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Case Series

Successful Management of COVID-19 in Hospital in-patients with Type-2 Diabetes

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Abstract

Objective: To identify and describe a cohort of patients who were admitted to a large Australian tertiary hospital with COVID-19 diagnosis, and background of Diabetes Mellitus (DM).

Design: Retrospective chart review of a de-identified list of in-patients who had tested positive to COVID-19 provided by the hospital health analytics team for the period of February 2020 to May 2020.

Setting: This case series reviewed a total of eight diabetic patients with COVID-19 who were admitted to the Gold Coast University Hospital, and this represented 12.5% of the population of total number of 63 COVID-19 infected patients requiring hospitalization during the study period.

Participants: All 63 hospitalised in-patients who had tested positive to COVID-19 between February 2020 to May 2020 were included in the study.

Main outcome measures: Eight cases were identified and included in the case series, who had Type 2 Diabetes. This group had significantly better clinical outcomes than other diabetic patients diagnosed with COVID-19 reported in the international literature to date.

Results: Only two of our in-patients with Diabetes and COVID-19 infection had long term follow up of their Diabetes approximately 4 - 10 months after the hospital admission, their HbA1c tests before and after admission revealing that the Diabetes control had not worsened. The mortality rate overall for all COVID-19 patients at the Gold Coast health service district, was zero.

Conclusion: Australia enjoys a taxpayer funded free Medicare health care system. Several other factors at play, including socioeconomic factors, influence the virulence of this pathogen.

Introduction

In December 2019, an outbreak of a highly infectious and communicable respiratory disease in Wuhan, China led to the discovery of the novel virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It is a positive single stranded RNA virus that primarily affects the respiratory system [1]. The clinical syndrome caused by the virus is commonly referred to as COVID-19. As of March 2021, there have been approximately 122.5 million confirmed cases and over 2.7 million confirmed deaths across 223 countries and territories [2].

Diabetes is a chronic health condition associated with multiple complications and greatly contributes to the global health-care burden [3,4]. Emerging evidence suggests it is a risk factor for, and is associated with more severe COVID-19 clinical course

and mortality [3]. In China up until the end of March 2020, 7% of patients who were COVID-19 positive were diabetics, although of those with more advanced disease, diabetic patients made up 16% of the population [5]. A study of 1099 Chinese patients, of which 7.4% had diabetes, found that 26.2% of the patients that reached the primary composite endpoints of an ICU admission, mechanical ventilation or death, were diabetics [6]. The largest COVID-19 whole-population study to date has recently been published covering majority of the English population. This study found that one third of all in-hospital COVID-19 deaths occurred in people with diabetes: 31.4% of deaths were in people with type 2 diabetes (T2DM) and 1.5% in people with type 1 diabetes (T1DM) [7]. Mortality rates increased with age, with rates significantly higher for people with both type 1 and 2 diabetes within each age group compared to those without diabetes [7]. Comparing figures of deaths in people with diabetes from England's National Diabetes Audit data, the findings from this paper suggest relatively higher COVID-19 mortality rates in patients with T1DM and T2DM during the pandemic [7].

Diabetes mellitus is a proinflammatory state which in turn contributes to a disturbed immune response [6,8]. Hyperglycemia stimulates vaso-injurious signaling pathways, ultimately resulting in an increase in oxidative stress, proinflammatory cytokines, including IL-1b, IL-6, and activation of immune responses [8]. IL-1b, IL-6 have been shown to modulate pancreatic islet cell insulin release and promote insulin resistance in peripheral tissues [8]. Patients with T2DM have been shown to have increased total leukocyte counts, specifically neutrophils and lymphocytes, which correlate with insulin sensitivity [8]. Antibacterial activities of neutrophils have also been shown to be impaired in diabetes, with reduced neutrophil chemotaxis, decreased bactericidal and phagocytosis activity. More recent studies suggest T-lymphocytes also play a pivotal role in immunity defects in T2DM, with delayed and impaired lymphocyte proliferative responses [8]. Thus in diabetic patients, dysfunction of both the adaptive and innate immune systems play a critical role in the severe clinical course seen in many COVID-19 positive patients.

Studies have shown that patients with severe COVID-19 have elevated levels of proinflammatory cytokines, particularly IL-6, IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1α and TNF [9]. This proinflammatory state, or cytokine storm, can lead to cardiac, hepatic and renal tissue damage, along with shock, respiratory and/or multi-organ failure [9]. Significant pulmonary pathology, such as diffuse alveolar damage, formation of hyaline membranes and diffuse thickening of the alveolar wall, is commonly observed [9]. IL-6 in particular appears to be more elevated in diabetic COVID-19 patients than in those without diabetes. Elevated levels of IL-6 have been correlated with poorer outcomes in patients with severe COVID-19 with pneumonia and ARDS [9]. The chronic state of low-grade inflammation in people with diabetes may facilitate this cytokine storm and predispose these patients to a more severe clinical course of COVID-19. Furthermore, this state has the potential to worsen pre-existing diabetes [10].

In T2DM there is enhanced endothelial dysfunction and platelet activation and aggregation. This, along with increased levels of clotting factors, predisposes diabetic patients to a hypercoagulable state. COVID-19 infection has also been shown to predispose patients to a prothrombotic state, with elevated D-dimer levels commonly seen as part of the disease process and strongly associated with higher morbidity and mortality [4,11].

This case series outlines eight patients with T2DM who were admitted to an Australian tertiary hospital with COVID-19. This group was part of a larger patient population of sixty-three patients who required an inpatient stay to manage the infection. This review will identify trends in the patients' severity of presentation, any identified COVID-19 complications, how this impacted their inpatient and post-discharge diabetic management, and length of stay. Other important parameters such as MET (medical emergency team) calls and admissions to intensive care unit will be discussed with a view to recognize critical clinical deterioration of these patients.

Methods

The study was conducted at the Gold Coast University Hospital (GCUH), the primary academic health service serving the Gold Coast region, Queensland. A retrospective clinical audit was conducted of all hospital in-patients with a confirmed diagnosis of COVID-19 and Type 2 DM for the following timeframe: February 2020 to May 2020. A list of suitable patients was acquired from hospital health analytics team. Clinical and demographic data was retrospectively collected from the electronic medical record system and recorded onto an electronic data spreadsheet. This study was conducted with an endorsement from the GCHHS human research ethics committee (HREC Reference number: LNR/2020/QGC/64595).

Results & Discussion

This case series reviewed a total of eight diabetic patients with COVID-19, representing 12.5% of the population of infected patients requiring hospitalization.

All of the diabetic patients admitted with COVID-19 within the timeframe of our study were classified as type 2, which is congruent with the proportion of type 2 diabetes in Australia [12]. Six of the eight patients were male, and the average age of the group was 69.8 years. All of the patients reported a diagnosis of diabetes some years prior to COVID-19 infection. Key research produced in China, the country with the most significant initial COVID-19 rates of infection, and research produced from the world's largest population study of COVID-19 from England highlighted an increased risk of infection and associated complications in older

patients [1,7]. Patients were most commonly exposed to the COVID-19 virus whilst undertaking international travel, with three subjects aboard an international cruise ship during infection and two subjects who had recently undertaken air travel. In the locality of this tertiary health service, there was very little community transmission as a result of community compliance with social distancing recommendations, the shutdown of many public areas and businesses, efficient roll out of community testing clinics and a proactive local infectious diseases and public health approach with possible cases promptly tested and isolated.

Seven of these patients (87.5%) required pharmacotherapy pre-admission for glycaemic control, with one patient reporting diet-controlled diabetes pre-infection. All of these patients were taking metformin. Two patients (25%) were insulin dependent. Both of these patients had a recorded HbA1c (glycated hemoglobin) of >7% prior to becoming unwell with COVID-19. Half of the patient cohort were on sodium-glucose co-transporter 2 (SGLT2) inhibitors preadmission. The addition of these medications is likely the consequence of known long-term diabetic complications, in particular cardiovascular disease for patients 2, 4 and 7, or poor long-term sugar control for patient 8 given that HbA1c on admission was 10.8%. All patients taking these drugs had this therapy interrupted at some point during their hospital stay. Consequently, all of these patients then experienced hyperglycemia whilst an inpatient, highlighting that these medications were pertinent to their regular control. Two of these patients required the use of short-term insulin (insulin Aspart) to manage this hyperglycemia and this could be hypothesized to be absolutely connected to their usual glycemic medications being withheld, but also possibly secondary to active COVID-19 infection. No patients required up titration of their normal diabetic regimen or addition of new medications on discharge and these findings are in stark contrast to the outcomes for diabetics reported internationally [6,7,10]. These findings support the notion that it was the withholding of the patients' medications that caused the hyperglycemia, rather than the infection leading to short to medium term changes in blood sugar control.

Two different groups of diabetic patients emerged in our study. The first group were subjects with well-controlled disease with no known micro or macrovascular complications (patients 1, 5, 6 and 8), with the second half of the group diabetics with known end-organ disease at varying degrees of severity (patients 2, 3, 4 and 7). There were mixed results in how these patients fared whilst infected with the virus. Patients with diabetes were generally considered to experience more severe infection with COVID-19 and be at higher risk of complications, particularly those who were also elderly and had known hypertension and/or heart disease. In this patient cohort, there was no clear trend to predicting which patients would experience complications secondary to the infection, making it difficult to compare this Australian cohort of diabetic patients with diabetic outcomes analyzed in international studies. Overall, two patients (25%) had MET (Medical Emergency Team) calls activated for clinical deterioration.

Patients 4 and 5 were identified as having the most significant experience with COVID-19 and presented febrile, fatigued and reporting headaches. Patient 4 also reported myalgia, whilst patient 5 experienced a myriad of other symptoms. On initial chest radiography both presented with unilateral opacification suggestive of an evolving pneumonia, whilst follow up imaging also revealed bilateral patchy infiltrates, common features associated with COVID-19 infection for both subjects [13]. Diabetics in China were identified as having more significant lung changes detected by CT imaging than non-diabetics, likely reflective of more aggressive infiltration [6]. A notable inflammatory response to infection was detected with CRPs (C Reactive protein) over 200 and levels of lactate dehydrogenase (LDH) over 300. These markers have been identified as reflecting significant COVID illness, most likely linked to the cytokine storm that has propelled many patients around the world into cardiorespiratory failure [6]. Both patients also had evidence of coagulopathy, severe in the case of patient 4 with an INR (International Normalized ratio) recorded of 2 and a D-dimer of 16.74 and mild in patient 5's case with an INR of 1.3. These biochemical changes were noted in other patients overseas who experienced severe viral illness and have become important markers for COVID-linked morbidity and mortality [6].

Both patients 4 and 5 experienced notable deteriorations on the ward, with evidence of hypoxia requiring increased oxygen requirements and climbing adult deterioration detection system (ADDS) scores prompting MET calls. Only patient 4 was transferred to intensive care and this was due to significant respiratory failure that was believed to require escalation in therapy. From a glycemic point of view, both patients were hyperglycemic during their stay, which is congruent with the experience seen internationally in other diabetics with marked infection.

The coagulopathy experienced by patient 4 in the setting of his established peripheral vascular disease led to a significant arterial vascular event and an initially undetected deep vein thrombosis. The clinicians involved in this patient's care needed to balance the risk of harm to the patient from the ischemic limb, the risk from operating on a patient who was in respiratory compromise and the risk of staff exposure during a procedure. This case has highlighted the difficulties faced by staff around the world when treating, or attempting to treat, patients with surgical and medical problems with active COVID-19 infection and the complexity of determining the most appropriate medical care that is beneficial to the patient, whilst not compromising the safety of others. Unfortunately, this patient heralded a lot of the risk factors for developing severe disease (>70 years of age, hypertension, diabetes and cardiac disease) and as a result could be predicted

to suffer from complications associated with the virus. On review of the literature, complications such as pulmonary embolism, have been found in almost 50% of COVID patients requiring respiratory support in the ICU and is perhaps a downplayed or underestimated risk to patient morbidity and mortality [14]. Whilst the exact mechanism has not been elucidated, it is hypothesized that the system-wide cytokine storm induces a proinflammatory and procoagulant state and when coupled with endothelial dysfunction and microvascular thrombosis in the lung particularly, creates the perfect environment for clot formation. There are other mechanisms at play, including reduced normal fibrinolytic mechanisms, which make thrombus formation quick and resistant to breakdown. This mechanism can be easily understood in the pulmonary vasculature, so it is feasible that similar phenomena occur in arterial vessels, which could explain the complications in this patient with significant pre-existing disease.

Of interest is that the second subject to experience significant infection-related complications was a 76-year-old gentleman with uncomplicated T2DM. This patient became significantly unwell whilst on the ward experiencing high fevers and evidence of clinical deterioration with derangements in heart rate, respiratory rate and oxygen saturation. He required a number of reviews by intensive care staff but deemed suitable for ward management. Of note, throughout his 14 day stay he had two episodes of delirium and during both times had a fall with head strike. All older adults admitted to hospital with infection, particularly those with medical comorbidities, pre-existing cognitive impairments, on certain medications or at risk of alcohol withdrawal are at risk of delirium. It has been postulated that both the penetration of the COVID-19 virus into the CNS and the rampant systemic inflammatory state are responsible for causing changes in mental state and level of consciousness, particularly in those with severe illness and especially in those who are elderly [15]. Whilst this patient did not have comorbid hypertension or heart disease and had evidence of well controlled diabetes, his blood results revealed a significant inflammatory and procoagulant state and his chest imaging revealed significant infiltration which is consequential of severe COVID-19 infection. Luckily, this patient did not experience sequelae from the falls, but his protracted change in cognitive status presented several challenges for the hospital staff. Whilst delirium can present in hypoactive and hyperactive forms, both can put the individual at further risk of harm. COVID-19 positive patients in isolation anecdotally receive less nursing and medical interaction and monitoring than uninfected patients, with communication often occurring through a window or over the telephone. Patients with hypoactive delirium have less of an ability to provide feedback on how they are doing, when their symptoms are changing or when they are starting to become more unwell. Hyperactive patients on the other hand, often require increased time and effort from staff to ensure compliance with isolation recommendations.

Patient 3 was the last subject to experience a temporary, but somewhat significant complication from his COVID-19 illness. He presented to the hospital emergency department with central chest pain and given his many cardiac risk factors and significant cardiac history, was worked up for acute coronary syndrome. Of note this patient did not present with any respiratory symptoms and was afebrile but did report a recent admission for fever of unknown origin. Whilst no new ischemic changes were identified on electrocardiogram, two raised troponin levels were detected. This patient was discussed with our Cardiology colleagues, and deemed not to be experiencing a non-ST elevation myocardial infarction as his peak troponin was small [13], just over the high sensitivity reference range (<10) and static when taken 3 hours apart. Given the evidence of proinflammatory state with a peak CRP of 124 and peak LDH of 430, it could be asserted that his illness was severe enough to exert stress on the myocardium resulting in a "troponin leak". This link between inflammation and myocardial injury has been well supported in the literature [13]. Moreover, COVID-19 has been known to unmask coronary artery disease with hypoxia and respiratory failure driving type 2 myocardial infarction, and in more severe cases, causing type 1 myocardial infarction via the cytokine storm. The cytokine storm disrupts atherosclerotic plaques and the suppression of ACE2 and Ang2 (Angiopoietin-2) creating conditions of vasoconstriction and oxidative stress [13].

Furthermore, whilst this review discusses a patient cohort of 8, there were another 55 patients who were admitted to our hospital for COVID-associated illness who were not diabetic. It has not been possible to compare these two groups as the small sample size of the Diabetes group does not allow for t-tests etc. due to high Type II error that comes with small sample sizes.

Table 1 summarises all of our inpatients' characteristics.

	SARS-CoV-2 positive with Comorbid Diabetes (n = 8)	**SARS-CoV-2 positive without Diabetes (n = 55)**
Age (mean, sd)	69.6 (10.6)	51.2 (18.6)
Gender		
Male	6 (75%)	22 (40%)
Female	2 (25%)	33 (60%)
Weight (mean, 95% CI)	89.36 (71.53-107.18)	74 (69.12-78.90)
Diabetes		
Type 1	0	N/A
Type 2	8	N/A
GDM	0	N/A
Diabetes Meds Pre-Admission		
Diet controlled	1	N/A
Metformin	7	N/A
Sulfonylurea	2	N/A
SGLT-2 Inhibitor	4	N/A
DPP-4 Inhibitor	1	N/A
GLP-1 Agonist	2	N/A
Insulin	2	N/A
MET calls	2 (25%)	2 (3.6%)
Transfer to ICU	1 (12.5%)	4 (7.3%)
Mean Venous sugars during admission (mean, sd)	7.21 (2.83)	5.89 (1.69)
Need for Short-Term Insulin	2	0
Readmission within 28 days	0 (1 still in ICU)	1
Length of Stay Days (mean,sd)	12.4 (21.8)	9.1 (9.8)
ACE Inhibitor / ARB		
ACE Inhibitor	1	4
ARB	1	2
N/A	6	49
Other Endocrine Conditions		
Hypothyroidism	1	5
Hypoadrenalism	0	0
Pregnancy	0	2
Nil	0	0

Steroids	1	0
HCQ (Hydroxychloroquine use)	3 (37.5%)	17 (30.9%)
Hypoglycaemic episodes	0	0

Table 1: Demographic characteristics and medical assessment findings.

Data regarding HbA1c (glycated Haemoglobin) values following hospital discharge, were available for only two subjects amongst the 8 patients with Diabetes. In one of the two subjects, their HbA1c changed from 7.1 % before the COVID-19 infection to 6.9 % ten months after the COVID-19 infection. In the other remaining subject, their HbA1c changed from 10.7 % before the COVID-19 infection to 9.9 % four months after the COVID-19 infection. The small numbers of subjects with available HbA1c limits our ability to reliably explain changes in HbA1c influenced by COVID-19 infection.

Conclusion

Overall, our cohort of patients fared well with only a few instances of definitive clinical deterioration and a small number of significant infection-related complications. There was zero mortality at the Gold Coast Hospital and Health service district. Further case reports and quantitative studies that pool patient data from other regions in Australia would be beneficial in better understanding the clinical variables and outcomes in this patient population during the current pandemic.

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