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Hyperosmolar Hyperglycemic State: Background, Precipitating Factors, Pathophysiology and Management

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Abstract

The hyperosmolar hyperglycemic state is typically characterized by hyperglycemia and dehydration caused by osmotic diuresis, which leads to hyperviscosity and a hypercoagulable state. Hyperosmolar hyperglycemic state occurs most commonly in elderly patients with type 2 diabetes mellitus. Infection represents the commonest precipitating cause of hyperosmolar hyperglycemic state in essentially all series and occurs in 40–60% of patients. The hallmark of hyperosmolar hyperglycemic state pathogenesis is an extreme elevation in serum glucose level and hyperosmolality without significant ketosis. These metabolic disturbances result from synergistic factors, including lack of insulin and increased counterregulatory hormone levels (glucagon, catecholamines, cortisol, and growth hormone). The goals of hyperosmolar hyperglycemic state treatment include correction of volume deficits while reducing and normalizing plasma hyperosmolality, which will correct hyperglycemia, uncovering and managing the underlying cause, resolving ketonemia, correcting acidosis, re-establishing euglycemia, improving mental status, optimizing renal perfusion, replenishing electrolytes and minerals, and avoiding complications. The goal of initial fluid therapy is expansion of the intra- and extravascular volume and restoration of normal renal perfusion. Vigorous fluid replacement is recommended for adults with hyperosmolar hyperglycemic state and rates of fluid replacement for hyperosmolar hyperglycemic state in children similarly should be more rapid than those recommended for diabetic ketoacidosis. The American diabetes association guideline recommends starting intravenous regular insulin in the same way as during diabetic ketoacidosis management. That is, starting intravenous regular insulin at either a fixed weight-based dose of 0.14 units/ kg/h or at a fixed weight-based dose of 0.1units/kg/h followed by a 0.1 units/kg bolus of intravenous insulin after initiation of fluid resuscitation and correction of any hypokalemia.

Keywords: *Background; Hyperosmolar Hyperglycemic State; Management; Pathophysiology; Precipitating Factors.*

Introduction

Diabetes mellitus is a serious, chronic metabolic disorders that characterized by high sugar level either when the pancreas does not produce enough insulin, or when the body cannot effectively use insulin. Type 2 Diabetes Mellitus (T2DM) accounts about 90% of all diagnosed cases of diabetes among adults [1]. Type-2 Diabetes Mellitus (T2DM) is the most common form of diabetes sometimes called age-onset or adult-onset diabetes. It is a milder form of diabetes because of its slow onset (sometimes developing over the years) and because it usually can be controlled with diet and oral medications [2]. The hyperosmolar hyperglycemic state (HHS) is typically characterized by hyperglycemia and dehydration caused by osmotic diuresis, which leads to hyperviscosity and a hypercoagulable state [3]. Hyperosmolar hyperglycemic syndrome is much less common than DKA; its incidence is estimated to be less than 1 per 1000 person-years. Hyperglycemic crises are severe, acute, metabolic complications of diabetes that include the hyperosmolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA). The rate of hospital admissions for HHS is lower than for DKA, accounting for less than 1% of all diabetes-related admissions. The diagnostic criteria for HHS include a plasma glucose concentration >600 mg/dl, a serum osmolality >320 mOsm/kg of water, and the absence of significant ketoacidosis. Although by definition patients with HHS have a serum pH >7.3, a serum bicarbonate >18 mEq/l, and negative ketone bodies in urine and plasma, mild ketonemia may be present. Approximately 50% of patients with HHS have an increased anion gap metabolic acidosis as the result of concomitant ketoacidosis and/or an increase in serum lactate levels [4, 5].

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Table 1: Criteria for diagnosis of hyperosmolar hyperglycemic state

Criteria	ADA[1]	UK[4]
Year of publication	2009	2015
Plasma glucose concentration, mmol/L	>33.3	≥30
pH	>7.30	>7.30
Bicarbonate concentration, mmol/L	>18*	>15
Anion gap: $Na^+-(Cl^-+HCO_3^-)$	NA	NA
Urine acetoacetate (nitroprusside reaction)	Negative or low positive	NA
Blood β-hydroxybutyrate, mmol/L	NA	<3
Osmolality, mmol/kg	>320†	≥320‡
Presentation	Stupor or coma	Severe dehydration and feeling unwell

ADA=American Diabetes Association; NA=not included in guideline document.
*Updated to >15 mmol/L in 2016 updated review cited in 2019 ADA guideline.[6,7]
†ADA guideline calculates effective plasma osmolality using equation 2×Na+glucose (mmol/L) or 2×Na+glucose (mg/dL)/18.
‡UK guideline calculates osmolality using equation 2×Na+glucose (mmol/L)+(blood urea nitrogen (mmol/L) or 2×Na+glucose (mg/dL)/18+blood urea nitrogen (mg/dL))/2.8.

Precipitating Factors

HHS occurs most commonly in elderly patients with type 2 diabetes. Infection represents the commonest precipitating cause of HHS in essentially all series and occurs in 40–60% of patients, with the most common precipitating infections being pneumonia (40–60%) and urinary tract infection (5–16%). Up to 20% do not have a previous diagnosis of diabetes. Underlying medical illness, such as stroke, myocardial infarction, and trauma that provoke the release of counterregulatory hormones and/or compromise the access to water can result in severe dehydration and HHS. In most patients, restricted water intake is due to the patient being bedridden or restrained and is exacerbated by the altered thirst response of the elderly. Certain medications associated with metabolic decompensation and HHS include glucocorticoid, thiazide diuretics, phenytoin, b-blockers, and more recently atypical antipsychotics [6-9].

Pathophysiology

The hallmark of HHS pathogenesis is an extreme elevation in serum glucose level and hyperosmolality without significant ketosis. These metabolic disturbances result from synergistic factors, including lack of insulin and increased counterregulatory hormone levels (glucagon, catecholamines, cortisol, and growth hormone). Following an increase in serum glucose and extracellular osmolality level, an osmolar gradient is formed, which pulls water out of the cells. Initially, glomerular infiltration rate (GFR) increased, which leads to glucosuria and osmotic diuresis. Consequently, this glucosuria prevents the progression of severe hyperglycemia as long as the GFR is normal. Eventually, when osmotic diuresis continued, hypovolemia developed, which leads to a progressive decline in GFR and hyperglycemia worsening. In contrast to DKA, a higher hepatic and circulating insulin concentration with low glucagon are present in HHS. The higher circulating ratio of insulin/glucagon in HHS patients prevents ketogenesis and ketoacidosis developments, especially those HHS patients have some functioning pancreatic beta-cells. The fluid shift from intracellular to extracellular resulting from osmotic gradients can cause hyponatremia in the early stage of HHS. Nevertheless, the profound dehydration that developed later leads to normalization of serum sodium concentration or even hypernatremia. The osmotic diuresis may lead to loss of potassium, sodium, magnesium, and phosphate through the urine. As a consequence, to free water loss over electrolytes, hypovolemia, intracellular and extracellular dehydration, and hyperosmolality develop. Persistent hypovolemia leads to counter-regulatory hormone release, which exacerbates hyperglycemia and contributes to insulin resistance. The total body deficit of water is estimated to be 7 to 12L in HHS, representing a loss of 10% to 10% of total body weight. Although mild ketosis can be present in HHS, it is considered to be absent in this state. Elderly patients with HHS usually have enough insulin to protect them from lipolysis and the consequence abundance of ketoacidosis, but they do not have enough insulin to protect them from hyperglycemia [6, 10-14].

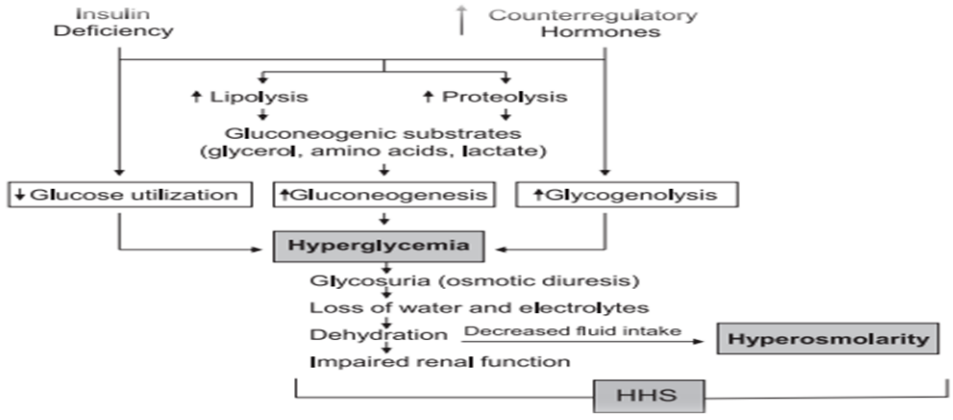

Figure 1: Pathophysiology of hyperosmolar hyperglycemic state

Treatment

The goals of HHS treatment include correction of volume deficits while reducing and normalizing plasma hyperosmolality, which will correct hyperglycemia, uncovering and managing the underlying cause, resolving ketonemia, correcting acidosis, re-establishing euglycemia, improving mental status, optimizing renal perfusion, replenishing electrolytes and minerals, and avoiding complications. The treatment of hyperosmolar hyperglycemic state involves a five-pronged approach: (1) vigorous intravenous rehydration, (2) electrolyte replacement, (3) administration of intravenous insulin, (4) diagnosis and management of precipitating and coexisting problems, and (5) prevention.

Fluid replacement: The goal of initial fluid therapy is expansion of the intra- and extravascular volume and restoration of normal renal perfusion. Vigorous fluid replacement is recommended for adults with HHS and rates of fluid replacement for HHS in children similarly should be more rapid than those recommended for DKA. The first and most important step in the treatment of hyperosmolar hyperglycemic state is aggressive fluid replacement, which should begin with an estimate of the fluid deficit (usually 100 to 200 mL per kg, or an average total of 9 L). The use of isotonic fluids may cause fluid overload and hypotonic fluids may correct deficits too rapidly with a potential for diffuse myelinolysis and death. Therefore, 1 L of normal saline should be given per hour to start. If the patient is in hypervolemic shock, plasma expanders also may be needed. If the patient is in cardiogenic shock, hemodynamic monitoring is required. Once there is only mild hypotension, the corrected serum sodium level should be calculated. If the corrected serum sodium level is high (greater than 145 mEq per L) or normal (135 mEq per L [135 mmol per L] to 145 mEq per L), then 0.45 percent sodium chloride may be administered at a rate of 4 to 14 mL per kg per hour depending on the state of dehydration. If the corrected serum sodium level is low (less than 135 mEq per L), 0.9 percent sodium chloride is infused at the same rate. When the serum glucose level is less than 300 mg per dL (16.7 mmol per L), the fluid may be changed to 5 percent dextrose solution with 0.45 percent sodium chloride. One half of the calculated deficit should be given in the first 18 to 24 hours and the remainder over the next 24 hours. In adults, the risk of cerebral edema is low and the consequences of undertreatment include vascular occlusion and increased rate of mortality. Good clinical judgment should be employed, especially when the patient has comorbid conditions such as acute myocardial infarction, a history of congestive heart failure, or renal failure. In such cases, close hemodynamic monitoring is indicated. Early in the course of treatment, the plasma glucose level will decrease, even before insulin is started, and this may serve as an index for the adequacy of fluid replacement. If the plasma glucose level fails to decline by 75 to 100 mg per dL (4.2 to 5.6 mmol per L) per hour, this usually implies inadequate fluid volume or renal impairment. Children are at greater risk of developing potentially fatal cerebral edema during treatment. For this reason, the rate at which serum tonicity is returned to normal should be somewhat slower than in adults [15-18].

Potassium and phosphate replacement: The rate of electrolyte administration required to maintain normal serum electrolyte concentrations is also likely to exceed that used for DKA. The typical potassium deficit ranges from 3 to 15mmol/kg (about the same as in DKA). The recommended replacement regimen also follows the DKA guidelines: for a potassium level greater than 3.3 mmol/L but less than 5.0 mmol/L, give 10 to 40 mmol of potassium chloride per liter of normal saline once diuresis has been established; for a potassium level of less than 3.3 mmol/L, give 40 mmol/L of potassium chloride until the potassium level reaches 3.3 mmol/L. Remember to omit insulin until the potassium level reaches 3.3 mmol/L [19-21]. Patients with HHS typically have more severe total body depletion than diabetic ketoacidosis patients, and close monitoring is advised. The American diabetes association (ADA) recommends adding 20-30 mmol (20-30 mEq) potassium in each liter of infusion fluid when serum potassium is below 5.2mmol/L (5.2mEq/L). By contrast, the UK guideline recommends 40 mmol/L (40 mEq/L) in each liter of normal saline when serum potassium is below 5.5 mmol/L (5.5 mEq/L) and the patient is passing urine. Because insulin therapy promotes an intracellular shift in potassium, it is recommended that insulin should not be started if the serum potassium is below 3mmol/L (3mEq/L) to avoid worsening of hypokalemia. The UK guideline recommends replacing phosphate if hypophosphatemia persists beyond the acute phase of treatment of HHS. Phosphate deficits are more severe in HHS than in DKA, increasing the risk for severe hypophosphatemia during treatment. Use of intravenous solutions containing a 50:50 mixture of potassium phosphate and potassium chloride generally permits adequate phosphate replacement and avoids deleterious hypocalcemia. Serum phosphate concentration should be monitored at least every 3-4 hr [22-24]. Bicarbonate therapy is absolutely contraindicated because of the increased risk of hypokalemia, the possible effect of decreased tissue oxygen uptake, and the absence of a therapeutic rationale for its use.

Insulin Therapy: The question of when to start insulin administration in the management of HHS has not been formally studied. The ADA guideline recommends starting intravenous regular insulin in the same way as during diabetic ketoacidosis management. That is, starting intravenous regular insulin at either a fixed weight-based dose of 0.14 units/ kg/h or at a fixed weight-based dose of 0.1units/kg/h followed by a 0.1 units/kg bolus of intravenous insulin after initiation of fluid resuscitation and correction of any hypokalemia. The ADA recommends reducing insulin infusion rates to 0.02-0.05 units/kg/h at the same time that dextrose 5% is added to the intravenous fluids when blood glucose declines to below 16.7mmol/L (300 mg/ dl) in patients with HHS. On the other hand, the UK guideline recommends delaying intravenous insulin therapy unless the patient has 3-β-hydroxybutyrate concentrations above 1.0 mmol/L (10.4 mg/dL) or above 1.5mmol/L (15.6 mg/ dL). HHS patients have extreme deficits of potassium and the rapid insulin-induced shift of potassium from the circulation to intracellular space can result in a fatal arrhythmia. The rationale for this recommendation is that early initiation of insulin in the setting of inadequate fluid replacement can aggravate hypoperfusion with an increase

in risk for circulatory compromise and thrombosis, and intravenous fluid alone will reduce hyperglycemia. The ideal decline in blood glucose is less than 5mmol/L/h [22-25]. Administration of insulin will help restore glucose homeostasis by entering high glucose in the blood into the cells and decreasing hepatic glucose production in case of concomitant mild ketoacidosis. Generally, low-dose insulin is recommended because most protocols advocate aggressive fluid resuscitation immediately before or during insulin commencing. Initially, during HHS management, blood glucose may not decline as renal impairment may coexist or inadequate fluid resuscitation rather than insulin resistance. Hence, adequate fluid replacement and monitoring of urea and creatinine levels are crucial when assessing insulin therapy's efficacy [10].

Correction of hyperglycemia: The role of insulin in HHS is to correct hyperglycemia and thus lower osmolality. Short-acting insulin (0.1unit/kg/h) is recommended; this is the same dose used to treat DKA. The decrease in plasma glucose concentration is predominantly due to the expansion of extracellular space and osmotic diuresis; insulin has been withheld successfully in HHS but generally its use is recommended.6 Insulin should be continued until the target glucose level is reached, hyperosmolality is corrected, and the patient's mental status improves. Because of the risk of cerebral edema with rapid reductions in osmolality, it is recommended that plasma osmolality be lowered no faster than 3mOsm/kg/h (ie, glucose reduction of 2 to 3mmol/L). If osmolality falls too rapidly, glucose can be added to the saline [19-21].

Complications of HHS Treatment

Complications from inadequate treatment include vascular occlusions (e.g., mesenteric artery occlusion, myocardial infarction, low flow syndrome, and disseminated intravascular coagulopathy) and rhabdomyolysis. Overhydration may lead to adult respiratory distress syndrome and induced cerebral edema, which is rare but often fatal in children and young adults. **Cerebral edema** should be treated with intravenous mannitol in a dose of 1 to 2 g per kg over 30 minutes and intravenous dexamethasone. Slowing the correction of hyperosmolarity in children may prevent cerebral edema [15].

Electrolyte abnormalities

More commonly observed complications in adults include hypokalemia and hyperkalemia, hypoglycemia, and non-anion gap hyperchloremic metabolic acidosis.

Hypokalemia is reported more frequently than hyperkalemia and usually results from delays in administration of or insufficient potassium containing supplementation. Hypokalemia is the second most common adverse outcome of HHS management [15]. Although the serum potassium is elevated upon admission, during insulin therapy, plasma potassium level sill invariably dropped secondary to increase cellular potassium uptake in peripheral tissues [15]. Therefore, IV potassium replacement is recommended when concentration falls below 5.2mEq/L [15]. In patients admitted with serum potassium below 3.3mEq/L, IV potassium replacement should be commenced immediately at a rate of 10-20 mmol/h and hold insulin therapy until potassium level is more than 3.3 mEq/L to avoid severe hypokalemia [10, 29, 30].

Hyperkalemia can result from overly aggressive potassium replacement, particularly in patients with underlying renal dysfunction [30].

Hypoglycemia can result from overly aggressive insulin infusions, insufficient frequency of blood glucose monitoring, or failure to add dextrose to intravenous fluids when blood glucose concentrations approach 13.9mmol/L (250 mg/dL). Hypoglycemia is the most expected adverse outcome during treatment, and it is associated with both immediate and late adverse clinical outcomes. Adverse outcomes include seizure, arrhythmias, altered sensorium, and cardiovascular events (myocardial infarction and stroke) [10, 22, 26-28].

Rhabdomyolysis: Rhabdomyolysis occurs more commonly in HHS than DKA resulting in an increased risk of acute kidney injury. The typical symptom triad includes myalgia, weakness, and dark urine. Rhabdomyolysis is potentially life-threatening; it may result in acute renal failure, severe hyperkalemia and hypocalcemia leading to cardiac arrest, and muscle swelling causing compartment syndrome. Monitoring creatinine kinase level every 2 to 3 hours is recommended for early detection [10, 29, 30].

Thromboembolic complications occur commonly in HHS and have been documented frequently in children with both HHS and DKA. Central venous catheters appear to be particularly prone to thrombosis. Prophylaxis with low-dose heparin has been suggested in adults. A disadvantage of low-dose heparin administration is the potential to cause gastrointestinal hemorrhage in the presence of hypertonicity-induced gastroparesis. Heparin treatment, therefore, should be considered only for children who are immobilized for prolonged periods due to CNS or other complications, or for those children in whom central venous catheterization is required for monitoring or venous access [31].

A malignant hyperthermia-like syndrome (MHLS) has been reported in several children with HHS. The etiology of MHLS is unknown. Dantrolene is thought to reduce the release of calcium from the sarcoplasmic reticulum and stabilize the calcium metabolism within muscle cells. Treatment with dantrolene should be initiated early for children who develop fever associated with a rise in creatine kinase concentration [32-34].

Prevention

Hyperglycemic emergencies are usually preventable. Infection and medical noncompliance are the two most common causes of DKA and HHS. The patient and another responsible party should be engaged in a significant educational effort that encourages adherence to blood glucose monitoring and compliance with prescribed medications. It is especially important that the patient have access to an adequate water supply. If the patient lives alone, a family member or friend should check in on the patient daily to watch for any changes in mental status and to notify the physician if this occurs. In the nursing home setting, the

above recommendations should be followed and the nursing home staff should be educated regarding the signs and symptoms of hyperosmolar hyperglycemic state and the importance of adequate fluid intake and monitoring. Established patients should be educated on how to manage their diabetes during stress or infection; this "sick-day management" includes never omitting insulin, preventing dehydration and hypoglycemia, monitoring blood glucose frequently, testing for ketosis, administering supplemental rapid-acting insulin doses according to prescribed guidelines, treating underlying triggers early and aggressively and having frequent contact with their diabetes health care team to evaluate their acute condition. Patient education and 24-hour access to care are cornerstones of preventive therapy [15, 36, 37].

Conclusion

Hyperglycemic crises are severe, acute, metabolic complications of diabetes that include the hyperosmolar hyperglycemic state (HHS) and diabetic ketoacidosis (DKA). The rate of hospital admissions for HHS is lower than for DKA, accounting for less than 1% of all diabetes-related admissions. Certain medications associated with metabolic decompensation and HHS includes glucocorticoid, thiazide diuretics, phenytoin, beta-blockers, and more recently atypical antipsychotics. The higher circulating ratio of insulin/glucagon in HHS patients prevents ketogenesis and ketoacidosis developments, especially those HHS patients have some functioning pancreatic beta-cells. The first and most important step in the treatment of hyperosmolar hyperglycemic state is aggressive fluid replacement, which should begin with an estimate of the fluid deficit (usually 100 to 200 mL per kg, or an average total of 9 L).

Abbreviations

ADA: American diabetes association; **DKA:** Diabetic ketoacidosis; **GFR:** Glomerular infiltration rate; **HHS:** Hyperosmolar hyperglycemic state; **MHLS:** Malignant hyperthermia-like syndrome; **T2DM:** Type-2 Diabetes Mellitus; **UK:** United Kingdom

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