and purpose to unite the entire world. Let us hope that such renewed focus on an indiscriminate threat to us all, results in diminishment of selfishness and self-centredness, with an attendant decline in conflict and wars between factions of peoples within and

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between countries. As healthcare professionals, we will emerge from this pandemic stronger and united, with renewed insights both as individuals and as clinical teams, with a better appreciation of the importance of comradery amongst colleagues not just during times of global crisis, but at all times. Ultimately, for the betterment of patient care.

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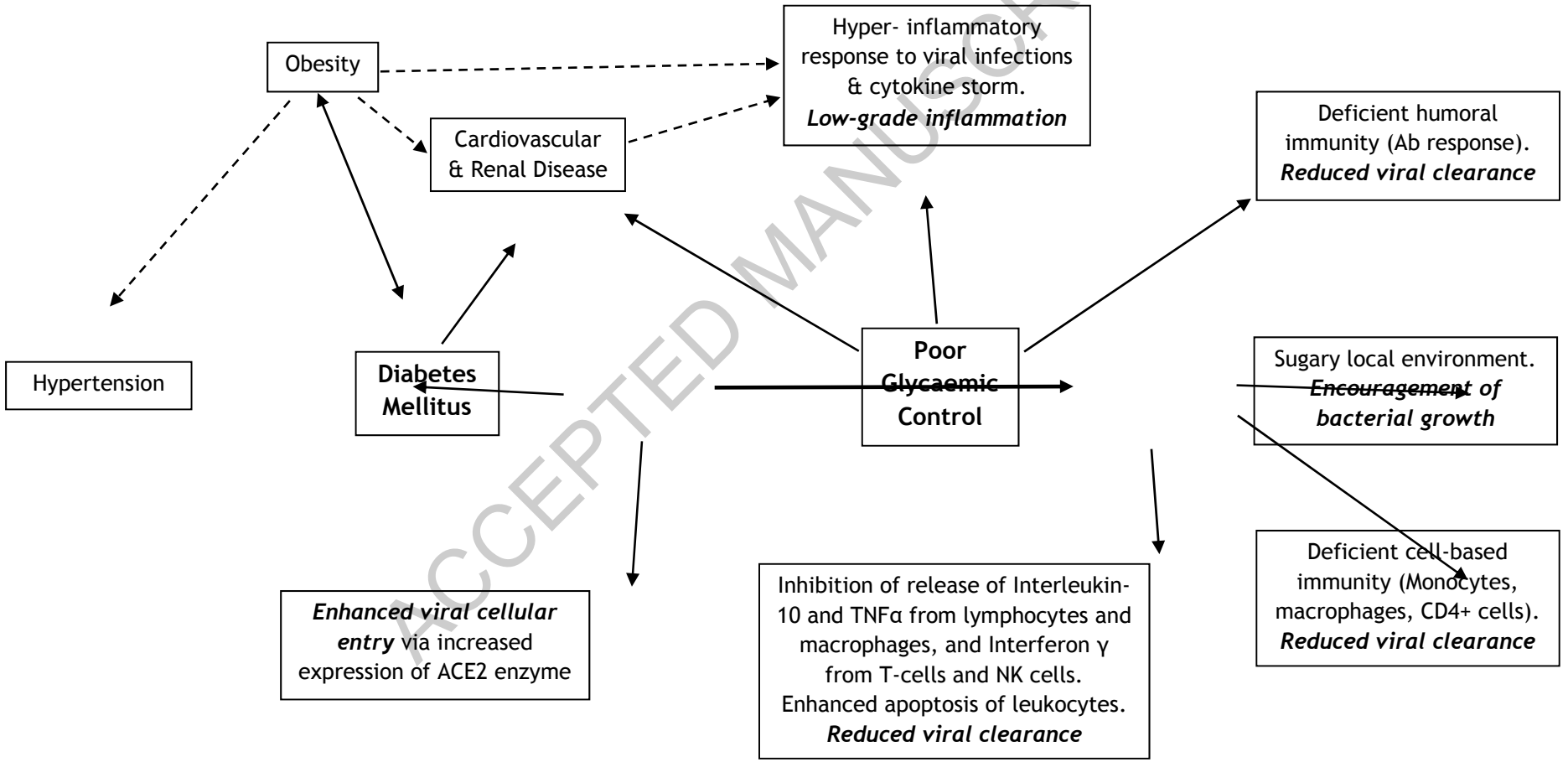
Figure 1: Summary of possible underlying mechanisms that mediate association between Diabetes Mellitus and susceptibility to and severity of COVID-19 infection. (Dashed lines show indirect effects of factors related to Diabetes Mellitus and poor glycaemic control).
(*Ab=Antibody; ACE2=Angiotensin-Converting Enzyme type 2; CD4=Cluster of Differentiation 4; NK=Natural Killer; T-cells=Thymus cells; TNFa=Tumour Necrosis Factor a*)



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