Severe hyperglycaemic complications of diabetes

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Introduction

Hyperglycaemia is a primary feature of diabetes mellitus. Sustained elevation of blood glucose (hyperglycaemia) is associated with significant long-term complications.

The presence of undiagnosed diabetes is common in Africa, e.g. about 85% of all diabetes in South Africa,[1] 80% in Cameroon,[2] 70% in Ghana,[3] and 80% in Tanzania.[4] Impaired glucose tolerance (IGT) and diabetes may thus be asymptomatic for years.

In 2010, about 4 million deaths were due to diabetes in adults (20–79 years) globally. This constitutes about 7% of global all-cause mortality.[5] In Africa, one in over 20 deaths in adults is due to diabetes. About 330 000 deaths were attributed to diabetes in 2010 in Africa.[5]

This review article will examine the problem of acute severe hyperglycaemia in diabetes, and how it disturbs normal metabolism and physiology, potentially leading to the clinical problems of diabetic ketoacidosis (DKA), or hyperglycaemic hyperosmolar states (HHS) – previously known as hyperglycaemic non-ketotic hyperosmolar coma (HONK or HNK).

Background physiology and biochemistry

Water and plasma osmolality

A 70 kg person has total body water (TBW) of about 42 litres, which constitutes 60% of the total body weight. Intracellular fluid (ICF) volume is 24 litres (67% of the TBW), while extra cellular fluid (ECF) volume is 18 litres (33% of TBW). Five litres of the ECF is intravascular (blood volume), therefore the interstitial fluid is 13 litres.

Both the intake and loss of water are controlled by osmotic gradient across cell membranes in the hypothalamic osmoreceptor centres. These centres control both thirst and the release of antidiuretic hormone (ADH).

Sodium (Na^+)

Sodium is the most abundant cation in the body (3000 mmol) and with it associated anion accounts for 92% of the osmotic activity of the ECF.[6–8] This is shown in Table 1.

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Sodium balance is mostly related to renal blood flow and aldosterone activity. Aldosterone affects Na^+K^+ and Na^+H^+ ion exchange across all cell membranes.[9] Increased plasma osmolality is associated with movement of fluid from the intracellular to the extracellular compartment, and the effect of this on the brain is dehydration. Decreased plasma osmolality on the other hand can lead to cerebral oedema by the reverse process.

Plasma osmolality

As well as being measured in the laboratory (usually by the freezing point depression method), plasma osmolality can be measured by the formula {2(Na) + 2 (K) + urea + glucose}, where all the mesurements are in mmol/L. Hyponatraemia in DKA is due to osmotic diuresis, and the shift of water from the intracellular to the extra-cellular fluid. Every approximate 5.6 mmol/L rise in plasma glucose reduces plasma Na^+ by about 1.6 mmol/L.

Gross hyperproteinaemia, hyperlipidaemia, and presence of osmotically active solutes (e.g. mannitol, methanol, ethanol, or ethylene glycol) increases plasma osmolality. The difference between measured and calculated osmolality is called the osmolar gap (OG).

Glucose metabolism

The liver is the predominant organ for glucose metabolism. The conversion of glucose to glucose-6-phosphate by the enzyme glucose-6-phosphatase (found only in the liver) is insulin dependent. Glucose-6-phosphate can be stored as glycogen (glycogenesis) or converted to triglyceride. Triglyceride is incorporated into VLDL

Table 1 Contribution of plasma solutes to osmolality

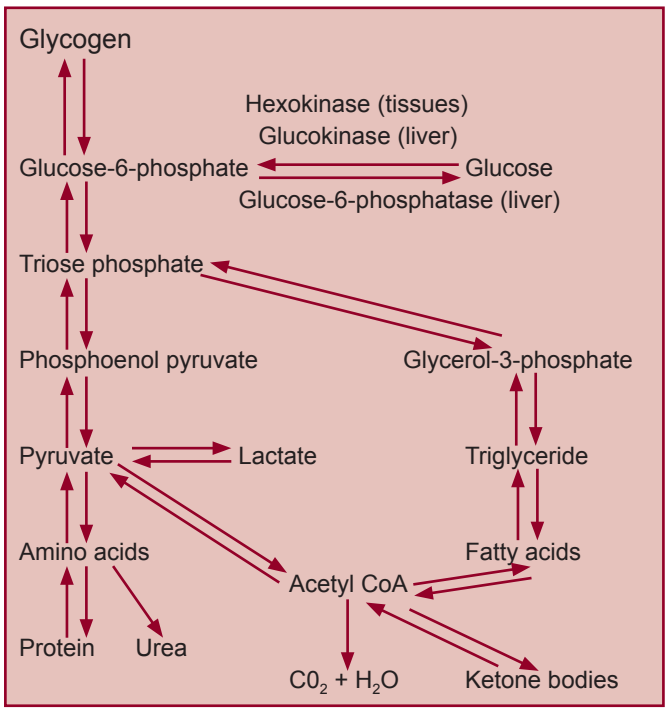
Solute	Osmolality (mOsmol/kg)	Total
Na^+ and anion	270	92%
K^+ and anion	7	
Ca^{2+} and anion	3	
Mg^{2+} and anion	1	8%
Urea	5	
Glucose	5	
Protein	1	
Total	292	100%

Note: Normal plasma osmolality = 285–295 mOsmol/kg.
In HHS plasma osmolality is >330 mOsmol/kg (>350 in severe cases).
In DKA plasma osmolality is usually <320 mOsmol/kg.

(very low-density lipoprotein) in the circulation and stored as fatty acids in the adipose tissue. Fatty acids can be converted to ketones which the brain can use as a source of energy in starvation. The liver can also synthesise glucose (gluconeogenesis) from glycerol, lactate, or carbon chains produced from the deamination of some amino acids, e.g. alanine, arginine, glycine, valine, histidine, methionine, and serine.

Although muscle and adipose tissue store glycogen, they do not have the glucose-6-phosphatase enzyme which converts glycogen to glucose, and therefore do not contribute to plasma glucose levels, but are metabolised for local use (see Figure 1). Excess glucose in other tissues, except the liver, is converted to glycogen by the enzyme hexokinase, which is the equivalent of hepatic glucokinase. The brain cells and erythrocytes do not need insulin for glucose diffusion and utilisation, unlike muscle and adipose tissue.

Figure 1 Interaction of carbohydrate, protein and lipid metabolism



Hyperglycaemic emergencies (DKA and HHS)

Insulin is important in glucose, lipid, and fat metabolism. In the absence of insulin, glucose utilisation by cells is impaired, the blood glucose rises, fat breakdown is increased, and ketoacids are formed. When the renal threshold for plasma glucose is exceeded, the excess is lost in urine , also with water and other mineral ions (e.g. sodium, potassium, magnesium, and calcium).[9-11] The ketones formed are beta-hydroxybutyrate, acetoacetate, and acetone. About 75% are beta-hydroxybutyrate. Alcohol use and lactic acidosis can increase the proportion to 90%. The sodium nitroprusside test ('Acetest') does not detect beta-hydroxybutyrate, measuring instead acetoacetate. Direct measurement of beta-hydroxybutyrate is now possible[10] (though measuring meters are expensive). Most patients with DKA have a high anion gap metabolic acidosis, while a few have combined high anion gap and hyperchloraemic metabolic acidosis. If alkalosis is present, it may be due to severe vomiting and/or diuretic therapy. Table 2 outlines the laboratory features and differences between ketoacidosis (DKA) and hyperglycaemic hyperosmolar states (HHS).

Table 2 Laboratory test findings in DKA and HHS

	DKA	HHS
Plasma glucose	>15.0 mmol/l	>30.0 mmol/l
Plasma osmolality	<330 mOsmol/kg	>330 mOsmol/kg
Ketones urine	3+	Nil or small amounts
Plasma bicarbonate	<15 mmol/l	>20 mmol/l
Blood pH	<7.30	>7.30
Plasma urea	<9.0 mmol/l	>12.0 mmol/l
Plasma sodium	<130 mmol/l	>145 mmol/l

Note: 1. The above figures are a guide, as there is often a lot of individual variation.
2. Though the blood or plasma glucose level is almost always >15.0 mmol/L,it can rarely be lower (usually 10.0–15.0 mmol/l). This is known as 'euglycaemic ketoacidosis'.
3. The plasma sodium in DKA is usually low (see text) and in HHS high (sometimes severely so, e.g. >155 mmol/l).

Patterns of hyperglycaemic emergencies

A plasma blood glucose of over 15.0mmol/l may be defined as severe hyperglycaemia, and this should prompt the consideration of DKA or HHS.[11,12] DKA is more common in poorly treated type 1 patients, while HHS is more common in poorly controlled type 2 diabetes. A mixed picture of DKA and HHS may also occur, which suggests that both are extremes of the same pathological process depending on the functional insulin available for metabolism.

DKA classically affects young type 1 patients, though it can occur at any age, and sometimes is seen in type 2 diabetes. It has an accute onset, and can be associated with abdominal pain, hyperventilation (Kussmaul's respiration), and sometimes the smell of ketones on the breath.[11] Dehydration is usually moderate. DKA is often precipitated by infection or insulin ommission.

HHS usually occurs in older type 2 patients and may be brought on by infection or diuretic drugs. Both DKA and HHS may be the initial presenting feature of diabetes. In HHS the onset may be more insidious than DKA, and ketotic features (e.g. hyperventilation, abdominal pain) foetor are not present. Dehydration is more severe, and the outcome poorer.

Management of DKA and HHS

All patients with severe DKA and HHS should be admitted to hospital for thorough evaluation and treatment. Treatment of precipitating factors, complications, and co-morbidities are mandatory.

Full protocols for the treatment of DKA (including in tropical settings) are available elsewhere.[12] Fluid replacement is of major importance – particularly for HHS where the fluid deficit is greater. 'Normal' (0.9%) saline is the main replacement fluid, though in signiicantly hypernatraemic HHS patients 'half-normal' (0.45%) saline may be indicated.

Low-dose soluble insulin is given, if possible by intravenous infusion. Rates of about 4–6 units/hour are usually appropriate in DKA, though the amount varies with the patient's needs. Patients with HHS are more insulin sensitive (because of the lack of ketosis), and lower infusion rates are used (e.g. 2–4 units initially). The aim should be a slow and steady reduction of blood glucose levels by about 2–3 mmol/hour. If insulin infusion cannot be used, the 'hourly intramuscular insulin' system can be used, i.e. 20 units of soluble insulin i.m. stat immediately, followed by 10 units i.m. hourly.

Potassium replacement is important, especially in DKA, and potassium chloride (KCl) should be added in appropriate amounts to the rehydration fluid. This ideally requires regular monitoring of plasma K levels, as well as renal function.

Antibiotics, anti-malarials, etc. should be used if appropriate for underlying infection. Prophylactic low-dose heparin should be used to prevent thrombotic complications, especially in HHS.

There is debate over the use of bicarbonate therapy. There are potential dangers of rapid osmotic shifts between ICF and ECF, and rebound alkalosis. Most authorities suggest using it only if the arterial pH is <7.0, and the patient very sick. A slow, single infusion of 50 mmol of sodium bicarbonate should be given in this case.

Conclusions

DKA and HHS are the major metabolic consequences of uncontrolled hyperglycaemia in diabetes. These are serious medical emergencies, with significant morbidity and mortality. Adequate and early treatment can greatly improve outcome, and is based on a physiological and metabolic understanding of the processes leading to these complications.

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