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Review Article

Diabetes Emergencies For the Acute Physician

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Abstract

Extreme levels of glucose in patients with diabetes is common, lack of education, noncompliance and poor monitoring can all lead to serious diabetes emergencies which can unfortunately cause significant morbidity and mortality. Many of these complications can occur while the patient is in hospital, partly because of loss of appetite during illness while on insulin or insulin secreting medications, food served at different times, stress hyperglycemia in patients admitted with acute illness, and poor knowledge of some junior doctors with the basics of in-patient diabetes management. It is briefly explained here the basics of managing diabetes emergencies including new presentation with hyperglycemia.

Keywords: DKA; HHS; Stress hyperglycemia; Hypoglycemia; Insulin sliding scale.

Abbreviations: DKA: Diabetic Ketoacidosis; AMU: Acute Medicine Unit; HHS: Hyperosmolar Hyperglycemic State; VBG: Venous Blood Gas; VTE: Venous Thromboembolism.

Introduction

Diabetic ketoacidosis (DKA) is common in patients under the age of 65, while hyperosmolar hyperglycemic state (HHS) occurs mainly in elderly. DKA hospitalization rate is increasing since 2009 with average annual rate of 6.3% but fortunately the mortality rate has declined In-hospital case-fatality rates declined to 0.4%.

The rate of hospital admissions for HHS is lower than the rate for DKA but mortality rate for HHS is much higher and accounts for up to 20% [1].

This review is for the basic management of DKA, HHS and optimum management of new onset diabetes or hyperglycemia in hospitalized patients. Hypoglycemia treatment will be discussed and some basics on initiating antidiabetic drugs according to indication and specially insulin to prevent over or under prescribing. Aiming by the end of this review to not only increase the awareness of possible morbidity and mortality associated with these conditions but also to provide guidance on pitfalls and

things to avoid as over correction can significantly worsen outcomes.

Discussion

Diabetic ketoacidosis (DKA) is a metabolic emergency which occur due to insulin deficiency leading to hyperglycemia, ketosis, and acidosis, glucose levels in DKA is usually over 11 mmol/L, however, euglycemic DKA can occur in pregnancy or in acutely ill patients on SGLT-2 inhibitors, the presence of ketosis is essential in making the diagnosis of DKA and levels over 3 mmol/L in serum or urinary ketones of 2+ or more in urine is required for diagnostic purposes, and finally acidosis with PH below 7.3 or venous bicarbonate level below 18 is part of the definition, however, early DKA can occur with PH over 7.3 as bicarbonate buffers ketoacids (early compensated DKA) and therefore frequent monitoring of PH is required in cases where ketosis is raised without acidosis [2,3].

It is important to be aware of the differential diagnosis of DKA to avoid unnecessary over investigation and treatment, for example hyperglycemia can occur without significant ketosis as in hyperosmolar hyperglycemic state or stress hyperglycemia and in these cases, acidosis is minimal or not present [3].

High anion gap metabolic acidosis can occur in other conditions than DKA and is commonly related to ingested toxins, renal failure, and hyperlactatemia. While ketosis on the other hand can occur in cases of alcoholic ketosis, starvation or hyperemesis without significant hyperglycemia or acidosis [4].

Clinically patients with DKA are present with vomiting and abdominal pain, dehydration, Kussmaul respiration due to acidosis, leukocytosis and raised amylase. How severe is DKA depends on several factors, like the presence of shock, impairment of consciousness, severe acidosis with PH below 7.0, and the presence of acute renal failure.

DKA is more common in patients with type 1 diabetes (T1DM) due to insulin deficiency but can occur in patients with type 2 diabetes (T2DM) who have insulin deficiency or on SGLT-2 inhibitors, common causes of DKA are insulin omission with gastroenteritis, alcohol excess, or simple infection [5].

Patients presenting with signs of severe DKA as mentioned above should be looked after in intensive care unit, while mild cases of DKA can be looked after in acute medical units (AMU) with frequent monitoring of vital signs as well as PH, ketosis, glucose, potassium, and urine output [6].

Targets for management are to correct the metabolic acidosis within four hours with hourly monitoring of the venous blood gas until PH is 7.3 or more, correction of ketosis within 12 hours with monitoring 4 hourly of ketone levels and aim for ketone levels below 0.6 mmol/L, hourly monitoring of glucose levels until acidosis and ketosis are corrected and patient can eat and drink, and treatment of the precipitating cause is also essential for optimum management of DKA.

Management of DKA

Immediately check glucose and ketones capillary levels with venous blood gas (VBG), insert a cannula and check routine bloods including (renal profile, complete blood count, CRP, electrolytes, CK, amylase, HCG, or troponin if appropriate) urine for ketones and infection. Start 500 mls crystalloid (normal saline 0.9%) as stat if signs of hypotension, otherwise one litre over an hour

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without potassium unless potassium (K) level is very low and below 3.5 mmol/L.

Start intravenous insulin infusion (rapid acting analogue) 50 units in 50 ml syringe pump and running at 0.1 unit/Kg/hour, usually 6 units per hour is safe and good start if weight is unknown. Omitting insulin if K level is low pending correction is sometimes allowed [3].

Request chest x-ray, ECG and CT brain if low GCS and start looking for causes of DKA in your patient, like evidence of infection, acute coronary syndrome, pancreatitis, alcohol excess, pregnancy, or simple causes like noncompliance with insulin and mild gastroenteritis. Initiate monitoring for urine output hourly and consider ITU if low GCS, refractory hypotension, very high or low K, severe acidosis PH below 7.0, and organ failure.

Prescribe venous thromboprophylaxis and ensure the usual basal insulin dose is prescribed.

After the first hour, patient should have had at least one liter of crystalloid, caution with rapid fluid replacement as risk of fluid overload or cerebral oedema in elderly and young respectively, also potassium level will determine the rate of infusion as KCL is safely given at a rate of 10 mmol/L, we suggest 250 mls of normal saline plus 10 mmol/L KCL if blood pressure is adequate and K level is between 3.5-5.5 mmol/L [3].

Regular monitoring of glucose, ketones, K, urine output and PH levels, consider adding 10% glucose at 125 ml/hour when serum glucose levels are below 14 mmol/L, this will prevent hypoglycemia and give you time to burn more ketones without causing hypoglycemia [3].

Once patient can eat and drink and off DKA (Ketones<0.6 and PH 7.3 or more) we can switch intravenous insulin to subcutaneous insulin, giving the basal insulin earlier would help here with sliding scale withdrawal. If the patient is unable to eat or drink but off DKA then a variable rate insulin infusion can be initiated. Please ensure adequate insulin supply given to patient and review by specialist diabetes nurse prior to discharge [4,5].

2-Hyperosmolar hyperglycemic state (HHS) has a high morbidity and mortality rates and is more difficult to manage than DKA, HHS occurs more commonly in patients with T2DM and presents over days with non-specific symptoms like delirium, drowsiness, and reluctance to oral intake. Hyperosmolality is a key finding in HHS, serum osmolality is more than 320 mOsmol/Kg which is calculated by the following equation (2xNa+Urea+glucose), hyperglycemia compared to DKA is almost always over 30 mmol/L and contributes more to the hyper viscosity and increased risk of venous thromboembolism (VTE).

As patients with HHS are usually insulin resistant rather than deficient the amount of insulin in their body is usually enough to suppress ketosis but not enough to control hyperglycemia, hence there is lack of ketosis or acidosis in HHS unless a mixed picture of DKA/HHS or acute renal failure present, and PH is usually over 7.3, bicarbonate over 18, and ketones are usually below 1 mmol/L in serum and 1+ in urine [7,8].

Indicators of severity of HHS are shock, low GCS with renal failure, severe acidosis or hypernatremia, and osmolality of more than 340 mOsmol/Kg. Management of HHS

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should be gentle compared to DKA, as HHS occurs over days and usually in elderly and frail patients, recommendations are to use lower amount of insulin and slower rate of fluid plus treating the acute illness if present while monitoring urine output, acidosis and electrolytes and avoid sudden significant drop in glucose or sodium levels. We suggest correcting osmolality over 1-2 days and target levels below 300, hypernatremia should never be treated aggressively, and we target Na level below 140 mmol/L with no faster than 8-12 mmol/24 hours. Glucose as mentioned above should be lowered slowly over 24 hours with a rate of 2-3 mmol/hour and target levels between 10-15 mmol/L per 24 hours and renal function target is back to baseline over 24 hours. Monitoring osmolality, renal function, and sodium 8 hourly so an adjustment in intravenous fluid can be made and difference checked while glucose and potassium can be checked hourly by venous blood gas until levels are stable.

Management of HHS

Immediate capillary glucose and ketones levels with venous blood gas, cannula and send for routine bloods as DKA but have lower threshold in sending troponin, amylase, CK, and magnesium. Start crystalloid like normal saline 250 to 500 mls stat if hypotensive or in shock or 1000 mls over one hour, then 125 to 250 mls/hour with 10 mmol of KCL per hour if levels are 5.5 or below [7].

Seek ITU help if extreme potassium levels, low GCS, persistent shock, oliguric renal failure, or severe acidosis. Insulin in HHS is usually started late unlike in DKA, as HHS is a state of insulin resistance rather than deficiency, glucose level will usually reduce with rehydration and insulin is started a bit later if ketones are over 1 mmol/L or glucose levels are not falling enough with rehydration [7].

While treatment is initiated do the monitoring as mentioned above and request chest X-ray, ECG as silent acute coronary syndrome is common in HHS, look for signs of venous thromboembolism, source of infection if present and urinary catheter to monitor for urine output if hypotension, acute renal failure, or urinary retention. Worth mentioning that true Na level is different than the laboratory level due to severe hyperglycemia, true Na is calculated by adding the laboratory Na to glucose in mmol/L divided by 4. If corrected Na is rising towards 150 or more or serum osmolality is rising or at least nor falling, then we recommend half normal saline 0.45% with close monitoring to avoid large deviation of Na of more than 8-12 mmol/24 hours.

HHS particularly severe one with osmolality >340 require full anticoagulation as it carries very high risk for venous and arterial thrombosis, obviously if no contraindication and after CT brain for patients who present with low GCS. Suggested insulin rate if glucose level is not falling or ketones are more than 1 mmol/L is 1-2 units/hour or 0.05 units/Kg/hour, there is no need to give higher doses of insulin as we do in DKA as there are no ketones to suppress and rapid drop in glucose levels can cause a large deviation in Na levels [9].

When HHS resolves and biochemistry stabilise options are to start variable rate insulin infusion if unwell or not eating and drinking, otherwise in previous insulin treated patients the regimen may require intensifying like biphasic BD dose instead of

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basal single dose or basal bolus regimen instead of BD biphasic dose if HbA1C has shown poor control on the initial regimen.

Patients previously treated on non-insulin drugs likely will require insulin upon discharge, at least basal insulin and this is based on HbA1C. Diabetes specialist nurse should review any patient who presented with HHS, insulin is required upon discharge if there was ketosis suggesting insulin deficiency, poor HbA1C of 8.5 or more on three antidiabetic medications or more than 9%, steroids is another common reason to start insulin, and commonly a basal insulin OD can be convenient for carers in patients who are not compliant with medications [10].

If HHS presents in a newly diagnosed T2DM with minimal ketosis, HbA1C below 9%, and or unwilling to start on insulin, then patient may be prescribed metformin and gliclazide and followed up in the diabetes clinic.

Hypoglycemia is defined as glucose level below 4 mmol/L and is common in patients with T1DM and T2DM who are treated with insulin or insulin secreting medications like sulfonylureas. Mild hypoglycemia is defined as an attack of hypoglycemia with preserved consciousness and usually presents with sympathetic signs and symptoms like tachycardia, tremors, and sweating, while severe hypoglycemia can present with hemiparesis, seizure, and loss of consciousness and usually occur at levels below 2.5 mmol/L [11].

Sulfonylurea induced hypoglycaemia can peak after 4-8 hours from the dose and can last for longer than 24 hours if long-acting one used or short acting in the presence of renal failure, avoid glucagon in treating patients with sulfonylurea induced hypoglycemia as it may make the hypoglycemia worse by inducing insulin release [12]. If the patient has mild hypoglycemia and can eat and drink, then 20-25 g of glucose can be given orally and repeat in 15 minutes if hypoglycemia persists, then after the loading dose a maintenance dose of carbohydrate rich snack should follow (sandwiches, bread, or 3-6 biscuits).

While if the patient suffered from a severe attack of hypoglycemia and unable to eat then a loading dose of 200 mls of 10% stat and repeat glucose level after 5 minutes aim to repeat the loading dose if still hypoglycemic and this regimen is followed by 100 mls/hour of 10% dextrose for 12-24 hours at least [10]. Adjusting the medication dose prior to discharge is essential and avoids treating post hypoglycemia hyperglycemia which commonly occurs.

Insulin treated patients who develop hypoglycemia will require a reduction of the culprit (prior insulin dose) by 20 % and if it is not clear if the basal (unlikely) or the rapid acting analogue is the culprit then reduction of all insulin by at least 10% is advisable, never stop basal insulin in someone who is insulin dependent [12].

Management of patients presenting to hospital with new hyperglycemia requires a formal and global assessment of the presenting complaint, presence of catabolic symptoms, HbA1C if available and if patient is known diabetic or not. Sliding scale is overused with multiple reports of complications and unnecessary extra staff workload, we recommend sliding scale if patient is presenting with acute illness like acute coronary syndrome, stroke, and sepsis for example where glucose level should be

kept between 6 and 10 mmol/L, hyperglycemia with raised osmolality over 300 mOsmol/Kg or ketones more than 0.6 which is suggestive of early HHS/DKA respectively. Other two common scenarios were insulin sliding scale is required are insulin dependent diabetic patients who are nil by mouth for medical reasons and persistent hyperglycemia which is not improving with Intravenous fluid or if fluids are contraindicated [13].

When none of the above clinical scenarios we recommend monitoring fasting and postprandial glucose levels pending HbA1C and if diabetes mellitus is confirmed then the treating doctor is advised to ask for symptoms and signs of catabolic state of hyperglycemia like dry mouth, polydipsia, polyuria, weight loss, dizziness, headache, and blurred vision. Based on HbA1C level and presence or absence of catabolic state the management of T2DM can be planned. If HbA1C is less than 9 in presence of catabolic state then oral metformin and sulfonylurea are recommended, but if HbA1C is 9 or more or fasting plasma glucose (FPG) is 10 mmol/L or more then basal insulin 0.2-0.3 units/Kg (0.1 units/Kg if glomerular filtration rate (GFR) <60). Biphasic insulin which is a mixture of basal insulin and rapid acting analogue in different concentrations has better control of post prandial glucose (PPG) while basal insulin has an effect on fasting glucose level (sleeping and between meals), recommended initial dose of biphasic insulin is 0.2 units/Kg if age over 60 or GFR below 60, 0.5 units/ Kg if obese (BMI 30 or more), and 0.4 units/Kg otherwise, adding Metformin and referral to dietician with healthy lifestyle advice is recommended prior to discharge with education by the diabetes specialist nurse and follow up plan [13].

For patients with new diagnosis of T2DM and without catabolic state recommendations are to treat according to risk factors for cardiovascular disease (CVD), if HbA1C is below 9 recommendations are Metformin plus SGLT2 inhibitor in presence of chronic kidney disease (CKD), proteinuria or Heart failure, GLP-1 RA in overweight, patients with established or high risk of CVD, and DPP4 inhibitor if none of the above. While if HbA1C is 9 or more or FPG 10 mmol/L or more than biphasic insulin or Basal insulin as mentioned above.

Target HbA1C is 7.5 if patient is on insulin or sulfonylureas and lower otherwise, in patients with short life expectancy or elderly with multiple comorbidities a higher HbA1C is advisable to prevent hypoglycemia [12]. New diagnosis T1DM: Initial insulin dosing for T1DM is usually between 0.3-0.5 units/Kg, Basal-Bolus regime (50% of the Total daily dose (TDD) in the form of basal and 50 % in the form of bolus divided with meals, for example a 72 Kg patient will have initially, 50% basal at night of the 0.5 units/Kg (18 units) and 50% bolus of rapid acting analogue with meals of the 0.5 units/Kg (aspart/Lispro/Glulisine) divided according to calories intake for each meal, for example 4 units breakfast, 6 units lunch, 8 units dinner (18 units). Specialist diabetes nurses and education programs are essential for patients with T1DM, patients learn, acquire confidence in dealing with diabetes and insulin injections and gain knowledge on how to monitor their diabetes and when to seek medical attention including sick days rule, Insulin carb ratio (how many units of rapid acting insulin required to cover the amount of

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carb in a meal) is decided after optimizing total daily insulin (TDD), 500/TDD=amount of carb in grams which is covered by 1 unit of insulin and correction factor (how much a unit of rapid acting insulin can burn extra glucose in blood) is 100/TDD (when using mmol/L) and the outcome is the amount of glucose which is burnt by 1 unit of insulin are among essential facts taught by specialist diabetes nurses and diabetes educational programs. Below is an example of how to calculate correction doses and carbs ratio [14]. Example: Pre-lunch CBG is 10, The advice is 4-7 mmol/L premeal, patient correction factor is 3 (1 unit of insulin for 3 units of glucose/mmol/L) =1 The amount of carb in the lunch is 100 g, insulin carb ratio for this patient is 1:10=10 units, therefore 11 units of insulin are required for lunch.

Conclusion

Diabetes emergencies are common and carry a significant risk of morbidity and mortality if delay in treatment and poor management occur, over or undertreatment may cause harm, prolong recovery, and put patient under risk of acquiring hospital acquired infection. Acute physicians should be aware of the optimum management and monitoring for these emergencies and when to refer for Level 2 or 3 when indicated.

Junior doctors in hospitals require more training and confidence when dealing with insulin and understand the basics of insulin treatment and when to start a sliding scale if indicated as overprescription of sliding scales is a rising issue which increases the burden on staff as well as risk of complications to patients. Involving the diabetes specialist nurses and dietician team early is essential, as this review is a basic educational review and can be used in emergencies, but optimum management should require a full multidisciplinary approach.

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