

COVID-19 and hyperglycaemic emergencies: perspectives from a developing country

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Background: Pre-existing diabetes mellitus (DM), hyperglycaemia and obesity emerged as prognostic factors in severe Coronavirus disease 2019 (COVID-19). To date, no published South African studies report on the incidence, presentation and outcomes of DM and diabetic ketoacidosis (DKA) during the COVID-19 pandemic.

Objective: To reflect on the diagnosis, management, obstacles to care and outcome of four patients who were admitted to Tygerberg Hospital, Cape Town, South Africa. The outcome of these cases that presented consecutively with DKA and COVID-19 between May and July 2020 are discussed, the presentation, management and long-term considerations with specific reference to DKA and COVID-19 are reviewed.

Results: Three of the four patients had newly diagnosed DM. These patients presented with non-specific symptoms and signs leading to a diagnosis of both DKA and COVID-19. The single surviving patient in this series was known to have pre-existing DM but discontinued his insulin upon becoming unwell. One patient required insulin therapy at the time of initial presentation a week or two prior to the current admission but received metformin instead. She was diagnosed with COVID-19 after having poor glycaemic control for over one week, after which insulin was initiated. Ultimately she died as a result of severe hypokalaemia. One patient primarily had respiratory complaints, severe COVID-19 pneumonia and received concomitant dexamethasone. Glycaemic control in this patient was complicated by both hypo- and hyperglycaemia.

Conclusion: These cases highlight the management challenges faced by many developing countries, and identify the missed opportunities in persons presenting with COVID-19 and hyperglycaemic emergencies.

Keywords: COVID-19, dexamethasone, diabetes, diabetic ketoacidosis, hypokalaemia

Introduction

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic has had devastating health, economic and social consequences. To date, more than 16 million individuals have been infected worldwide, with close to 700 000 lives lost. The Coronavirus disease 2019 (COVID-19) pandemic introduced unique healthcare challenges with specific reference to its severity in individuals with obesity and diabetes mellitus (DM).^{1,2}

Pre-existing DM, hyperglycaemia and obesity emerged as prognostic risk factors in severe COVID-19.³ People living with diabetes (PLWD) who present with COVID-19 have prolonged in-hospital stay, a higher risk of ICU admission, intubation and death compared with individuals without DM.^{1–5} This echoes observations made during the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak, when DM and elevated fasting plasma glucose (FPG) levels were both identified to be independent predictors of severity and death.^{6,7} The severity of COVID-19 in PLWD is attributed to a combination of immune dysregulation and a pro-inflammatory state.²

From an epidemiological perspective, it appears that PLWD are not more susceptible to COVID-19, but rather that the background prevalence of DM is reflected by individuals who

contract SARS-CoV-2 in a geographic area.^{1,8,9} Provincial data from the Western Cape COVID-19 mortality rates depict DM and hypertension to be the leading comorbidities resulting in mortality.¹⁰ If the profile of South African patients with COVID-19 parallels that of the rest of the world and an increased susceptibility to COVID-19 in PLWD is excluded, plausible explanations for the high rate of DM as a comorbidity includes: inaccurate DM prevalence figures in South Africa, potentially a high number of undiagnosed DM, and/or new-onset DM as a result of COVID-19. In a recent study in New Jersey, it was noted that 29 of the 184 patients hospitalised with COVID-19 were newly diagnosed with DM, six of whom had normal glycated haemoglobin levels (HbA_{1c}) on admission with no prior history of DM before admission.⁷

Abnormal glucose metabolism has been observed in individuals with and without pre-existing DM with COVID-19.¹¹ The clinical presentation reflects variable degrees of insulinopenia and ranges from mild aberrations in glucose concentration to hyperglycaemic emergencies such as diabetic ketoacidosis (DKA).^{12–15} Guo et al. reported that 1 in 10 patients with DM and COVID-19 in China presented with a DKA.¹⁶ Mortality rates also appear to be higher, with figures as high as 50% reported in patients with COVID-19 and DKA, a number significantly higher than historically observed.¹⁷

Although there are case reports of patients with COVID-19 presenting with DKA and hyperglycaemic hyperosmolar state (HHS) in those with previously well-controlled diabetes, there is still a paucity of data on the management and complications of hyperglycaemic emergencies in patients with COVID-19.^{13,15,18} Presently there are few data commenting on the unique challenges faced in managing hyperglycaemic emergencies in developing countries. With the following case reports, we aim to reflect on the diagnosis, management, obstacles to care and outcome of four patients who were admitted to Tygerberg Hospital, Cape Town, South Africa during the period May to July 2020.

Case 1

A 23-year-old man, Mr KT, had a background history of type 2 DM and hyperlipidaemia of four years' duration. He presented to the Emergency Unit (EU) in May 2020 complaining of a four-day history of a non-productive cough, myalgia, vomiting and abdominal pain. His antihyperglycaemic medication included metformin 1 000 mg twice daily and 30/70 pre-mix insulin (36 and 18 IU before breakfast and supper, respectively). He had no previous admissions for DKA. His mother was also known to have type 2 DM. The patient discontinued his medication when he became unwell but reported good adherence before this episode.

There were no known COVID-19 exposures. The most recent HbA_{1c} was 10.1%, performed nine months earlier (Table 1). The autoimmune screen (Anti-GAD/IA2 antibodies) for diabetes was negative in 2017 at the time of initial DM diagnosis.

Mr KT was clinically unwell with notable tachypnoea and Kussmaul breathing on arrival. Oxygen saturation was 89% in ambient air, with a heart rate (HR) of 100 bpm and a blood pressure (BP) of 110/50 mmHg; he also appeared dehydrated. Metabolic features included acanthosis nigricans and central adiposity with a body mass index (BMI) of 30 kg/m² (World Health Organization category obese).¹⁹ Bilateral fine late inspiratory crackles were audible mainly at the lung bases, with no signs of congestive cardiac failure. The point-of-care (POC) fingerprick blood glucose was 21 mmol/l. Urine dipstick indicated 3+ ketones, 4+ glucose and 3+ protein. Arterial blood gas (ABG) analysis on 40% face mask oxygen indicated a P_{O₂} of 14 kPa (PaO₂/FiO₂ ratio = 236) and a metabolic acidosis (Table 1). The β-hydroxybutyrate (BOHB) and chloride levels were not performed.

Mr KT's chest radiograph was in keeping with COVID-19 pneumonia, and SARS-CoV-2 PCR testing was positive. He was managed as for DKA and received a total of 7 litres of 0.9% saline and 50 units of insulin intravenously (IV) over a period of 10 hours. No corticosteroids were administered. The ketoacidosis resolved after 8 hours and the DKA regimen was bridged with subcutaneous insulin.

Shortly after admission the patient's oxygen requirements increased and he was escalated to a non-rebreather mask. Ventilatory support was never required. The patient remained in hospital for five days. As soon as he started eating, premix insulin was re-initiated. Respiratory support was de-escalated, metformin reintroduced, and the insulin dose increased to 38 IU and 22 IU before breakfast and supper respectively. The glucose levels ranged between 7 and 20 mmol/l. Care was de-escalated, and it was requested that further adjustments to the insulin dosage be made at the step-down facility.

Case 2

A 56-year-old female patient presented to the EU in June 2020 complaining of nausea, vomiting and diarrhoea for two days. She had no significant previous medical history and tested negative for COVID-19 three weeks prior to this presentation. A repeat nasopharyngeal swab was performed on this presentation as she now complained of symptoms suggestive of possible COVID-19 infection. There were no complaints of polydipsia, polyuria or unintended weight loss and she was of sober habits. She reported a strong family history of DM, with two first-degree relatives affected (mother and brother).

On arrival she was noted to be acutely unwell with tachypnoea (RR 25 BPM) and Kussmaul breathing. Peripheral circulation was poor, and her vitals revealed a BP of 120/75 mmHg and tachycardia (HR 121 bpm). Examination findings included dehydration, but no pyrexia was documented. Her phenotype was compatible with T2DM, with marked central adiposity (BMI not documented). A POC fingerprick blood glucose revealed marked hyperglycaemia (glucose 27 mmol/l) and the urine dipstick indicated 3+ ketones, 3+ glucose and 1+ protein. Venous blood gas analysis was in keeping with severe metabolic acidosis (pH < 6.91, bicarbonate 5.4 mmol/l [Table 1]). Oxygen saturation improved to 98% on a 40% oxygen face mask. Based on the above clinical and biochemical parameters, the institutional DKA protocol was commenced. Thromboprophylaxis and antibiotics were initiated empirically. Blood results included elevated HbA_{1c} (11.1%), lipase (3207 U/l), lactate (5.5 mmol/l) and triglyceride level (Table 1). The autoimmune diabetes screen was negative (Anti-GAD/IA2 antibodies negative). A BOHB was not performed.

A total of 7 litres of Ringer's lactate and 72 IU of IV insulin was administered over a period of 9 hours. Despite these measures the patient remained profoundly acidotic and sustained an acute kidney injury (urea = 22.9 mmol/l, creatinine = 175 µmol/l). The baseline creatinine prior to this presentation was normal. The chest radiograph showed asymmetrical ground glass infiltrates, more prominent on the left and in the lung bases.

The patient's clinical condition continued to deteriorate requiring a high level of care in our five-bed emergency unit. She died almost 9 hours after initial presentation. The SARS-CoV-2 PCR test was positive; however, this result was obtained only after the patient had already died.

Case 3

A 32-year-old female patient presented to the EU in June 2020, referred by the primary healthcare clinic. She previously attended the clinic a week earlier with symptoms of polydipsia, polyuria and polyphagia. The POC fingerprick glucose at that time was 16 mmol/l and metformin was initiated.

One week later she presented again. Her family now reported a three-day history of epigastric pain, nausea, vomiting and diarrhoea. Glucose was markedly elevated (fingerprick glucose 27 mmol/l). The urine dipsticks indicated 4+ ketones, 3+ glucose and 1+ protein. She appeared acutely unwell with tachypnoea, tachycardia and hypotension (RR 25BPM, HR 101 bpm, BP 72/38 mmHg). Clinically features of hypovolemic shock were evident with marked dehydration and a depressed level of consciousness (Glasgow Coma Scale [GCS] 12/15). The patient had a slim body habitus, phenotypically suggestive of type 1 DM. Chest auscultation was normal and fever was not documented. Oxygen saturation on pulse oximetry was 96%

Table 1: Biochemical and haematological characteristics of Cases 1–4

	Normal values	Case 1	Case 2	Case 3	Case 4
HbA _{1c} (admission)		13%	11.1%	10.9%	13.4%
HbA _{1c} (most recent)		10.1% [†]	N/A	5.9% [‡]	N/A
Arterial blood gas:					
pH	7.35–7.45	7.26	< 6.91	6.8	6.99
P/F ratio (mmHg) [§]		263	122	111	301
FiO ₂ (%)		40	40	40	21
pO ₂ (kPa)	11.0–14.4	14	6.5	5.9	8.4
pCO ₂ (kPa)	4.6–6.4	4.5	3.6	8.5	1.7
HCO ₃ ⁻ (mmol/l)	21–28	23	5.4	LDL	3.1
Ca ²⁺ (mmol/l)	1.15–1.33	1.07	1.2	1.45	1.3
HCO ₃ ⁻ std (mmol/l)	22–26	18	5.1	LDL	3.5
Lactate (mmol/l)	0.6–1.4	2.5	5.5	3.8	3.7
Na ⁺ (mmol/l)	136–145	141	131	150	140
K ⁺ (mmol/l)	3.5–5.1	5	Invalid	1.8	5.5
Chloride (mmol/l)	98–107	N/A	N/A	121	N/A
Urea (mmol/l)	2.1–7.1	5.1	22.9	17.9	7.7
Creatinine (μmol/l)	49–90	85	175	189	69
Lipase (U/l)	13–60	N/A	3207	2399	N/A
CRP (mg/l)	< 10	171	N/A	54	505
Haemoglobin (g/dl)	12.0–15.0	16	15.9	12.8	14.1
White cell count (×10 ⁹ /l)	3.9–12.6	7.16	17.36	4.83	22.35
Lymphocytes (× 10 ⁹ /l)	1.4–4.5	0.37	2.9	1.02	N/A

HbA_{1c} available before index presentation in Case 1 and 4; [†] performed (26 August 2019); [‡] performed (1 March 2018). LDL = Lower than detectable limit. N/A = not available. [§] P/F ratio = PaO₂/FiO₂ ratio. 2012 Berlin definition of ARDS: mild: P/F ratio 200–300; moderate: P/F ratio 100–200; severe: P/F ratio < 100[42]. Normal reference ranges obtained from NHLS and for Gem 3500 blood gas machine.

in ambient air. Fluid resuscitation and IV insulin administration was initiated at the peripheral clinic. These facilities have basic amenities and are not equipped to manage patients requiring high level of care. Transfer to our facility took almost 5 hours, despite the urgency of this case.

While awaiting transfer to our facility the patient decompensated requiring full cardio-pulmonary resuscitation for an estimated duration of 10 minutes, whereafter return of spontaneous circulation was achieved. The initial chest radiograph findings were not suggestive of a COVID-19 pneumonia. On presentation to Tygerberg Hospital the IV insulin and fluid infusion was continued. The ABG indicated a profound hypokalaemia (potassium 1 mmol/l) with a severe metabolic acidosis and hypoxemia (pO₂ 5.9kPa, pH 6.8, lactate 3.8 mmol/l, bicarbonate lower than detectable limit). The ECG showed features keeping with severe hypokalaemia (Figure 1).

The patient received a total of 20 IU insulin and four litres of Ringer's lactate IV at our facility over two hours. It is unclear how much she received at the peripheral clinic. A BOHB level was not performed. Biochemistry indicated an HbA_{1c} of 10.9%, elevated Lipase (2399 U/l), and impaired renal function (Table 1). Serum calcium was normal (2.17 mmol/l) and Anti-GAD/IA2 antibodies were negative. Despite potassium replacement and aggressive fluid resuscitation, the patient died. A cardiac arrhythmia due to profound hypokalaemia was deemed the most likely cause of death. A nasopharyngeal swab for COVID-19 was performed on arrival, as per institutional protocol. The SARS-CoV-2 test was positive, but again this was only obtained one day after the patient had already died.

Case 4

Ms SM, a 65-year-old female, presented to the EU on 19 June 2020 with a one-week history of generalised body weakness and dry cough. Her family reported a two-day history of rapid breathing and confusion. She was known to have a background history of long-standing essential hypertension.

Clinical examination revealed an acutely unwell patient, with Kussmaul breathing and tachypnoea. The oxygen saturation was 83% in ambient air with a BP of 153/100 mmHg and a sinus tachycardia (HR 127 bpm). Fingertip glucose was 27 mmol/l. She had marked central obesity but did not have an accurate BMI available. Fine bi-basal inspiratory crackles were audible on chest auscultation with no signs indicative of left ventricular dysfunction. Her GCS fluctuated between 12 and 14 with no localising signs.

An ABG revealed type I respiratory failure (pO₂ 8.4 kPa, pCO₂ 1.7 kPa, P/F ratio:301) and a severe high anion gap metabolic acidosis (pH 6.9, HCO₃ 3.5 mmol/l, BE -26 mmol/l, lactate 3.7 mmol/l, anion gap = 19). Urine dipstick indicated glucose 4+, ketones 3+, leucocyte 1+ and protein 3+. The HbA_{1c} on admission was 13.4%. No BOHB level was available. The initial chest radiograph was in keeping with COVID-19 pneumonia (Figure 2). The diagnosis was confirmed with a positive SARS-CoV-2 PCR test.

The institutional DKA protocol, dexamethasone (8 mg twice daily) and therapeutic anticoagulation with low molecular weight heparin (enoxaparin 80 mg twice daily) was initiated and continued throughout her stay. The metabolic acidosis resolved after two days. IV fluids were changed from 0.9% saline to rehydration solution (0.45% saline with 5% dextrose)

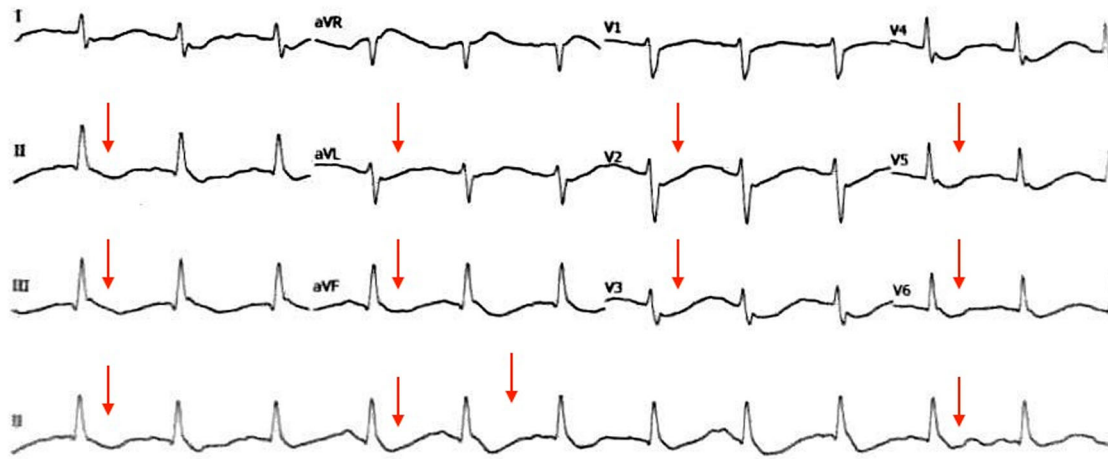


Figure 1: ECG of case 3 with abnormalities characteristic of hypokalaemia. This ECG demonstrates regular sinus rhythm (HR 120 bpm) with prolonged PR (180 ms) and QTc (580 ms) intervals. Widespread ST segment depression (leads V2–V6) are indicated by arrows.

and potassium supplemented, when hypernatraemia ($\text{Na}^+ = 152 \text{ mmol/l}$) and hypokalaemia ($\text{K} 2.7 \text{ mmol/l}$) developed respectively. She received a total of 361 IU short-acting IV insulin and 14 litres of IV fluids over the two days. Insulin glargine (20 IU) was subsequently initiated to overlap with the IV insulin infusion before its discontinuation.

Ms SM's respiratory condition deteriorated despite receiving supplemental oxygen via a non-rebreather mask ($\text{FiO}_2 100\%$). She developed type II respiratory failure ($\text{pO}_2 7.1 \text{ kPa}$, $\text{pCO}_2 14.3 \text{ kPa}$). The patient did not tolerate high flow nasal oxygen therapy and was subsequently intubated. The initial $\text{PaO}_2/\text{FiO}_2$ ratio post intubation was 135 (severe ARDS PF ratio < 200). Inotropic support was also briefly required. Two episodes of hypoglycaemia (glucose $< 4 \text{ mmol/l}$) were documented over the six days of her intensive care unit (ICU) stay. Glucose values ranged from 1.8–15.7 mmol/l during this period, glycaemic control being erratic with the concomitant use of steroids for the COVID-19 pneumonia. Glycaemic management was according to our facility's ICU protocol by means of a short-acting insulin infusion.

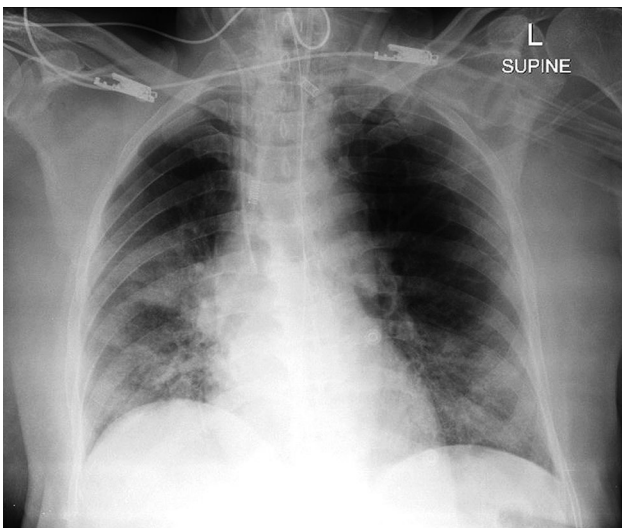


Figure 2: Chest radiograph of case 4. The chest radiograph depicts bilateral interstitial infiltrates with a basal predominance. These findings are in keeping with COVID-19 pneumonia.

The patient later developed hospital-acquired sepsis, with ongoing deterioration despite optimal supportive care. She died nine days after admission.

Discussion

We report on four cases presenting with hyperglycaemic emergencies and COVID-19 after the peak of the pandemic in the Western Cape province, South Africa. Three of the four patients died in hospital. Only one was known to have pre-existing DM. Case 3 was a young woman who likely required insulin therapy at index presentation but received metformin instead. She was diagnosed with COVID-19 after having uncontrolled hyperglycaemia for over one week and ultimately died as a result of severe hypokalaemia. Case 4 was a female with newly diagnosed Type 2 DM and severe COVID-19 pneumonia, whose glycaemic control was complicated by hypoglycaemia and hyperglycaemia, with concomitant dexamethasone use and nosocomial sepsis. These cases highlight the broad clinical spectrum at presentation and emphasise the management challenges as well as high mortality reportedly associated with COVID-19 and concurrent hyperglycaemic emergencies.

From a pathophysiologic perspective, DKA occurs in the presence of relative or absolute insulin deficiency coupled with increased counterregulatory hormones, driving gluconeogenesis, lipolysis and ketogenesis.²⁰ Whilst DKA is characteristically associated with Type 1 DM it is well documented in patients with Type 2 DM, which may also include individuals with the so-called 'ketosis-prone diabetes' (KPT2D). Individuals with KPT2D who present in DKA, but phenotypically resemble Type 2 DM, are characteristically overweight or moderately obese and lack autoimmune antibodies associated with Type 1 DM.²¹ It has been postulated that the increased insulin resistance and decreased insulin secretion are the result of lipotoxicity.²² As opposed to Type 1 DM, pancreatic beta cell function may recover after achieving normoglycemia with insulin therapy in KPT2D, allowing some individuals to become insulin independent.^{21,22}

The biochemical diagnosis of DKA is confirmed by demonstrating the triad of hyperglycaemia (glucose $> 13.8 \text{ mmol/l}$), ketosis (ketonaemia or ketonuria) and a high anion gap metabolic acidosis ($\text{HCO}_3^- < 15 \text{ mmol/l}$ and/or $\text{pH} < 7.3$).^{20,23,24} All four of the cases we describe had significant hyperglycaemia, but lacked BOHB levels. It should be emphasised that other

conditions such as alcoholic keto-acidosis, lactic acidosis and ingestion of substances such as ethylene glycol should be considered in the differential diagnosis of individuals with acidosis and milder glycaemic increases. β -Hydroxybutyrate (BOHB), the strongest and most prevalent acid in DKA, provides a direct measure of the pathophysiologic derangement as compared with the non-specific measurements (pH and bicarbonate) and can be useful to differentiate between the aforementioned conditions. The measurement of BOHB is readily available on a POC device that doubles as a glucometer and uses capillary blood obtained by fingerprick.²⁵ BOHB measurement by means of POC device is much less invasive than ABG, and allows for improved distancing between healthcare workers and patients with COVID-19 infection. In South Africa biochemical results at state-sector facilities are often significantly delayed, hindering patient management. POC BOHB is a low-cost initiative that could counterbalance this problem.

Acute illness leads to various pro-inflammatory stress responses and is well known to precipitate DKA and HHS.^{20,24} Cortisol, growth hormone and increased sympathetic activity all play a role in stress-related insulin resistance.²⁶ The use of steroid therapy in patients with COVID-19 can therefore precipitate DKA or contribute to the insulin resistance.

Case 4 in this series describes the concurrent use of dexamethasone for COVID-19 and a high insulin dose requirement (361IU over 2 days) suggestive of marked insulin resistance. Additional mechanisms to explain insulinopenia in the patients who presented in DKA with COVID-19 are direct viral infection of pancreatic endocrine cells and indirect inhibition of insulin secretion via the angiotensin converting enzyme 2 receptor (ACE2).^{4,7,27} The third case in our series had a one-week history of poly-symptoms, was phenotypically not insulin resistant and was found to be auto-antibody negative shortly after presenting in DKA. It is certainly plausible that COVID-19 pneumonia may aggravate beta cell dysfunction and precipitate DKA, but the possibility should also be considered that COVID-19 may have had a direct effect on insulin secretion in addition to the stress-related response of glucose metabolism.^{16,28}

The cornerstone of hyperglycaemic crises management is fluid resuscitation, potassium replacement, insulin administration and management of the underlying precipitant.²⁹ All of these may be more challenging than usual to manage, due to the complex pathophysiology of SARS-CoV-2. Angiotensin II (Ang II) increases pulmonary vascular permeability and worsens damage to an already compromised lung parenchyma.³⁰ Excessive fluid management may precipitate pulmonary oedema and worsen respiratory distress. Ang II also stimulates aldosterone secretion. This potentiates the risk of hypokalaemia, which may necessitate more aggressive potassium monitoring and supplementation in order to continue the IV insulin that is required to suppress ketogenesis.³⁰ As depicted in Case 3, hypokalaemia may potentiate cardiac dysrhythmias, thus this needs to be aggressively monitored and proactively managed. These management facilities are often not available at our peripheral clinics.

Concomitant acute pancreatitis should be considered in DKA with severe abdominal pain. Abdominal pain was a common symptom in our series. Two cases were demonstrated to have elevated lipase levels. It is well known that lipase and amylase can be increased in DKA, and lipase levels as high as

2000–3500 IU/l have been described without pancreatic pathology on imaging with normalisation after resolution of DKA.³¹ However, pancreatitis as a result of direct pancreatic damage by SARS-CoV-2 has also been reported, and clinicians should consider the possibility of this in the appropriate clinical setting.^{32–35} ACE 2 is widely expressed in the pancreas, yet only mild pancreatitis has been described in patients with severe COVID-19, suggesting that the endocrine pancreas might be affected disproportionately.³⁶

HbA_{1c} reflects the average glucose for the preceding 8–12 weeks and is a recognised diagnostic test for DM. A value $\geq 6.5\%$ has a high specificity for DM but lacks sensitivity below 6.5%.³⁷ The HbA_{1c} can be influenced by pre-analytical and analytical factors and the utility of the $\geq 6.5\%$ threshold to diagnose new-onset diabetes in the acute setting is controversial.^{38,39} A sustained elevation in glucose as a result of stress hyperglycaemia has an impact on the HbA_{1c}, with 50% of the HbA_{1c} being determined by the glucose levels in the preceding month.⁴⁰ Stress hyperglycaemia can therefore theoretically affect the specificity of the HbA_{1c} diagnostic threshold for DM ($\geq 6.5\%$). Thakker et al. prospectively evaluated the HbA_{1c} levels of 589 patients seen in the emergency unit for conditions unrelated to DM and demonstrated a high correlation between the initial and follow-up HbA_{1c} ($r^2=0.829$). Most patients maintained the classification initially assigned to them based on HbA_{1c} and the duration of follow-up did not influence the categorisation.³⁹ Whilst the severity of acute illness in our setting might not be comparable, we demonstrated significantly elevated HbA_{1c} levels (10.9–13.4%) at presentation in this case series. It would therefore be reasonable to presume that at least two of the three patients who were unaware they had DM had in fact longstanding pre-existing hyperglycaemia before the index presentation.

Other factors such as non-adherence to diet and medication, late presentation and lack of access to healthcare facilities may lead to delays in the diagnosis and management of diabetic emergencies and are often associated with high morbidity and mortality.^{29,41} In South Africa the COVID-19 pandemic has exacerbated these factors by imposing travel restrictions, worsening unemployment and creating a fear of healthcare facilities.⁴² The delay in transport for case 3 may have contributed to her early demise as early management needed to be instituted at a facility that was equipped with adequate monitoring.

Furthermore, consideration needs to be given to the intensity of care that is required for management of hyperglycaemic emergencies and COVID-19 patients. In an era where patient contact is often limited, the management of hyperglycaemic emergencies demands aggressive vigilance by healthcare workers. Assessing fluid status, glucose monitoring, intravenous insulin therapy and potassium supplementation all increase the frequency of patient–healthcare worker contact. Due to resource constraints and patient load, clinicians are forced to employ pragmatic methods in an attempt to improve outcomes in patients with DKA at lower levels of care. The (self-)administration of subcutaneous short-acting insulin with or without basal insulin to treat mild to moderate DKA has been utilised in situations where intravenous infusion pumps and skilled healthcare workers were not available at the peak of the pandemic in the Western Cape. Modifications in DKA protocols with early initiation of basal insulin have also been attempted, but the risk:benefit ratio of this strategy should

ideally be assessed in prospective studies before the universal application of these protocols can be advocated outside of the pandemic.

With regard to long-term follow-up, a study by Yang et al. showed that only 2 of the 20 patients noted to have been treated for DM while hospitalised with SARS were still diabetic at 3-year follow-up,^{6,27} postulating a recovery in beta cell function post-infection. This will mean that strict follow-up will be required for patients with hyperglycaemic emergencies and COVID-19, so as to adjust therapy appropriately. Therefore, clinicians should prioritise and document the medium- to long-term outcome of patients diagnosed with DM during COVID-19 — a task that may prove to be difficult given that most of our DM patients are followed up at peripheral clinics, which are overburdened by large patient numbers. Although this study included only four case reports, it does highlight the challenges faced in dealing with these clinical scenarios.

Conclusion

There appears to be considerable variation in the presentation of COVID-19 in DM. In the absence of appropriate care in resource-poor regions, hyperglycaemic emergencies may carry a high mortality in the setting of COVID-19 infection. Clinicians should maintain a high index of suspicion for COVID-19 in individuals who present with hyperglycaemic emergencies. The pandemic highlighted the fact that a significant number of people at risk of DM remain undiagnosed in South Africa. Earlier detection, improved access and adherence to diabetes care, including self-management education, is imperative. Anti-hyperglycaemic therapy to prevent both acute and long-term complications should take priority in people living with DM. Hyperglycaemic emergencies with concurrent COVID-19 have created unique challenges for South African healthcare, but this has also helped unmask some of the existing barriers in the management of DM.

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