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Discuss the Pathogenesis, Presentation and Management of HHS

By Ismat Abdelrhman Alborhan
Cardiff University

Introduction- Hyperosmolar hyperglycaemic state (HHS) classically happens in type 2 diabetes formerly recognised as hyperosmolar non-ketotic (HONK) state. The level of blood glucose can be greater than that is DKA (>50 mmol/litre) however there is no ketone in urine. It is accompanying with severe dehydration and patients necessitate importunate, directed fluid resuscitation, correction of electrolyte disturbances and insulin. The characteristic features of HHS a syndrome are severe hyperglycaemia, hyper osmolality and excessive water loss in the non-appearance of ketoacidosis. Occurrence of HHS among diabetic patients is approximately less than 1%. Higher percentage of cases occur in elder type 2 diabetic patients still, young adult and children are also prone to develop HHS. The mortality rate approximately 20% which is around 10 times DKA mortality rate. The dehydration severity, existence of comorbidities and old age determined the prognosis of HHS. The management of HHS is focussed on correction of volume deficit, hyper osmolality, hyperglycaemia, and electrolyte abnormalities in addition to treating the underlying causes which trigger the metabolic decompensation. Although regime of intravenous low dose insulin meant for mange DKA seem to be effectual, the better therapy approaches for the treatment of HHS have not established by any prospective randomized studies.

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Discuss the Pathogenesis, Presentation and Management of HHS

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I. Introduction

Hyperosmolar hyperglycaemic state (HHS) classically happens in type 2 diabetes formerly recognised as hyperosmolar non-ketotic (HONK) state. The level of blood glucose can be greater than that is DKA (>50 mmol/litre) however there is no ketone in urine. It is accompanying with severe dehydration and patients necessitate importunate, directed fluid resuscitation, correction of electrolyte disturbances and insulin.1 The characteristic features of HHS a syndrome are severe hyperglycaemia, hyper osmolality and excessive water loss in the non-appearance of ketoacidosis. Occurrence of HHS among diabetic patients is approximately less than 1%.2 Higher percentage of cases occur in elder type 2 diabetic patients still, young adult and children are also prone to develop HHS.3 The mortality rate approximately 20% which is around 10 times DKA mortality rate.45 The dehydration severity, existence of comorbidities and old age determined the prognosis of HHS.67 The management of HHS is focussed on correction of volume deficit, hyper osmolality, hyperglycaemia, and electrolyte abnormalities in addition to treating the underlying causes which trigger the metabolic decompensation. Although regime of intravenous low dose insulin meant for mange DKA seem to be effectual, the better therapy approaches for the treatment of HHS have not established by any prospective randomized studies. 8

II. Pathophysiology

The pathophysiological abnormality of HHS is determined by life-threatening raises in glucose serum levels besides hyper osmolality without noteworthy ketosis. These metabolic imbalances outcome from synergistic factors including deficient insulin and augmented levels of counter regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone.910 In patient with HHS shows higher hepatic and circulating insulin and lower glucagon in comparison with DKA patients.6 11 Hyperglycaemia results in a rise in oxidative stress markers such as membrane lipid peroxidation.12 The Pathophysiology of HHS can be summarized in the following diagram 8

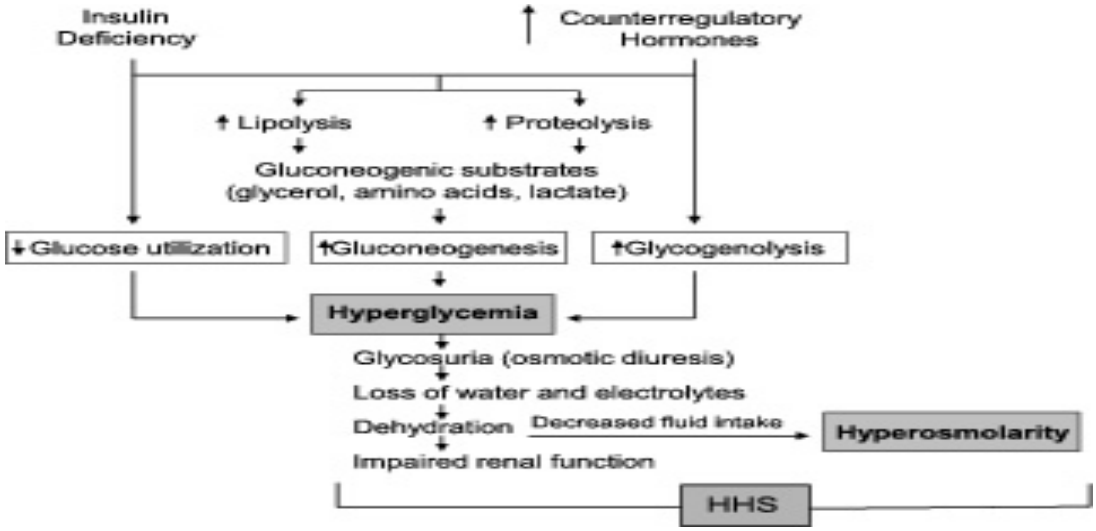

Figure 1

III. Presentation

HHS occurred typically in non-discovered diabetes between 55 – 70 years old. HHS in many patients develops over several days and weeks through patients develops over several days and weeks through which they develop polyuria, polydipsia and deterioration conscious level. HHS patients commonly presented clinically with altered sensorium.13 On physical examination of HHS there are:14

- Sign of Dehydration.
- Fever is common for underlying infection.

Author: Fujairah Hospital, Emergency Department, United Arab Emirates. e-mail: asmat5me@gmail.com

- Usually absent signs of acidosis (Kussmaul respiration, acetone breath).
- Abdominal pain and vomiting is not typical feature of HHS although common in DKA.
- Focal neurological signs (hemiparesis, hemianopsia) and seizures occurred in some patients.

The standards for hyperglycaemic hyperosmolar state (HHS) consist of1516:

1.	Plasma glucose level >33.3 mmol/L.
2.	Arterial pH > 7.30; venous pH > 7.25.
3.	Serum bicarbonate >15 mmol/L.
4.	Small ketonuria, absent to small ketonemia.
5.	Effective serum osmolality >320 mOsm/kg.
6.	Altered consciousness e.g. Obtundation, combativeness, or seizures.

Classically patients with HHS may not look dehydrated due to the fact that hypertonicity leads to safeguarding of intravascular volume (producing intracellular water shifted to the extracellular compartments) and it is well demonstrated in below diagram 1718

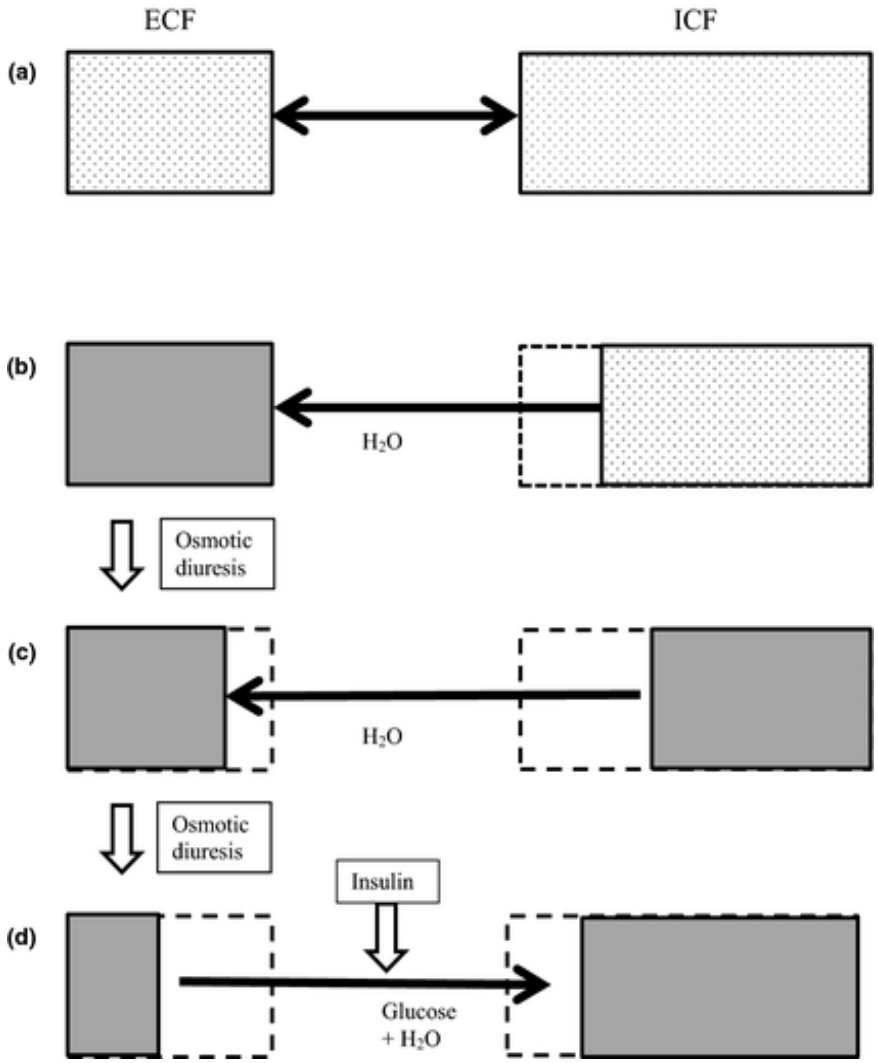

Figure 2

IV. Management

Treatment of HHS necessitates regular patient's monitoring, adjustment of hypervolemia and hyperglycaemia, electrolyte disturbances correction, and wise investigate for the triggering reason(s). The suggested algorithm recommended by the recent American Diabetes Association position statement on treatment of HHS:19

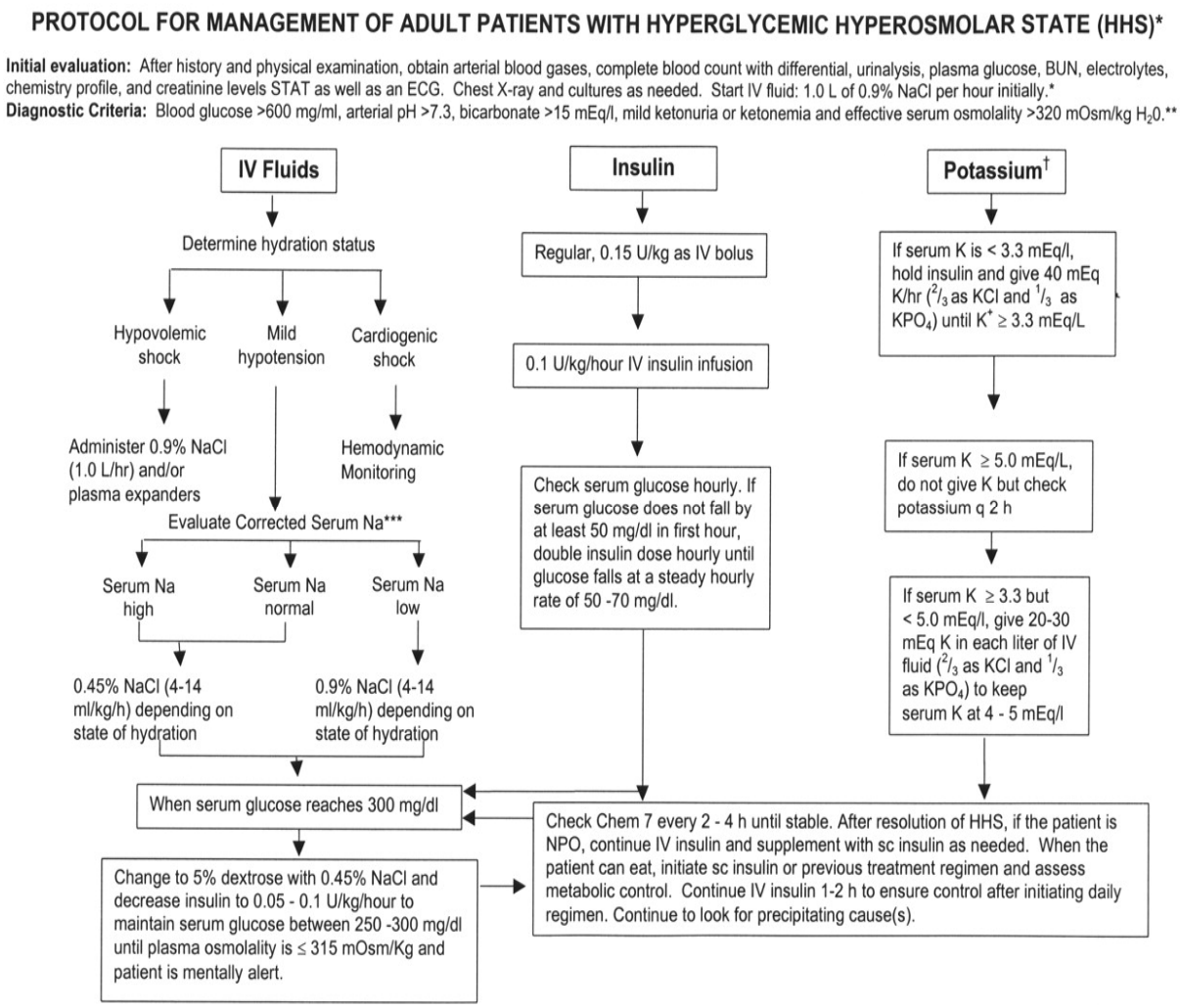

Figure 3:

a) Fluid Therapy

The water deficit in HHS patients is approximately 100 ml/kg.20 In HHS sick patients' crystalloid fluids is recommended instead than colloid fluids.21 Ringer's Lactate is not indicated in in management of HHS while 0.9% normal saline solution with potassium added as necessitated is highly recommended.2223 The aim of first fluid infusion is to increase intravascular volume and restore kidney perfusion. During the first 2-hour infusion of 500–1,000 mL/h 0.9% normal saline is generally acceptable, nevertheless in patients with hypovolemic shock, 3 to 4 liter of normal saline may be required to maintain normal blood pressure and restore tissue perfusion. According to serum sodium level and state of hydration, reduction of the rate of 0.9% sodium chloride infusion to 250 mL/h or altered to 0.45% saline (250–500 mL/h) is required. The target is to restore half of the assessed water deficit over a period of 12–24 h.16 When the plasma glucose attains 250 mg/dl in 300 mg/dl, additional infusion should include 5–10% glucose while averting hypoglycaemia. Replacement the volume of urinary losses is key part of fluid management in hyperglycaemic states. Inability to correct fluid replacement for urinary losses may defer adjustment of water and electrolytes deficit.24 Extracellular volume depletion necessitates correction, reliant upon the degree of free sodium and water deficit in any specific case as shown in below table:25

Table 1: Typical Fluid and Electrolyte Losses in HHS 12

	Typical Rates of Loss	For a 60 kg Patient	For a 100 kg Patient
Water	100-220 mL/kg	6-13 L	10-22 L
Na^+	5-13 mmol/kg	300-780 mmol	500-1300 mmol
Cl^-	5-15 mmol/kg	300-900 mmol	500-1500 mmol
K^+	4-6 mmol/kg	240-360 mmol	400-600 mmol

Treatment of hyperglycaemic hyperosmolar state (HHS) sown in below diagram: 26

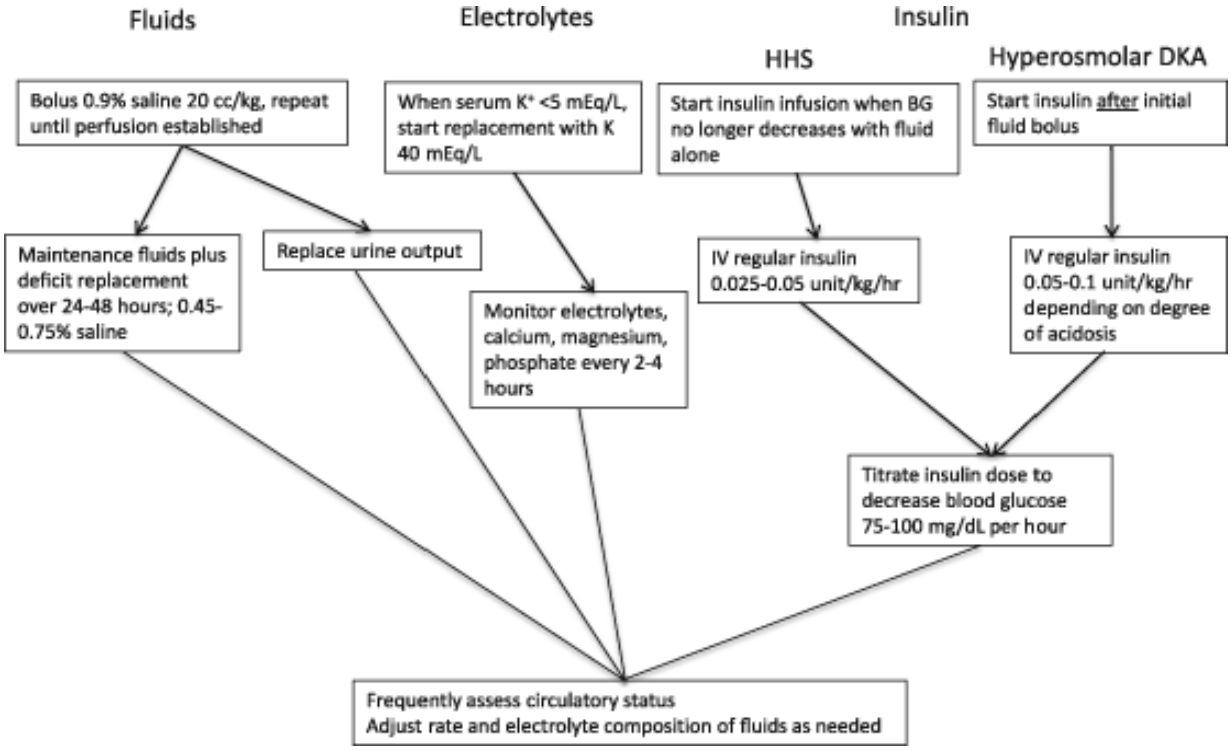

Figure 4

b) Insulin Therapy

Insulin enhances peripheral glycolysis and reduces liver gluconeogenesis, thus decreasing blood glucose levels. Moreover, insulin treatment prevents the release of FFAs from adipose tissue and reduces ketone bodies production, both of which direct to the reverse of ketogenesis. Regular continuous insulin infusion is the optimal treatment for critically sick patients. Regular insulin intravenous of 0.15 unit/kg as bolus dose should be given initially, followed by administration a continuous infusion of regular insulin at a dose of 0.1 unit/kg/h (5–10 unit/h). This regime will help reducing plasma glucose concentration at a rate of 65–125 mg/h.27

Reduction of insulin infusion rate to 0.05 unit/kg/h (3–5 units/h) is required when plasma glucose reached 300 mg/dl in HHS pulse addition of dextrose (5–10%) to the intravenous fluids. Afterwards, adjustment of insulin rate is required to sustain the above glucose values until mental obtundation and hyper osmolality are fixed. Throughout therapy, close monitoring of blood glucose, blood urea nitrogen, creatinine, magnesium, phosphorus, and venous pH are essential. The standards for resolve of HHS include progress of mental status, blood glucose <300 mg/dL, and a serum osmolality of <320 mOsm/kg. Subcutaneous insulin can be initiated whenever these standards are achieved. regular (short-acting) and intermediate-acting insulin in split dose can be started when patient tolerate oral intake.16 It is suggested that existence of more than one of the following may direct the necessity for admission to a high-dependency unit/ level 2 environment:28

➢ Osmolality >350 mOsm/kg
➢ Sodium >160 mmol/L
➢ Venous/arterial pH <7.1
➢ Low potassium (<3.5 mmol/L) or high potassium (>6 mmol/L) on admission
➢ GCS <12
➢ O2 saturation <92% on air
➢ SBP <90 mmHg
➢ Pulse >100 or <60 bpm
➢ Urine output <0.5 mL/kg/h
➢ Serum creatinine>200 μmol/L
➢ Body core temperature below 35.0 °C
➢ Macrovascular event (e.g. myocardial infarction or stroke)
➢ Other serious co-morbidity

Depletion of potassium is recognized in HHS, nevertheless less acidotic than DKA so potassium transfers are less noticeable, the insulin dose is lesser, and there is frequently co-existing kidney failure.28

Table 2: Potassium Replacement in HHS

Potassium Level in first 24h (mmol/L)	Potassium Replacement in Infusion Solution
> 5.5	Nil
3.5 – 5.5	40 mmol/L
< 3.5	Senior review as additional potassium required (via central line in High Dependency Unit)

V. Complications

- ✓ Insertion of central venous line in HHS can lead to venous thrombosis. 29
- ✓ Rhabdomyolysis can happen in children with HHS.30
- ✓ Unexplained malignant hyperthermia can occur in many children with HHS.313233
- ✓ Adults with serum osmolality more than 330 mOsm/kg commonly experience altered mental status; nevertheless, cerebral edema is rare.34

VI. Conclusion

It is highly recommended for prospective clinical trials to address many unanswered queries about the pathogenesis and management of HHS in adults and children. A chief enquiry is the reason of the absence of ketone bodies in HHS patients equated with DKA patients. Further researches are required to determine the function of oxidative and inflammatory stress markers and clinical results in patients with hyperglycaemic emergencies.35

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