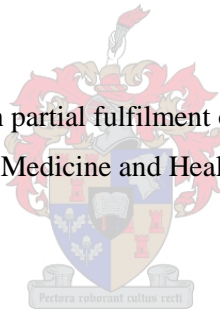


The burden of diabetic emergencies on the resuscitation area of a district-level public hospital in Cape Town

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Division of Emergency Medicine

Research assignment presented in partial fulfilment of the requirements for the degree
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Declaration

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Abbreviations

ADA	American Diabetes Association
CI	Confidence interval
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
HIC	High-Income Country
HIV	Human Immunodeficiency Virus
HHS	Hyperosmolar hyperglycaemic state
ICU	Intensive care unit
IQR	Interquartile range
LMIC	Low- and Middle-Income Country
MIC	Middle-Income Country
SATS	South African triage scale
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEWS	Triage Early Warning Score
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UK	United Kingdom
US	United States of America
WHO	World Health Organization

Part A: LITERATURE REVIEW

Introduction

Diabetic emergencies include a group of conditions in which an elevated or diminished glucose level exists. This can result in metabolic emergencies causing patients to present with an array of symptoms including severe abdominal pain, shortness of breath, and even altered mental status.[1] The acute metabolic complications of diabetes (diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS), and hypoglycaemia) occur frequently in Africa. Factors such as non-compliance with medication, late presentation, and lack of access to health facilities lead to delays in the diagnosis and management of these complications.[1] These life-threatening emergencies carry high morbidity and mortality and require prompt lifesaving interventions. These interventions are not always possible due to a combination of factors including inadequate access to health services, poor health-seeking behaviour and overburdened health care facilities.[1]

The rapid increase in the prevalence of diabetes in developing countries seems secondary to the effect of westernization, although the prevalence varies between regions. It is thus imperative to establish local trends in order to facilitate future health care planning.[2] Socio-economic circumstances, infections and access to health care are some of the known factors affecting disease outcome and progression. These factors do not always apply to high-income countries (HICs) where most of the currently available data originates from. It is thus important to collect data that is relevant to low-and middle-income-countries (LMICs) in order to facilitate better health care for all.

The goal of this literature review was to discern the burden of diabetic emergencies. Academic literature was comprehensively searched for articles related to diabetes and its complications. The review is divided into diabetes mellitus in general, diabetic emergencies (DKA, HHS, uncomplicated hyperglycaemia, severe hypoglycaemia), and the burden of diabetic emergencies on the emergency centre. The information within each diabetic emergency is presented according to the definition, prevalence, risk factors, clinical presentation, precipitants, management, resolution, and mortality. Animal studies and non-English studies were not included.

Diabetes Mellitus

Diabetes can be divided into different subgroups, which include type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is a result of autoimmune destruction of pancreatic beta cells, causing an absence of insulin. Treatment regimes, therefore, aim to correct the insulin-deficient state, typically by exogenous insulin replacement. T2DM can be defined as insulin resistance, and to a degree, insulin release defects, in which genetic, lifestyle and environmental factors play a role. Historically it was only thought to occur in middle-aged to older patients; however, younger patients are being diagnosed more frequently. The clinical presentation of T2DM is similar to T1DM, but patients can go undiagnosed for long periods of time as the presenting symptoms are generally less severe. Management regimes involve the reduction of glucose levels by oral anti-glycaemic agents and exogenous insulin replacement.^[3]

The current global prevalence of diabetes is 9.3%, with a higher prevalence occurring in HICs (10.4%) compared to middle-income countries (9.5%) and low-income countries (4%). The prevalence of diabetes in Africa is reported to be 3.9%; while South Africa has a slightly higher prevalence of 5.4%. It is expected that LMICs will experience an excessive rise in diabetes prevalence over the next 25 years.^[4]

T2DM occurs more frequently than T1DM as reported by both the International Diabetes Federation and the Centre for Disease Control and Prevention (CDC) in the United States (US).^[2,5] In 2000-2014, the prevalence of T2DM in the US was 8.6% compared to 0.55% of T1DM.^[6]

The prevalence of diabetes (and the two subgroups) is variable and changes according to geographical location, age, and socio-economic status.^[2] It is estimated that more than two-thirds of people living with diabetes are from LICs, despite the low reported prevalence of diabetes in these countries.^[4] Roughly half of the people living with diabetes are oblivious to the diagnosis, with Africa having the highest number of undiagnosed cases.^[2] In keeping with global data, T2DM is more prevalent than T1DM in Sub-Saharan Africa.

Urban populations have a higher prevalence than rural populations (10.8% versus 7.2%), and this difference was also documented in South Africa in 2016.^[2,7] Differences due to age is also noticeable with the prevalence in HICs peaking in older patients (>75 years old); while the prevalence in LMICs peaks in younger age groups.^[2] The prevalence also differs between income levels, where the less affluent had a prevalence of 9% compared to 4.3% in the more affluent group.^[8] A direct link between poverty and a higher prevalence of T2DM has also been documented.^[9]

Diabetes is notorious for its systemic effect on the human body. A wide array of diabetes-related complications exist, which can be divided into curable (DKA, HHS and hypoglycaemia) and incurable (macrovascular and microvascular complications) complications.^[2,3,10] Macrovascular complications include an umbrella of conditions such as coronary artery disease, cerebrovascular disease and peripheral artery disease. Microvascular complications include nephropathy, retinopathy and neuropathy.^[2] All of these complications are linked to a decrease in quality of life and life expectancy.^[3]

Worldwide diabetes is responsible for about 11.3% of deaths, most of them occurring in the economically active population.^[5] In Africa, 75% of diabetic-related deaths occurred in people younger than 60 years old.^[2] Diabetes is also one of the leading causes of natural deaths amongst South Africans;^[11] in 2016, diabetes contributed to 7.2% of deaths amongst women and 4.0% of deaths in males.^[12]

Diabetes and its complications remain a massive health issue and concern, despite many enhancements in health care services around the world.

Diabetic emergencies

Diabetic emergencies can be divided into conditions with increased glycaemic states (DKA, HHS and symptomatic uncomplicated hyperglycaemia) and decreased glycaemic states (hypoglycaemia).

Diabetic ketoacidosis (DKA)

Definition

The American Diabetes Association (ADA) and the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), define DKA using the following criteria: i) Hyperglycaemia (plasma glucose >13.9 mmol/L), ii) Acidosis (blood pH <7.3 or bicarbonate <18 mmol/L), and iii) Ketonemia (blood beta-hydroxybutyrate > 3 mmol/L).^[3,10] The severity of DKA can be categorized according to the blood pH level into mild (7.25 - 7.3), moderate (7.0 - 7.24), and severe (<7.0) categories.^[3,10]

Prevalence

The number of patients presenting with DKA in the US and the United Kingdom (UK) has been increasing. The CDC reported an age-adjusted increase of DKA hospitalizations in the US from 2000 through 2014; the rate increased by 54.9%, from 19.5 to 30.2 per 1000 persons.^[5] A similar increase also occurred in Canadian children with T1DM where the age- and sex-standardized rate of DKA increased 7.6% from 22% between 2001 and 2014.^[13] The true prevalence of DKA in Africa and South Africa remains undetermined.

Risk factors

DKA is a frequent complication of diabetes globally and most often occurs in patients with T1DM.^[14] Patients with T2DM are also susceptible to DKA under stressful conditions, e.g. trauma or surgery.^[15] South African data similarly indicate the higher prevalence in T1DM patients (61% compared to 39% in T2DM); however one study reported a higher prevalence in T2DM (54% versus 47% in T1DM).^[16,17]

No sex preference seems to be associated with DKA. In a UK based study, interrogating three groups (one admission, two to five admissions and greater than five admissions), no significant difference was seen across all of these groups. In those who presented with more than five admissions, no statistical significance was seen

(women 26% compared to men 21.7% ($p=0.186$)); similar results were documented in South Africa (male 51%; female 49%).^[17,18]

Poor socio-economic circumstances, younger age, and antidepressant use or psychiatric comorbidity are other risk factors for DKA.^[8,15,17-19]

Clinical presentation

The clinical presentation of DKA is not always easily recognised, as a large proportion of patients present with non-specific signs and symptoms.^[17,20] The clinical presentation may include polyuria, polydipsia, gastrointestinal symptoms (nausea, vomiting, abdominal pain), visual disturbance, lethargy, tachycardia, shortness of breath, and altered sensorium.^[17,21,22] Gastrointestinal symptoms are frequently reported when patients present with DKA and is present between 51% and 74% of the time.^[17,23,24] Physical findings may also include Kussmaul breathing and features of hypovolemic shock.^[3]

Precipitants

Non-compliance and infection are the commonest precipitants in DKA admissions, while other causes include concurrent illnesses (i.e., trauma, myocardial ischemia).^[3,25] A study in the US reported medication omission as a reason for presentation in 90% of the study population, while a small North Indian study reported non-compliance in more than 50% of patients.^[23,24] Non-compliance is also a frequent cause of DKA in South Africa, ranging between 27% and 32%.^[17,26] Concurrent infection is the other major cause of DKA in diabetic patients and were present in 36% to 38%; both internationally and within South Africa.^[23,24,26] In reality, no precipitant can be identified in a substantial proportion of patients.

Investigations

Recommended bedside and laboratory evaluation of patients with DKA should be aimed at confirming the diagnosis and identifying the cause and potential complications of the disease.³ This includes measuring the glucose level (serum glucose or finger prick), the presence of ketones (serum and urinary ketones), assessment of dehydration (serum urea and serum creatinine), and the presence of electrolyte derangement, which can be seen on blood gas and renal function test.³

The osmolality and anion gap should be calculated as it assists with determining the degree of acidosis and dehydration, in addition, it can assist with measuring trends. The osmolality gives an indication of the degree of dehydration and can also be used to distinguish DKA from HHS, which is usually associated with a higher osmolality ($>320\text{mmol/l}$). The anion gap is a measurement of ions in the body and DKA is usually associated with a high anion gap ($>12\text{mEq/L}$). Narrowing of the anion gap in a DKA patient is reassuring and a sign of improvement.³

Measuring for the presence of ketonemia is important, as it helps to discern the type of diabetic emergency in hyperglycaemic patients. As serum ketone tests are not everywhere readily available, the presence of ketones

in the urine (ketonuria) is often used as a surrogate marker.^[2,3] However, there are two ketones playing a role in the acidosis of a DKA, acetoacetate and beta-hydroxybutyrate (the latter being the predominant ketone in severe untreated DKA). Acetoacetate is detected by the urine dipstick, but beta-hydroxybutyrate is not;^[27] with the potential to miss the diagnosis of DKA. A US-based study found a similar sensitivity for blood beta-hydroxybutyrate strips and urine acetoacetate dipsticks (both 98%) in diagnosing DKA, but blood beta-hydroxybutyrate strips had higher specificity (79%) than the urine acetoacetate dipsticks (35%).^[28] This decreased specificity raises concerns of potentially unwarranted medical work-ups as a result of false-positive tests. Similarly, a systematic review indicated that measuring serum beta-hydroxybutyrate was found to be more effective than urine acetoacetate, leading to a reduction in hospitalization and shorter time to resolution.^[28] Beta-hydroxybutyrate strips have the advantage of being used at the point of care and is an affordable alternative to serum beta-hydroxybutyrate.^[29] The use of urine dipsticks compared to serum ketones as the primary detection mode of ketone bodies is often used in low resourced settings, and health care personnel should understand the potential diagnostic pitfalls.

Additional investigations should include an electrocardiogram (ECG) and a chest X-ray. Both these investigations can assist in diagnosing the precipitant cause and in monitoring management; ECG to evaluate for ischaemic events and the effect of electrolyte derangements, and chest X-ray to identify pulmonary infections and features of fluid overload. Further selective case-based testing should be aimed at determining the reason for presentation, e.g. an abdominal ultrasound for appendicitis, mesenteric ischaemia, and gallbladder pathology.^[30,31]

Management

Globally, similar pathways are followed for the management of patients with DKA. The cornerstone of management includes restoration of fluid depletion, resolving the acidosis, monitoring and correcting potassium abnormalities, and managing precipitating causes.^[17,22,32,33]

The infusion of fluids improves the intravascular volume and restore perfusion.^[32] Patients presenting in DKA have an estimated fluid deficit between 5 and 10 litres. The ideal fluid type remains a contentious subject for debate, both internationally and locally. Both the US and UK accept the use of normal saline as the initial fluid replacement of choice,^[33] while South African protocols recommend either normal saline solution or ringer's lactate.^[3,21] A small trial in South Africa, found no difference in the time it took for the pH to normalise (pH = 7.32) between ringer's lactate (540 minutes (95% confidence interval (CI) 184-896)) and normal saline (683 minutes (95% CI 378-988)) as the primary. Additional investigations should include an electrocardiogram (ECG) and a chest X-ray. Both these investigations can assist in diagnosing the precipitant cause and in monitoring management; ECG to evaluate for ischaemic events and the effect of electrolyte derangements, and chest X-ray to identify pulmonary infections and features of fluid overload. Further selective case-based testing should be aimed at determining the reason for presentation, e.g. an abdominal ultrasound for appendicitis, mesenteric ischaemia, and gallbladder pathology.^[30,31]

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Insulin inhibits the ketogenic pathway. Short-acting insulin is recommended as a continuous insulin infusion at a rate of 0,14 units/kg/hour in a high care or intensive care setting with intensive glucose monitoring.^[35,36] Different routes of insulin therapy exist, such as continuous intravenous (IV) infusion, bolus IV, subcutaneous (SC) or intramuscular (IM) insulin therapy.^[16] In a recent study, a bolus IV insulin regime was successfully used as the primary treatment modality in managing patients with DKA.^[16] The rationale behind this method of managing DKA stems from an anticipated cost and resource benefit in managing patients outside of the intensive care setting, which is vital in low resource environments.^[16] Most protocols recommend changing to subcutaneous insulin only when the hyperglycaemic emergency has resolved, however successful management of mild cases with regular subcutaneous bolus regimes has been documented.^[3,16,22]

Blood ketone testing is a useful parameter in managing DKA patients, as the resolution of acidosis is usually represented by the reduction of ketonemia and thus is a valuable tool to measure improvement.^[37]

Potassium levels should be strictly monitored, and potassium should be replaced if needed. If the initial potassium is less than 3.5 mmol/l, potassium should be replaced before initiating the insulin infusion. This is recommended to avoid severe hypokalaemia (insulin drives potassium intracellular) and its complications, such as arrhythmias or respiratory muscle weakness. Potassium levels should be monitored 4-hourly to guide the need for further replacement.^[3,38]

The use of bicarbonate is not routinely recommended.^[31,39] However, the ADA guidelines do suggest using bicarbonate when the serum pH is less than 6.9 until it reaches no higher than 7. Although there is insufficient data to prove the value of bicarbonate, the theory behind its use is to assist with lessening the severe acidotic state, which is associated with life-threatening organ dysfunction.^[10,30]

Patients with moderate to severe DKA require intense monitoring, ideally in a high care setting or intensive care unit (ICU). In reality, high care and ICU beds are not available in all hospitals,^[3,40] and these patients are often

cared for in the emergency centre.^[41] However, the treatment and management of diabetic emergencies should not be delayed or affected when scarcity of high care or ICU beds exist, as this can lead to high morbidity and mortality.

Resolution

The ADA defines the resolution of DKA as maintaining normoglycaemia (blood glucose level < 11.1 mmol/L), absent ketonemia and acidosis resolution (bicarbonate ≥ 15 mEq/L, pH >7.3, and anion gap ≤ 12 mEq/L)^[10] Time to resolution could be seen as a surrogate of efficacy in managing diabetic emergencies,¹⁸ although the length of hospital stay varies depending on the institution and the specific management protocol. In an Australian retrospective audit between 2010 to 2014, it took around 11 hours for DKA to resolve;^[42] which was similar to a retrospective study done in the UK in 2012.^[43] Contrary, an Ethiopian based study reported a significantly longer time to resolution (2.7 days \pm 3 days); however, participants were primarily managed in a medical ward with ward friendly protocols.^[44] The median time to resolution at a tertiary hospital in South Africa, using IV hourly insulin boluses, was 21 hours.^[16]

The length of hospital stay varies between 2 and 8 days and are influenced by factors such as comorbidities, precipitants, and the setting.^[23,43,45] A study by *Umpierrez et al.* demonstrated the importance of comorbidities; those who presented with non-compliance had a length of stay of 3.1 ± 1.6 days compared to 7.2 ± 3 days in those who had an underlying medical condition.^[45] Studies from South Africa indicate an extended length of stay, with 8.9 ± 7.5 days documented in the KwaZulu/Natal province and 7-9 days in the Eastern Cape province (7-9 days).^[17,46] Striving to decrease hospital length of stay is an essential goal in resource-limited environments.

Mortality

Worldwide diabetes (in general) is responsible for about 11.3% of deaths, most of them occurring in the economically active population.^[5] The exact mortality rate for DKA is unclear, but varies considerably. Mortality rates in Scotland have been under 0.2%,^[18] in contrast to 8% in Zambia and 30% in Kenya.^[47,48] The mortality rate also differ widely within South Africa; 8% in the Western Cape province,^[26] 17% in KwaZulu/Natal,^[17] and 20% in the Eastern Cape province.^[49]

Various factors are associated with increased mortality risk. The presence of elevated serum urea levels, renal failure in general and altered mental status put patients at an increased risk of death.^[47,50] Patients with recurrent admissions for DKA also have an increased risk of death. The mortality for patients who had one DKA admission over a median of 2.4 years was substantially lower than those with recurrent DKA admissions (5.2% versus 23.4%).^[18] Age, gender and economic activity have been identified as contributing factors to recurrent DKA admissions.^[25,51]

Hyperosmolar hyperglycaemic state (HHS)

A considerable amount of overlap exists between hyperglycaemic emergencies. The review on HHS and uncomplicated hyperglycaemia will therefore mainly highlight the differences to DKA, which was extensively described above.

Definition

HHS usually develops over a long period (several days to weeks) and is characterised by severe hyperglycaemia (serum glucose >33.3 mmol/L), hyperosmolality (serum osmolality >320 mOsm/kg), marked dehydration and the absence of significant acidosis (pH > 7.3 , bicarbonate >15 mEq/L). Ketonuria may be slight or absent. Complications may result from the metabolic crises itself or the related dehydration and include seizures, arterial occlusion, deep vein thrombosis, rhabdomyolysis, and life-threatening electrolyte disturbances.^[3,10]

Prevalence

HHS accounts for fewer diabetic-related admissions than DKA.^[45] In a retrospective study, HHS only accounted for 3.3% of diabetic emergency-related admissions in the US,^[52] whereas 12% of patients who presented with a diabetic emergency in a South African study had HHS.^[53] HHS typically present in the middle-aged or older patients, but cases have been described in paediatric and adolescent groups.^[54]

Risk factors

Older patients and patients with T2DM are at highest risk of developing HHS. The use of diuretics together with restricted water intake predispose the elderly to dehydration and ultimately HHS.^[3]

Clinical presentation

Patients with DKA and HHS present similarly,^[3,38,55] although neurological symptoms and signs occur more often in the HHS group. The change in mental status can vary from mild confusion to profound lethargy or coma, with a lower level of consciousness being linked to a higher osmolality (>340 mOsm/kg).^[56] Other neurological-related presentations may include seizures and focal neurological signs, although it might rather point towards a possible underlying condition instead of the metabolic derangement.^[3]

Precipitants

HHS may be brought on by infection, other illnesses (e.g. myocardial infarction or stroke), the concomitant use of medications that either decrease the effect of insulin or increase fluid loss and poor management of diabetes (including non-compliance to medication and diabetic diet). The most frequent precipitant is an infection, with rates documented to be as high as 57%.^[55] The most common infection sites are pulmonary and urinary tract.^[24,38]

Management

The management of HHS and DKA are very similar, and many societies have adopted a single treatment guideline for the management of these diabetic emergencies.^[3,10] The treatment principles are fluid replacement, correction

of hyperglycaemia, electrolyte management, and finding (and treating) the cause. Prophylactic antithrombotic treatment should also be considered.

The same fluid regime as for DKA can be used if there is no cardiac compromise (1 litre of normal saline in the first hour). The serum sodium, state of hydration and urinary output should guide the choice and rate of subsequent fluid replacement. Patients with renal or cardiac comorbidities should be closely monitored to avoid fluid overload.

Insulin regimes and potassium replacement guides are similar than for DKA. As HHS typically present in elderly patients who are likely to have comorbidities, additional emphasis should be placed on monitoring for hypoglycaemia and electrolyte abnormalities to limit the more detrimental effect than expected in younger healthier patients.^[3,38,43]

Resolution

The resolution of HHS is defined as a normalised serum osmolality (< 320 mOsm/kg) together with an improvement in the patient's mental state.^[10] Longer periods of time are compared to DKA.^[33,38,51] One study reported a resolution time of 11 hours, while another study reported a time to resolution of 29 ± 20.6 hours.^[44,45]

Mortality

HHS is associated with a considerably higher mortality rate than DKA since it occurs more frequently in older patients with underlying comorbidities.^[38] A Taiwanese study documented a mortality rate of 24%, with the degree of depressed level of consciousness associated with mortality.^[57] Even higher mortality rates have been reported in Nigeria (35%);^[58] whereas a mortality rate of 31% was described in the Eastern Cape province of South Africa.^[46]

Uncomplicated hyperglycaemia

Uncomplicated hyperglycaemia is strictly not defined as a diabetic emergency. These patients may be encountered early in the course of their DKA or HHS, and thus have not yet developed acidosis or hyperosmolarity, or they may be chronically hyperglycaemic. However, it is associated with increased hospital mortality in both critically ill patients and in patients admitted to general hospital wards.^[59] Many such patients also present to the emergency centre and is therefore shortly described.

Definition

Uncomplicated hyperglycaemia is defined as a fasting glucose level of >7 mmol/L or a random blood glucose level of >11.1 mmol/L, in the absence of DKA, HHS, and any neurological symptoms or signs. If ketonaemia is present, it should be less than 1.5 mmol/L, with a normal serum osmolality.^[60,61]

Prevalence

The prevalence of uncomplicated hyperglycaemia is expected to rise along with the global rise in diabetes.^[61] The prevalence varies, from 38% in the US to 42% in North Sudan.^[59,62]

Risk factors

Risk factors involved in hyperglycaemia are the same as for DKA and HHS and typically includes genetic predisposition, advanced age and factors associated with a sedentary lifestyle (smoking, obesity, physical inactivity).^[3]

Clinical presentation

Patients presenting with symptomatic uncomplicated hyperglycaemia typically present with polyuria, polydipsia, rapid weight loss, blurred vision, or suspicious infections (e.g. significant yeast infections, abscesses, anaerobic infections and foot infections).^[10,63,64] Other non-specific complaints may include fatigue and weakness. Patients may also be dehydrated as a result of the osmotic diuresis. Unless the patient suffered a stroke, there should be no neurological abnormality and patients are generally well appearing.

Management

The main management goals should be to ensure adequate rehydration, to manage any comorbidities or precipitating causes and to return the patient to a euglycaemic state. The management of the hyperglycaemia can be accomplished by either continuous insulin infusion or subcutaneous insulin use.^[61] In-hospital teams manage these patients until resolution after being adequately resuscitated.

Severe hypoglycaemia

Definition

Hypoglycaemia has historically been characterized by a triad of symptoms consistent with hypoglycaemia, a low blood glucose level, and relief of hypoglycaemic-symptoms when the blood glucose level has been raised.^[65] The ADA categorised hypoglycaemic episodes as i) Severe hypoglycaemia, ii) Documented symptomatic hypoglycaemia, iii) Asymptomatic hypoglycaemia, iv) Probable symptomatic hypoglycaemia, and v) Relative hypoglycaemia.^[65] The review will focus on the first two categories: severe hypoglycaemia and documented symptomatic hypoglycaemia.

Severe hypoglycaemia, as defined by the ADA, is “an event requiring the assistance of another person to actively administer carbohydrate, glucagon’s, or other resuscitative actions.”^[65] Blood glucose levels might not always be available as patients often present with seizures or coma; however, neurological recovery after correction of the blood glucose level is deemed sufficient evidence that the episode was a result of neuroglycopenia. On the other

hand, documented symptomatic hypoglycaemia occurs in patients with a measured blood glucose level <3.9 mmol/L, presenting with typical symptoms of hypoglycaemia.^[65]

Prevalence

The true prevalence of hypoglycaemia is difficult to attain, as a large portion of patients are trained to recognise its effects and correct the hypoglycaemic state without presenting to hospital. Several self-reported both internationally and locally driven studies have shown variable prevalence, from 30% up to 90%.^[20,66,67] A Denmark study indicated that 36% of T1DM patients had experienced severe hypoglycaemia at some point in their lives.^[68] Despite the high self-reported prevalence an overall decline in hypoglycaemic linked admissions was seen in the US (1.8 to 1.4 per 100 adults) from 2006–2011.^[69] In South Africa, 51 episodes of hypoglycaemic have been observed in 43 patients over a 5-month period.^[70]

Risk factors

Hypoglycaemia is an expected complication in diabetic patients. The associated risk factors include hypoglycaemic unawareness, aggressive glycaemic therapy, recent moderate or intense exercise, sleep, and renal failure.^[65]

Mild hypoglycaemic episodes frequently precede severe hypoglycaemia and analysing self-monitored glucose data over time can be used to predict severe hypoglycaemia.^[71,72]

Both T1DM and T2DM are at risk of developing hypoglycaemia. The prevalence of severe hypoglycaemia in T2DM in a meta-analysis of population-based studies was 6%.^[66] In South Africa, hypoglycaemia was experienced in 49% of T1DM patients and 68% among T2DM patients over a four-week period.^[20]

The treatment regime also affects the risk of severe hypoglycaemia. In T2DM, the prevalence of severe hypoglycaemia in patients on insulin was 21%, compared to 5% for those that took a sulphonylurea.^[66]

The elderly are predisposed as a result of their impairment of autonomic responses, as well as underlying organ dysfunction due to ageing.^[69,73,74] Frail persons, those using multiple medications, and those who are frequently hospitalized are at highest risk for drug-associated hypoglycaemia.^[75]

The association between increased HbA1C level and hypoglycaemia is controversial, although an increased level has been associated with an increased risk.^[67,76] Lastly, comorbidities such as chronic kidney disease increase the risk for hypoglycaemia by 27%.^[77,78]

Clinical presentation

Hypoglycaemia typically presents with either autonomic (diaphoresis, nausea, palpitations and anxiousness) or neuroglycopenic symptoms (dizziness, confusion, cognitive impairment, seizure and coma).^[79] The former tends to occur at glucose levels above 3mmol/L and the latter at glucose levels less than 2,8mmol/L.^[80] A decreased level of consciousness occurred in over 60% of patients presenting with hypoglycaemia in India,^[81] whereas 70% of patients in Nigeria presented with dizziness.^[74]

Precipitants

Hypoglycaemia can be a consequence of poor dietary intake, comorbidities, infection and diabetic treatment itself.^[66,79,82] Infection is a key precipitant for hypoglycaemia, with one study reporting an infection rate of 55%.^[82] Specifically infections of urinary (33%) and respiratory origin (23%) were frequent.^[82]

Other associated precipitants are inadequate dietary intake and alcohol use. Poor dietary intake accounted for 36% and the use of alcohol for 22% of admissions in hypoglycaemic patients in a South African study.^[70]

Risk factors in patients with recurrent hypoglycaemic episodes include: Inappropriate treatment, poor adherence to treatment, alcohol abuse, self-induced hypoglycaemia, Renal and liver disease, hypoglycaemia unawareness, drug interactions, and non-diabetic causes of hypoglycaemia e.g. insulinoma.^[37]

Management

The management of hypoglycaemia involves attaining euglycemia (blood glucose level 4-7 mmol/L). Symptomatic patients can self-correct the hypoglycaemia by ingesting a carbohydrate.^[65] Patients with severe hypoglycaemia will need intravenously administered dextrose.^[37] Finding and treating the cause for hypoglycaemia should be a priority in its management.^[37,73] Individualized management approaches to prevent future hypoglycaemic episodes needs to be put in place. Patients with recurrent hypoglycaemic episodes should be referred to a specialist endocrine facility.^[37]

Mortality

Hypoglycaemia in diabetic patients is associated with the risk of death. In T1DM, up to 6% of all deaths have been attributed to hypoglycaemia, and around 9% in T2DM receiving sulfonylurea monotherapy.^[83] Patients with severe hypoglycaemia had 3.4-fold higher 5-year mortality rate than those who presented with mild hypoglycaemia.^[76]

Burden of diabetic emergencies on the emergency centre

Patients with poorly controlled diabetes frequently present to the emergency centre for care. Limited access to primary health care facilities, low socioeconomic status, poor adherence to treatment, and predisposition to certain conditions are factors that increase the frequency of emergency centre visits.^[10,69,84,85] Additionally, the emergency centre is often the sole provider for diabetic care. A US- based study reported that more than 50% of diabetic patients who presented to the emergency centre, were exclusively managed by emergency centre staff.^[86]

Patients with a hyperglycaemic crisis often presents to the emergency centre. In Canada, about 17 patients are treated monthly for hyperglycaemic emergencies in the emergency centre.^[64] Similarly in the US, 0.9 of every 100 adults seen in the emergency centre relates to a hyperglycaemic crisis.^[69] Also of note, is that 17% of patients

that presented with a hyperglycaemic crisis visited the emergency centre during the previous 14 days.^[85] In South Africa, 10 patients presented monthly with DKA to a regional hospital in the KwaZulu/Natal province.^[17]

Severe hypoglycaemic episodes are also frequently encountered in the emergency centre. In the US, 1.4 per 100 adult emergency centre visits were due to hypoglycaemia, despite the frequency having decreased by 22% over a 5-year period.^[69] Patients who experienced hypoglycaemic episodes are also likely to revisit the emergency centre, with 5% returning within 48 hours after their initial presentation.^[87] Data regarding hypoglycaemic episodes in South African emergency centres are lacking.

The burden of diabetic emergencies on emergency centres is high. These patients usually require intense monitoring that should be provided in a high care or intensive care unit. In resource-limited settings, these patients are managed in the emergency centre till complete resolution as the emergency centre is often the only place equipped to provide continuous monitoring (except for the theatre-complex).^[41] The mean length of stay in the emergency centre of DKA patients in South Africa was 1.5 (\pm 0.8) days.^[17] This prolonged stay within the emergency centre often creates bedshortages.^[31]

Conclusion

The expected increase in diabetes prevalence in LMICs are evident. The economic effect of diabetes and its complications is major, considering that most patients are part of the economically active group. This necessitates the need for prevention, early detection and avoiding of microvascular and macrovascular complications of diabetes, which, inadvertently increase the risk for hospitalisation and decreases the quality of life. Despite the currently low prevalence in Africa, diabetes is a significant contributor to mortality.^[10,12]

The global burden of diabetic emergencies is substantial. Management strategies are effective, but resource intensive. This become problematic in lesser resourced settings where prolonged care is often provided in the emergency centre. The exact burden of diabetic emergencies on South African emergency centres is not well-known, and no studies were reported from entry-level hospitals. A better understanding of the burden will potentially identify setting specific risk factors that might be amenable to prevention strategies to decrease the effect of diabetes and its emergency complications.

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Part B: MANUSCRIPT IN ARTICLE FORMAT

(African Journal of Emergency Medicine)

[Title page]

The burden of diabetic emergencies on the resuscitation area of a district-level public hospital in Cape Town

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Abstract

Introduction

Diabetes and its complications continue to cause a daunting and growing concern on resource-limited environments. There is a paucity of data relating to the care of diabetic emergencies in the emergency centres of entry-level hospitals in Africa. The aim of this study was to describe the burden of diabetic emergencies presenting to the emergency centre of an urban district-level hospital in Cape Town, South Africa.

Methods

The Khayelitsha Hospital Emergency Centre database was retrospectively analysed for patients presenting with a diabetic emergency within a 24-week randomly selected period. The database was supplemented by a retrospective chart review to include additional variables for participants with diabetic ketoacidosis (DKA), uncomplicated hyperglycemia, severe hypoglycaemia and hyperosmolar hyperglycaemic state (HHS). Summary statistics are presented of all variables.

Results

The prevalence of all diabetic emergencies was 8.1% (197/2424) (DKA n=96, 48.7%; uncomplicated hyperglycaemia n=45, 22.8%; severe hypoglycaemia n=44, 22.3%; HHS n=12, 6%). The median age was 48 years, with those presenting with DKA being substantially younger (36 years). A likely precipitant was identified in 175 (88%) patients; infection was the most common precipitant (n=79, 40.1%). Acute kidney injury occurred in 80 (40.6%) cases. The median length of stay in the resuscitation area was 13 hours (IQR 7.2-24) and 101 (51.3%) participants represented with a diabetic-related emergency within six months of the study period. The overall mortality rate was 5% (n=10).

Conclusion

This study highlights the high burden of diabetic emergencies on the provision of acute care at a district-level hospital. The high prevalence of diabetic emergency presentations (8%), the high infection rate (40%), and the high percentage of patients returning with a diabetic emergency (51%) could be indicative of the need for improved community-based diabetic programmes.

Keywords

diabetes, emergency, South Africa, diabetic ketoacidosis, burden

Introduction

Diabetes is a significant contributor to morbidity and mortality and remains a global health concern. An estimated 382 million people had diabetes in 2013, and this number is expected to double by 2035; the majority of this increase is expected in low- and middle-income countries.^[1] The World Health Organization further projects that diabetes will be the seventh leading cause of death in 2030.^[2] In South Africa, an estimated 7% of economically active citizens have diabetes, and along with other non-communicable diseases, pose a major socio-economic threat to South Africa.^[3,4]

Diabetes is globally one of the most prevalent chronic diseases amongst emergency centre patients,^[5,6] and patients often present with a diabetic emergency (diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS), uncomplicated hyperglycaemia and severe hypoglycaemia). Patients with diabetic emergencies should ideally be treated in intensive care or high care settings,^[7] but this may not always be possible.^[8] As a result, these acutely ill patients are often treated for extended periods in the emergency centre.^[9] This places undue strain on emergency centre staff and resources, as these patients require precise monitoring and ongoing management.^[7]

There is currently a paucity of data about the burden of diabetic emergencies on emergency centres at entry-level hospitals, as most studies focussed on intensive or high care units within well-resourced countries. South Africa has a mounting burden of diabetes and other non-communicable diseases,^[10] and knowledge of the burden of diabetic emergencies within the local context is essential as part of the effort to reduce diabetic-related morbidity and mortality. The study set out to describe the burden of diabetic emergencies on the emergency centre of a district-level hospital in Cape Town, South Africa.

Methods

Study design

A retrospective analysis of a prospectively collected observational database was conducted at Khayelitsha Hospital covering a period of 24 randomly selected weeks between 1 January 2017 and 30 June 2018. The database was supplemented by a retrospective chart review to include additional variables. The study was approved by the Health Research Ethics Committee of Stellenbosch University (S18/10/215). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist was used to guide the report.^[11]

Study setting

Khayelitsha Hospital is a 340-bed hospital situated in the partially informal township of Khayelitsha, Cape Town. It serves a health district with a population just fewer than 500 000 people; a substantial proportion of which are unemployed (38%).^[12] The resuscitation area within the emergency centre consists of four adult-sized beds and one paediatric/neonatal resuscitation cot. Each bed is individually equipped with non-invasive and invasive monitoring tools, a fully stocked resuscitation trolley, a ventilator, and a defibrillator. A blood gas machine is

also situated within the resuscitation area. Patients managed within the resuscitation area are selected based on a high acuity level on the South African Triage Scale or by a senior physician's clinical gestalt.^[13] Other than theatre, the resuscitation area is the only place capable of continuous patient monitoring, as the hospital does not have a high care or intensive care unit.

Data collection and management

The Khayelitsha Hospital Emergency Centre database is a prospectively collected observational database and has previously been described.^[6] In brief, data is captured electronically, is coded and stored onto a password-protected server. A decoding sheet is separately stored. The database has been registered at the Stellenbosch University Health Research Ethics Committee (Ref: N15/10/107)

Convenience sampling was used, and 24 weeks within 18 months was randomly selected (using a computer randomizer). The sample size was limited due to restricted resources; however, it was expected to be representative of the population. All patients who presented to the resuscitation area with a diabetic emergency (DKA, HHS, uncomplicated hyperglycaemia or hypoglycaemia) were eligible. Patients presenting with uncomplicated hyperglycaemia were included as many patients with elevated glucose levels are unable to produce urine at triage. These patients are often severely ill despite well looking and true hyperglycaemic emergencies (DKA, HHS) have previously been missed. All patients with elevated or decreased glucose levels are thus managed within the resuscitation area until a senior clinician have evaluated the patient. Patients who presented with a diabetic emergency in the absence of pre-existing or newly diagnosed diabetes were excluded (e.g. hyperglycaemic stress response). Patients with missing folder numbers or medical notes were also excluded.

Diabetic emergencies were defined using criteria from the American Diabetes Association (ADA) and the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA).^[7,14] DKA was defined as hyperglycaemia with glucose >13.9 mmol/l, metabolic acidosis with pH <7.3 and bicarbonate <18 mmol/l, and presence of ketonemia (>3 mmol/l). As serum ketones were not readily available, the presence of urine ketones was used as a surrogate marker when indicated. The serum pH was used to classify severity: mild (7.25 - 7.3), moderate (7.0 - 7.24), severe (<7.0). Resolution of acidosis (pH >7.3 , bicarbonate >18 mmol/l) and ketonemia (<3 mmol/l) were used to determine the resolution of DKA. severe hyperglycaemia (serum glucose >33.3 mmol/L), hyperosmolality (serum osmolality >320 mOsm/kg), marked dehydration and the absence of significant acidosis (pH >7.3 , bicarbonate >15 mEq/L); ketonuria may be slight or absent. Uncomplicated hyperglycaemia was defined as random blood glucose >11.1 mmol/l in the absence of ketonemia and acidosis. Hypoglycaemia was defined as a blood glucose level <3.9 mmol/l with an altered level of consciousness.

The Triage Early Warning Score (TEWS) was used to determine patient acuity. The TEWS is a composite score of physiologic parameters measured at arrival to the hospital. It forms part of the South African Triage Scale and categorizes patients as non-urgent (green), urgent (yellow), very urgent (orange), and emergency (red).^[13]

Data was collected after a decoded cleaned extract of the electronic database has been obtained (cleaned: copied into an Excel spreadsheet with all non-diabetic emergencies removed). The password-protected Excel

spreadsheet was further populated using the hospital's electronic clinical records. Data collected include diagnosis, demographic profile, clinical presentation, precipitating factors, comorbidities, biochemical profile, diagnostic tests performed, interventions received while in the resuscitation area, length of stay in the resuscitation area, length of hospital stay, disposition from resuscitation area, and in-hospital mortality. Patient folder numbers, the primary identifier used in the database was removed once the entire data collection was complete. A pilot study was conducted on 10 participants to standardise data abstraction (data were included). A single data collector, not blinded to the study's objective, collected the data.

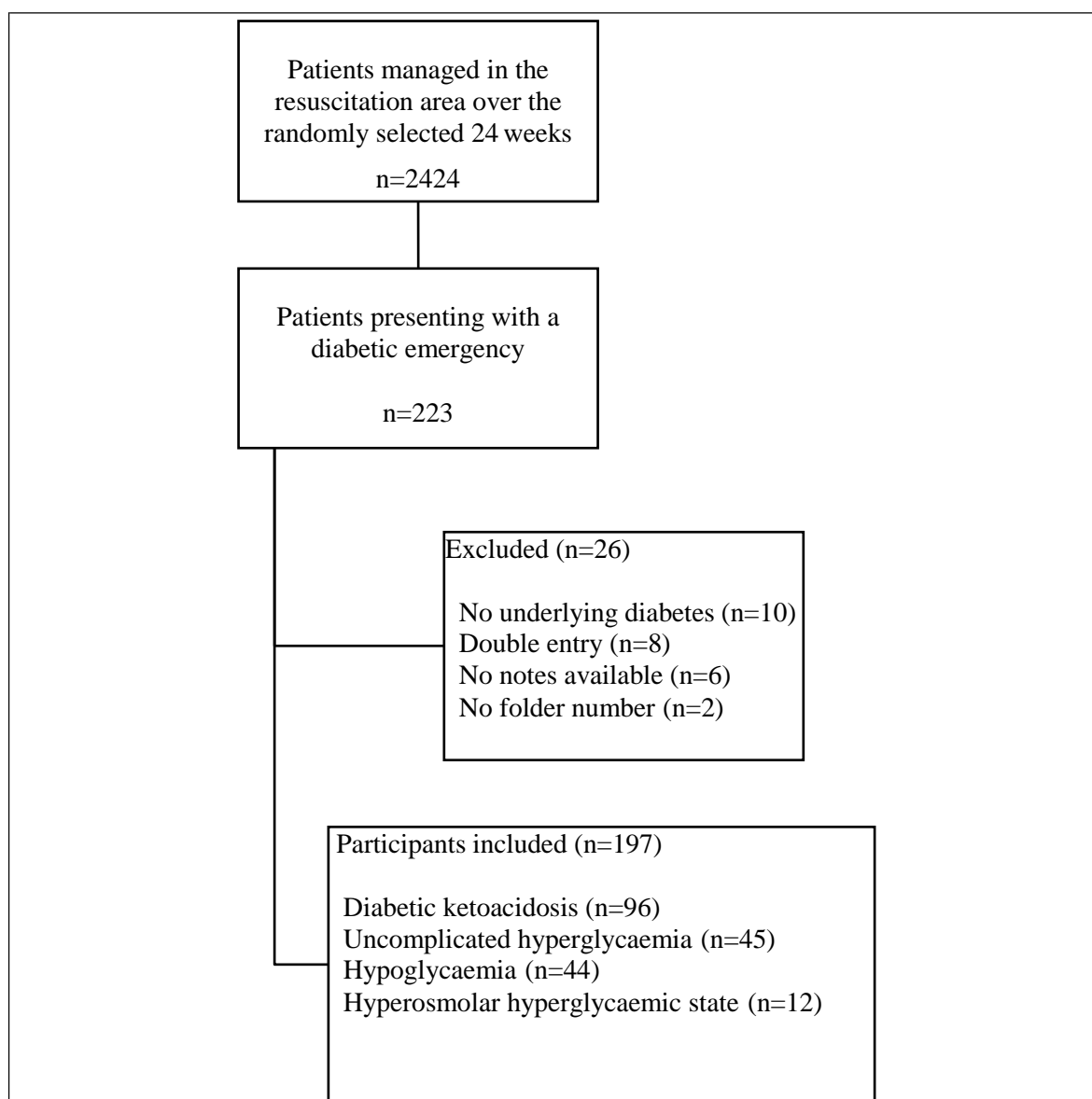
Data analysis

Incomplete data points were excluded from the analysis. Summary statistics were used to describe all variables. Categorical data were summarised using frequency counts or percentages, and distributions of variables were presented as two-way tables. Medians and means were used as the measures of central tendency for ordinal and continuous responses and standard deviations or quartiles as indicators of spread. Analysis was performed using Microsoft® Excel for MAC Version 16.30(19101301).

Results

A total of 197 patients with a diabetic emergency were included after 26 cases were excluded. The prevalence of all diabetic emergencies was 8.1% (197/2424), with DKA occurring most frequently (48.7%, 96/197) (Figure 1).

Figure 1. Flow diagram of study participants



Demographic details of participants are given in Table 1. Most participants were female (n=113, 57.4%). The median (25th - 75th percentile) age was 48 (31-62) years, with participants diagnosed with DKA being substantially younger (36 (25-46) years). The majority of the participants (n=135; 68.5%) had type 2 diabetes, and overall, 31 (15.7%) was newly diagnosed with diabetes. A total of 135 (68.5%) participants presented outside regular office hours (weekdays 08h00-15h59) and 101 (51.3%) represented with a diabetic-related emergency within six months; 60 (59.4%) re-presenting within 30 days. The median (25th - 75th percentile) age for re-presenters in this study was 48 (29-61) years. Most were T2DM (n=70; 69.3%), 66 (65.3%) on insulin, and 32 (31.7%) on oral anti-diabetic agents. The main precipitants identified were infection (n=40; 39.6%) and non-compliance (n=25; 24.7%). The in-hospital mortality rate amongst the re-presenters was 6.9 %.

Table 1. Demographic details of patients admitted with a diabetic emergency to the resuscitation area of Khayelitsha Hospital

	DKA^a (n=96) n (%)	HHS^b (n=12) n (%)	Uncomplicated hyperglycaemia (n=45) n (%)	Severe hypoglycaemia (n=44) n (%)	Overall (n=197) n (%)
Male	48 (50%)	7 (58.3%)	17 (37.8%)	12 (27.3%)	84 (42.6%)
Median age (years) (Q1-Q3) ^c	36 (25-46)	63 (56-71)	54 (44-63)	62 (54-70)	48 (31-62)
New diabetic diagnosis	19 (19.8%)	4 (33.3%)	8 (17.8%)	0	31 (15.7%)
Type of diabetes					
Type 1	48 (50%)	0	4 (8.9%)	2 (4.5%)	54 (27.4%)
Type 2	43 (44.8%)	12 (100%)	39 (86.7%)	42 (95.4%)	136(69%)
Unknown	5(5.2%)	0	2(4.4%)	0	7 (3.6%)
Transported by					
Self	22 (22.9%)	1 (8.3%)	8 (17.7%)	12 (27.3%)	43 (21.8%)
Ambulance	58 (60.4%)	9 (75%)	33 (73.3%)	26 (59%)	126 (63.9%)
Unknown	16 (16.7%)	2 (16.7%)	4 (8.9%)	6 (13.6%)	28 (14.3%)
Transported from:					
Home	44 (45.8%)	4 (33.3%)	20 (44.4%)	37 (84%)	105 (53.3%)
Other health facility	39 (40.6%)	7 (58.3%)	21 (46.7%)	2 (4.5%)	69 (35%)
Unknown	13 (13.5%)	1 (8.3%)	4 (8.9%)	5 (11.4%)	23 (11.6%)
Presenting time					
Office hours ^d	32 (33.3%)	4 (33.3%)	18 (33.3%)	8 (18.2%)	62 (31.5%)
After hours	64 (66.7%)	8 (75%)	27 (60%)	36 (81.8%)	135 (68.5%)
Participant mobility					
Walking	33 (34.4%)	2 (16.7)	18 (40%)	3 (6.8%)	56 (28.4%)
With Help	46 (47.9%)	4 (33.3%)	21 (46.7%)	13 (40.9%)	84 (42.6%)
Stretcher/immobile	14 (14.5%)	6 (50%)	6 (13.3%)	28 (63.6%)	54 (27.4%)
Unknown	3(3.1%)	0	0	0	3 (1.6%)
Participant acuity ^e					
Non-urgent (green)	5 (5.2%)	0	2 (4.4%)	0	7 (3.5%)
Urgent (yellow)	20 (20.8%)	1 (8.3%)	0	9 (20.5%)	30 (15.2%)
Very urgent (orange)	39 (40.6%)	8 (75%)	2 (4.4%)	14 (31.8%)	63 (32%)
Emergent (red)	8 (8.3%)	2 (16.7%)	0	15 (34%)	25 (12.7%)
Unknown	24 (25%)	1 (8.3%)	41 (91.1%)	6 (13.6%)	72 (36.5%)

^a Diabetic Ketoacidosis, ^b Hyperosmolar hyperglycaemic state, ^c 25th percentile to 75th percentile, ^d Monday to Friday (08h00 – 15h59), ^e According to Triage Early Warning Score (TEWS) of the South African Triage Scale (SATS)

Gastrointestinal symptoms, which includes at least one of either nausea, vomiting, abdominal pain and/or diarrhoea, occurred in most patients (n=143, 72.6%). Infection and poor drug compliance were the most frequent precipitants (79 (40.1%) and 52 (26.4%) respectively). Most infections related to the respiratory tract (n=23; 29.1%), and the gastro-intestinal system (n=15; 19%). Other infections included soft tissue infections (n=12; 16%), urinary tract infections (n=11; 15%), undefined sepsis (n=8; 10%), central nervous system infections (n=5; 6.3%) and gynaecological infections (n=3; 4%). In hypoglycaemic only participants, infection (n=15; 34%), overmedication with prescribed hypoglycaemic agents (sulphonylureas and insulin)(n=11, 25%), inadequate food intake (n=9; 20.5%) and acute renal failure (n=7, 15.9%) were the main reasons for presentation (Table 2).

Table 2. Precipitants, presenting symptoms and comorbidities in patients admitted with a diabetic emergency to the resuscitation area of Khayelitsha Hospital

	DKA^a(n=96) n (%)	HHS^b (n=12) n (%)	Uncomplicated hyperglycaemia (n=45) n (%)	Severe hypoglycaemia (n=44) n (%)	Overall (n=197) n(%)
Precipitant identified	86 (89.6%)	10 (83.3%)	37 (82.2%)	43 (97.7%)	175(88.8%)
Precipitant					
Infection	36 (37.5%)	7 (58.3%)	21 (46.7%)	15 (34%)	79 (40.1%)
Non-compliance	38 (39.6%)	2 (16.7%)	12 (26.7%)	0	52 (26.4%)
Medication related	2 (2%)	0	0	11 (25%)	13 (6.6%)
Alcohol related	7 (7.3%)	0	0	1 (2.3%)	8 (4%)
Diet related	2 (2%)	0	0	9 (20.5%)	11 (5.6%)
Other	1 (1%)	1 (8.3%)	4 (8.9%)	7 (15.9%)	13 (6.6%)
Presenting signs and symptoms					
Gastrointestinal symptoms	95 (99%)	5 (41.7%)	33 (73.3%)	10 (22.7%)	143 (72.6%)
Polyuria & Polydipsia	17 (17.7%)	1 (8.3%)	7 (15.5%)	0	22 (11.2%)
Lethargy	2 (2%)	0	0	2 (4.5%)	4 (2%)
Shortness of breath	19 (19.8%)	0	4 (8.9%)	4 (9%)	27 (13.7%)
Weakness	32 (33.3%)	6 (50%)	18 (40%)	4 (9%)	57 (28.9)
Altered level of consciousness	14 (14.6%)	10 (83.3%)	3 (6.7%)	26 (59%)	53 (26.9%)
Comorbidities					
Hypertension	31 (32%)	10 (83.3%)	28 (62.2%)	34 (77.3%)	103 (52.3%)
Chronic kidney disease	3 (3.1%)	2 (16.7%)	2 (4.4%)	7 (15.9%)	14 (7.1%)
HIV ^c positive	19 (19.8%)	0	6 (13.3%)	7 (15.9%)	32 (16.2%)
Alcohol abuse/binge	11 (11.4%)	0	0	1 (2.3%)	12 (6%)
Macrovascular complications ^d	5 (5.2%)	3 (25%)	10 (22.2%)	10 (22.7%)	28 (12.7%)
Microvascular complications ^e	20 (20.8%)	7 (58.3%)	9 (20%)	19 (43.1%)	55 (27.9%)

^a Diabetic Ketoacidosis, ^b Hyperosmolar hyperglycaemic state, ^c Human immunodeficiency virus, ^d Includes coronary artery disease, peripheral arterial disease, and stroke, ^e Includes diabetic nephropathy, neuropathy, and retinopathy

The investigations performed and treatment given are reported in Table 3. In total, 60 serum ketone tests were done of which 38 (63%) were found to be positive. In the DKA group, 41 patients had a serum ketone test with urinary dipsticks used to diagnose 55 patients. Twenty (10.1%) of the 62 urine cultures sent were positive; the most common organisms were *Escherichia coli* (n=5) and *Klebsiella pneumoniae* (n=5). A total of 77 blood

cultures were sent and 16 (21%) were positive; coagulase-negative staphylococcus was identified as the most common organism (n=6), followed by *Klebsiella pneumoniae* (n=2) and *Escherichia coli* (n=2). The median (25th – 75th percentile) amount of fluid given in all patients was 3.9 (2.0-5.6) litre, and 72 (37%) patients received antibiotics (Table 3.)

Table 3. Investigations done and treatment given for patients with a diabetic emergency managed in the resuscitation area of Khayelitsha Hospital

	DKA ^a (n=96) n (%)	HHS ^b (n=12) n (%)	Uncomplicated hyperglycaemia (n=45) n (%)	Severe hypoglycaemia (n=44) n (%)	Overall (n=197) n (%)
Antibiotics	39(40.6%)	7(58.3%)	13(28.9%)	13(29.5%)	72(37%)
Blood culture	50(52%)	10(83.3%)	8(17.8%)	9(20.4%)	77(39%)
Blood gas	94(97.9%)	12(100%)	45(100%)	35(79.5%)	186(94.4%)
Bolus insulin /sliding scale	16(16.7%)	1(8.3%)	36(80%)	1(2.3%)	54(27.4%)
Chest x-ray	88(91.7%)	12(100%)	38(84.4%)	39(88.6%)	177(89.3%)
Electrocardiogram	73(76%)	12(100%)	21(46.7%)	24(54.4%)	130(65.9%)
Insulin infusion	78(81.3%)	11(91.7%)	4(8.9%)	1(2.3%)	93(47.2%)
Intravenous fluids	88(91.7%)	12(100%)	28(62.2%)	28(63.6%)	156(79.2%)
Investigations					
Litres received (median (Q1- Q3) ^c)	5.3 (3.2- 7.2)	4.8 (2.55- 6.35)	1.9 (1.0-2.25)	1.7 (1.0-2.0)	3.9 (2.0- 5.6)
Positive blood culture	9(18%)	3(30%)	0	4(44.4%)	16(20.8%)
Positive for pulmonary tuberculosis	2(50%)	0	2(66.7%)	0	4(57.1%)
Positive urine culture	11(28.9%)	2(28.6%)	3(37.5%)	4(44.4%)	20(32.3%)
Serum ketones	40(41.7%)	5(41.7%)	13(28.9%)	1(2.3%)	59(29.9%)
Sputum testing for pulmonary tuberculosis (Xpert MTB/RIF)	4(4.2%)	0	3(6.7%)	0	7(3.6%)
Treatment					
Urine culture	38(39.6%)	7(58.3%)	8(17.7%)	9(9%)	62(31.4%)
Urine dipstick	78(81.3%)	8(66.7%)	41(91.1)	9(20.4%)	136(69%)

^aDiabetic Ketoacidosis, ^bHyperosmolar hyperglycaemic state, ^c25th percentile to 75th percentile

A summary of laboratory investigations are presented in Supplementary Table 1. Acute kidney injury occurred in 80 (40.6%) cases; 48 (60%) in the DKA group, 18 (23%) in the uncomplicated hyperglycaemia group, and 8 (10%) in the HHS group. Six (13.6%) of the hypoglycaemic cases had acute kidney injury. Hyperkalaemia (potassium >5 mmol/L) occurred in 34 (22.2%) of all hyperglycaemic cases and hypokalaemia (potassium <3 mmol/L) in 7 (4.6%) cases.

The median time spent in the resuscitation area was 8.4 hours, with the longest times shared between patients with DKA and HHS (Table 4). Patients spent a median of 3.2 days in the hospital (Table 4). In-hospital teams

managed 123 (62.4%) of the patients, with 20 (9.8%) of the patients transferred for tertiary care. The in-hospital mortality during the study period was 5.0% (n=10; DKA n=1; HHS n=2; severe hypoglycaemia n=7). Only one death occurred in the resuscitation area. While most deaths occurred in the hypoglycaemic group (n=7, 70%), the actual cause of death mainly related to an intracranial event (n=3, 30%) or undefined sepsis (n=4; 40%).

Table 4 Length of stay and disposition of patients managed with a diabetic emergency in the resuscitation area of Khayelitsha Hospital.

	DKA^a (n=96) n (%)	HHS^b (n=12) n (%)	Uncomplicated hyperglycaemia (n=45) n (%)	Severe hypoglycaemia (n=44) n (%)	Overall (n=197) n (%)
Median length of stay (Q1-Q3) ^c					
Resuscitation area (hours)	13 (7.2-24)	18 (7.2-24)	5 (2.4-9.6)	5 (2.4-7.2)	8.4 (3.8-18)
Hospital (days)	4.4 (2.1-7.6)	6.9 (5.3-8.9)	1.1 (0.5-4.0)	1.8 (0.8-5.4)	3.2(0.9-6.3)
Disposition					
Discharged directly home	15 (13.5%)	0	24 (53.3%)	20 (45.4%)	57 (28.9%)
Referred to in-hospital disciplines	74 (77%)	10 (83.3%)	18 (40%)	21 (47.7%)	123 (62.4%)
Referred to tertiary facility	7 (7,3%)	2 (16.7%)	3 (16.7%)	2 (4.5%)	14 (7.1%)
Died in resuscitation area	0	0	0	1 (2.3%)	1 (0.5%)

^aDiabetic Ketoacidosis, ^bHyperosmolar hyperglycaemic state, ^c25th percentile to 75th percentile

Discussion

The prevalence of diabetic emergencies (8%) is indicative of the high burden on the resuscitation area of Khayelitsha Hospital. Almost half of the presentations related to DKA and urine dipsticks were mainly used to assess for ketosis. Infection was the main precipitant in all groups (40%). The high percentage of patients (51%) returning with a diabetic emergency to the emergency centre within six months is of concern and further increases the burden.

The prevalence of hyperglycaemic emergencies was 6.3% and 4.5% for DKA and HHS combined (i.e. uncomplicated hyperglycaemia excluded). This equates to about 18 patients per month, which is similar to a Canadian emergency centre where 17 patients with hyperglycaemic emergencies were treated.^[15] However, the majority of patients had DKA (about 16 per month), which is substantially more than the ten patients per month with DKA seen in the emergency centre of a rural regional hospital in the KwaZulu/Natal province of South

Africa.^[9] Exact reasons for this difference remains unclear but could relate to geospatial differences (urban vs rural) in diabetes in general.^[16,17]

More than 30% (60/197) of the participants returned within 30 days to the emergency centre with a diabetic-related emergency. This is higher than the 19% documented in Canada.^[15] Recurrent hyperglycaemia visits have been associated with patients <25 years of age, a glucose level >20 mmol/L, being on insulin, and a recent visit to the emergency centre for hyperglycaemia.^[15] Associated factors in our study still need to be formally explored, but it is clear that poorly controlled diabetes cause a great burden on the emergency centre of Khayelitsha Hospital as they typically require intensive monitoring, for potentially extended periods of time. Returning patients (especially those with DKA) are also at high risk of mortality, as seen in this study and prevention of recurrent presentations will thus benefit both the patient and the hospital.^[18]

Severe hypoglycaemic episodes were also regularly encountered in the resuscitation area (1.8 per 100 adults). This is similar to the 1.4 per 100 adult emergency centre visits in a US-based study.^[19] Patients who experienced hypoglycaemic episodes were also likely to revisit the emergency centre; 50% returned within six months compared to 5% returning within 48 hours in a US study.^[20] Comparative data regarding hypoglycaemic episodes in South African emergency centres are lacking, but internationally patients using oral anti-diabetic agents are at higher risk to return to the emergency centre than those treated with insulin alone.^[20]

Urinary ketone assessment (using a dipstick) was more frequently used than testing for serum ketones (laboratory done) to detect the presence of ketosis in hyperglycaemic patients (urine 127/153, 83%; serum 58/153, 38%). The presence of ketones in the urine (ketonuria) is often used as a surrogate marker for serum ketones (ketonemia),^[7] as serum ketone laboratory tests are more costly and not everywhere readily available. However, there are two ketones that play a role in DKA, acetoacetate and beta-hydroxybutyrate, with the latter being the predominant ketone in severe untreated DKA. The urine dipstick detects acetoacetate, but beta-hydroxybutyrate is not.^[21] Point-of-care blood beta-hydroxybutyrate strips are available, although not at Khayelitsha Hospital at the time of the study. A US-based study found a similar sensitivity for blood beta-hydroxybutyrate strips and urine acetoacetate dipsticks (both 98%) in diagnosing DKA, but blood beta-hydroxybutyrate strips had higher specificity (79%) than the urine acetoacetate dipsticks (35%).^[22] The decreased specificity of the urine dipstick raises concerns of potentially unwarranted medical work-ups as a result of false negative tests.

Infection was deemed to be the precipitant factor in 40% of patients which confirms the high rate of infection in patients presenting with diabetic emergencies.^[23-25] This further indicates the need for the diligent search for infection, which should include cultures of blood, urine and pulmonary specimens. One in every five blood cultures done were positive, while urine cultures had a slightly higher yield (1.5 in every 5). Although only a few sputum cultures were collected, more than half (57.1%) was positive for tuberculosis. Diabetics are predisposed to infection and increased, and specialised screening programmes should be considered in settings with a high tuberculosis prevalence.^[26,27]

Strengths and limitations

A strength of the study was the use of a pre-piloted standardized data collection form. However, the results could have been affected by various limitations. Firstly, the study reflects the experience at a single urban emergency centre with standardised protocols and care should be taken to generalise the results to different settings. The retrospective nature of the study led to the reliance on adequate documentation for quality data. Participants could have received treatment at referring clinics or from ambulance crews before arrival; this could have led to specific parameters being different by the time the patients presented to the hospital. Lastly, included weeks were randomly selected from the existing database, and seasonal variation could have influenced the prevalence.

Conclusion

This study highlights the high burden of diabetic emergencies on the provision of acute care at a district-level hospital. The high prevalence of diabetic emergency presentations (8%), the high infection rate (40%), and the high percentage of patients returning with a diabetic emergency (51%) could be indicative of the need for improved community-based diabetic programmes. Future studies could explore barriers to care, such as delayed access to health care and challenges to follow effective treatment protocols.

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Supplementary material

Supplementary Table 1. Summary of laboratory investigations done at presentation in patients with a diabetic emergency managed in the resuscitation area of Khayelitsha Hospital

Mean±SD ^a unless otherwise stated	Normal range	DKA ^b (n=96)	HHS ^c (n=12)	Uncomplicated hyperglycaemia (n=45)	Severe hypoglycaemia (n=44)	Overall (n=197)
pH	7.35-7.45	7.1±0.18	7.2±0.15	7.38±0.06	7.3±0.1	7.2±0.18
Bicarbonate (mmol/L)	18-28	12.7±8.6	16.6±6.3	23.7±3	21.1±7.9	16.4 ±8.9
Base excess (meq/l)	-2 to +2	-12.2±11.2	-9.1±8	-0.12±3.8	-3±9.1	-7.3±10.7
Lactate (mmol/L)	<2	3.2±1.9	4.1±3.6	1.98±0.8	2.7±3.2	3±2.4
Haematocrit (%)	36-46	47.3±8.8	45.5±8.4	40.8±7.7	36.1±7.9	43.6±9.4
Sodium (mmol/L) (median ((Q1-Q3)) ^d	135-145	130 (126-134.5)	127.5 (118-136.3)	130.5 (127-134.8)	135 (131.5-137.5)	131 (127-135)
Potassium (mmol/L) (median ((Q1-Q3)) ^d	3.5-5.5	5.0 (4.4-5.9)	5.3 (4.6-6.6)	4.4 (4.8-4.8)	4.4 (3.9-5.2)	4.7 (4.2-5.7)
Urea (mmol/L) (median ((Q1-Q3)) ^d	2.5-7.1	7.10 (5.5-11.7)	26.1 (17.2-36.6)	7.0 (4.0-4.8)	9.0 (5.1-20.0)	7.9 (5-15.9)
Creatinine (mmol/L) (median ((Q1-Q3)) ^d	60-120	112 (90.5-168)	310 (188.5-448)	95 (71-128)	120.50 (60.5-212.3)	113.5 (77.8-179.3)
White cell count (x 10 ⁹ /L)	3.9-12.6	19±12	15.4±8.1	10.5±5	8.7±4	14.7±10.3
Haemoglobin (g/dL) (median ((Q1-Q3)) ^d	12.0-15.0	13.8 (11.5-15.0)	12.7 (10.3-14.9)	12.3 (10.2-13.1)	10.3 (9.2-11.5)	12.5 (10.2-14.4)
Platelets (x 10 ⁹ /L)	186-454	368.4±167.7	271.7±76.9	334±139.8	329.5±116.1	345.8±148.4
Haemoglobin A1c (%)	<7	13.4±5.6	11.6 ±4.9	12.9±3.2	8.3±2.4	12.1±5.1

^a Standard deviation, ^b Diabetic Ketoacidosis, ^c Hyperosmolar hyperglycaemic state, ^d 25th percentile to 75th percentile

Conflicts of interest

The authors declare no conflicts of interest.

Part C: SUPPORTING DOCUMENTATION

A] Proposal

The burden of diabetic emergencies in the resuscitation area at a district-level public hospital in Cape Town

Principal Investigator (MMed candidate): Dr Nuraan Lotter
Division of Emergency Medicine
University of Stellenbosch

Supervisor: Dr Daniël J van Hoving
Division of Emergency Medicine
University of Stellenbosch

Co-supervisor: Dr Sa'ad Lahri
Khayelitsha Hospital

Background

Diabetes remains a global health concern as it contributes significantly to morbidity and mortality. In 2013 it was estimated that 382 million people had diabetes; this is predicted to rise to 592 million by 2035.(1) Subsequently, up to 12% of global health expenditure is spent on diabetes and its complications.(2) Diabetes mortality rates are as high as 30%,(3) with about 73% of these deaths occurring in the economically active group.(4) The World Health Organisation (WHO) projects that diabetes will be the seventh leading cause of death in 2030.(5)

The biggest increase of people living with diabetes is expected to occur in low-and-middle-income countries in the next two decades.(1) Recent data suggest that 7% of economically active South Africans have diabetes. This means that 3.85 million people between the ages of 21 and 79 years may be living with the disease.(2) These numbers reflect the mounting burden of non-communicable diseases in South Africa,(6) despite the declaration that non-communicable diseases are a focus area on the African continent.(7) Additionally, a large focus is still on communicable diseases,(8) despite the major social, economic and psychological threat diabetes poses.(9)

Patients with hyperglycaemic emergencies should ideally be treated in an intensive care or high care setting.(10) This indeed happens in South Africa,(11) but may not always be possible due to a host of reasons, including the paucity of freely available intensive care and high beds.(12) As a result, these acutely ill patients often end up in the emergency centre of the hospital.(13)

Diabetes is one of the most prevalent chronic diseases amongst all visitors to the emergency centre, both internationally and locally.(14,15) These patients are often managed in the resuscitation area of the emergency centre as it often is the only monitored area in the hospital outside of theatre.(14) This is not ideal for both the patient and the emergency centre staff as these patients have a mortality rate around 17%.(13)

Motivation

Diabetes and its emergency complications (hyper- and hypoglycaemic) are highly prevalent in patients managed within emergency centres. Unfortunately, the exact burden remains unknown, especially at the district health care level. The purpose of this study is to quantify the burden of diabetic emergencies on the resuscitation area of a district-level hospital, and if possible, to identify setting specific risk factors that might be amenable to prevention strategies.

Aim and objectives

The aim of the study is to determine the burden of the various types of diabetic emergencies on the resuscitation area of Khayelitsha Hospital over a six-month period.

The objectives are:

- i. To determine and describe the prevalence of diabetic emergencies (diabetic ketoacidosis, hyperosmolar hyperglycaemic state and hypoglycaemia)

- ii. To determine precipitant(s) and risk factors for the diabetic emergencies
- iii. To determine and describe the diagnostic tests performed and interventions received while in the resuscitation area
- iv. To determine the length of stay in the resuscitation area and in hospital
- v. To determine the in-hospital mortality of the patients
- vi. To determine the prevalence (and possible precipitating factors) of re-admissions relating to diabetic emergencies within six months

Methodology

Study design

A retrospective analysis of a prospectively collected observational database will be conducted of a period of six months. This will be supplemented by a retrospective chart review to include additional variables.

Study setting

Khayelitsha Hospital is a 300-bed hospital situated in the expansive township of Khayelitsha, Cape Town. It serves a health district with a population of more than 390 000, which is predominantly Black African (99%) with significant levels of unemployment (38%).⁽¹⁶⁾ There is a tremendous burden of disease related to HIV, TB and interpersonal violence.⁽¹⁷⁾

Khayelitsha Hospital provides inpatient services such as surgical, medical, paediatric and obstetrics.⁽¹⁸⁾ It houses a large emergency centre, which is 30% larger than that of a standard district hospital trauma unit.⁽¹⁸⁾ The resuscitation area consists of four beds and a paediatric cot. Each equipped with its own monitor containing a blood pressure, pulse oximetry, and capnography capabilities. In addition, there is a fully stocked emergency trolley for airway management with a defibrillator and a standalone ventilator for each bed. The admission criteria are either a high acuity score according to the South African Triage Scale or at any senior practitioner's discretion.⁽¹⁹⁾ With no high care or intensive care beds available at the facility.

Study population

The electronic Khayelitsha Hospital Emergency Centre database is a prospectively collected observational database capturing all patients managed within the resuscitation area since 1 November 2014. Data are captured electronically, are coded and stored onto a password protected server. A decoding sheet is separately stored. The database has been registered at the Stellenbosch University Health Research Ethics Committee (Ref: N15/10/107) as well as at the National Health Research Database (Ref: WC_2014RP10_967).

Sampling

A total of 24 weeks will be randomly selected (using a computer randomiser) from the Khayelitsha Hospital Emergency Centre database between 1 January 2017 and 30 June 2018. This sample should be representative of most confounding variables e.g. seasonal variations. We expect a sample size of ± 150 patients.

Data collection and management

Diabetic emergencies will be defined using the definitions of the American Diabetic Association and will include the following groups:

- Diabetic ketoacidosis (DKA): Blood glucose > 13.9 mmol/L, presence of serum or urine ketones, anion gap > 10 , arterial pH < 7.3 , serum bicarbonate < 18 mmol/l.(20)
- Hyperosmolar hyperglycaemic state (HHS): Absence of ketones, blood glucose > 33.3 mmol/l, pH > 7.3 , serum bicarbonate > 20 mmol/l and serum osmolarity of 320 mOsm/kg.(20)
- Hypoglycaemia: Blood glucose < 3.9 mmol/l.(21)

Data will be collected by the investigators on site at Khayelitsha Hospital after a decoded cleaned extract of the electronic database has been obtained (cleaned: copied into an Excel spreadsheet with all non-diabetic emergencies removed). The Excel spreadsheet will then be further populated through the hospital's electronic clinical record.

The following variables will be collected:

- Type of diabetic emergency
- Patient demographics (Age/ Gender)
- Patient acuity (according to the South African Triage Scale)
- Likely precipitant(s)
- Diagnostic tests performed and their results
- Interventions received while in the resuscitation area
- Time spent in the resuscitation area
- Disposition from the resuscitation area
- Re-presentation within 6 months after the study period
- In-hospital mortality

Incomplete data points will be excluded from analysis. A Western Cape Government computer within Khayelitsha Hospital Emergency Centre, with a password protected account, will be used for data capture and

storage. Patient folder numbers, the main identifier used in the database will be removed and the data incorporated with the original database once the entire data collection is complete. The database is stored in an internationally recognised, password protected database in the 'cloud'. The final dataset will not contain patients' names, addresses, folder numbers or other identifying information. A pilot study will be conducted using an Excel spreadsheet collecting the data specified above.

Statistical analysis

Summary statistics will be used to describe all variables. Categorical data will be summarised using frequency counts or percentages, and distributions of variables will be presented as two-way tables or bar charts. Medians or means will be used as the measures of central tendency for ordinal and continuous responses and standard deviations or quartiles as indicators of spread. Data will be analysed by the research team using Microsoft Excel and SPSS statistical software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). A STROBE checklist will be used to structure the final report.(22)

Time schedule

- December 2018: SU HREC approval
- February 2019: Western Cape Government approval
- March – May 2019: Data collection and management
- June – July 2019: Data analysis
- August to October 2019: Write up and submission

Ethical and legal considerations

Risks and benefits: As this study will not involve direct or indirect patient care, risk to patients is likely minimal. The electronic Khayelitsha Hospital Emergency Centre database has already passed through an ethics committee. Potential risk due to loss of patient data is however possible. For this reason identifiable data will be removed as soon as the data collection for that specific patient is completed. Having a better idea of the specific burden related to diabetic emergencies at a mid-level hospital may lead to improved public health practices, improved emergency practices and may improve morbidity and mortality.

Informed consent process: The database from which the initial data will be drawn is registered with the Stellenbosch University Health Research Ethics Committee (Ref: N15/10/107) as well as on the National Health Research Database (Ref: WC_2014RP10_967). The information obtained from the database will be supplemented from the patient record. As this will be retrospective, taking individual consent will be near impossible and a disproportionate effort will be needed. We thus request a waiver of informed consent.

Privacy and confidentiality: As described earlier, the study will make use of a combination of safeguards to ensure anonymity of study subjects. This will include on-site data management using a Western Cape Government account and computers, a password protected Excel document containing the data sample, and coding data immediately after data collection is completed.

Limitations

This is a retrospective study using an existing database and therefore has inherent risks of error. Selection bias is primarily a result of either inappropriate inclusion or exclusion of subjects into the database or due to missing data. Inclusion criteria for the Khayelitsha Hospital Emergency Centre database is well defined and should not lead to any significant error.

Missing data allow for selection bias by allowing preference for study subjects with complete data. Patients with missing data will be reported and will not be excluded from analysis; only the incomplete data points will be excluded. Missing patients from the database is also limited since the database manager regularly does quality checks to ensure all patients are captured. The nursing register is used for this.

Data entered into the database may also be imprecise or invalid, resulting in information bias. This is again limited by the quality control performed by the database manager.

Reporting and implementation of results

Publication as an original article or short report in a peer reviewed journal is anticipated. The study results will also be distributed to the management team of Khayelitsha Hospital Emergency Centre.

Resources

Resources used will be mainly non-clinical. This will include use of an existing Western Cape Government account and computers. As most patient information will be electronically available, Khayelitsha Hospital clerks will not be utilised to access hard copy folders. The investigators will not conduct the study when on-duty. The study will be self-funded.

Budget

Personnel Compensation		R 0
Principal Investigator	R 0	
Co-Investigators	R 0	
Consulting services		R 0
Statistical services	R 0	
Travel		R 3620
Transport Twenty visits @ R 181 per day (50km/return visit @ R3.61/km)	R 3620	
Equipment & Furniture		R 0
Other		R 0
Telephone, cell phone, fax	R 0	
Internet & e-mail	R 0	
Printing & copying	R 0	
Total costs		R 3620

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B] Health Ethics Review Committee approval

Approved with Stipulations
New Application

19/11/2018

Project ID: 8414

HREC Reference #: S18/10/215

Title: Diabetic emergencies in the emergency centre

Dear Dr Nuraan Lotter

The **New Application** received on 16/10/2018 12:24 was reviewed by members of the Health Research Ethics Committee via Minimal Risk Review procedures on 19/11/2018 and was approved with stipulations.

Please note the following information about your approved research protocol:

Protocol Approval Period: 19-Nov-2017 – 18-Nov-2019.

The stipulations of your ethics approval are as follows:

1. Attention to spelling and grammar is still required on the study summary and protocol.
2. In the protocol, with regards to References: a single reference style should be chosen and applied consistently throughout (compare references 1, 12 and 17).
3. On the HREC New Application Form: -
 - ◊ The Faculty has been incorrectly indicated, it should be Medicine and Health Sciences.
 - ◊ There are two other Investigator's Declaration forms both with Dr Lotter's name in section 1 and both marked as Principal Investigator but one is unsigned while the signature of the other is not Dr Lotter's signature. Personally signed Investigator's Declaration forms the supervisor as well as the co-investigator must be provided.

Please remember to use your project ID 8414 and ethics reference number S18/10/215 on any documents or correspondence with the HREC/UREC concerning your research protocol.

Translation of the consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note that this decision will be ratified at the next HREC full committee meeting. HREC reserves the right to suspend approval and to request changes or clarifications from applicants. The coordinator will notify the applicant (and if applicable, the supervisor) of the changes or suspension within 1 day of receiving the notice of suspension from HREC. HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note you can submit your progress report through the online ethics application process, available at: <https://apply.ethics.sun.ac.za> and the application should be submitted to the Committee before the year has expired. Please see [Forms and Instructions](#) on our HREC website for guidance on how to submit a progress report.

The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: <https://www.westerncape.gov.za/general-publication/health-research-approval-process>. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: [Forms and Instructions](#) on our HREC website (www.sun.ac.za/healthresearchethics)

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mrs. Melody Shana

Coordinator,

HREC1

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)*REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372

Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)*IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013), Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; the South African Department of Health (2006), Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015), Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

C] Author guidelines: African Journal of Emergency Medicine

The author guidelines are available at:

https://www.elsevier.com/wps/find/journaldescription.cws_home/725742?generatepdf=true