Hyperosmolar Hyperglycemic State: A Historic Review of the Clinical Presentation, Diagnosis, and Treatment

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REVIEW

The hyperosmolar hyperglycemic state (HHS) is the most serious acute hyperglycemic emergency in patients with type 2 diabetes. von Frerichs and Dreschfeld described the first cases of HHS in the 1880s in patients with an "unusual diabetic coma" characterized by severe hyperglycemia and glycosuria in the absence of Kussmaul breathing, with a fruity breath odor or positive acetone test in the urine. Current diagnostic HHS criteria include a plasma glucose level >600 mg/dL and increased effective plasma osmolality >320 mOsm/kg in the absence of ketoacidosis. The incidence of HHS is estimated to be <1% of hospital admissions of patients with diabetes. The reported mortality is between 10 and 20%, which is about 10 times higher than the mortality rate in patients with diabetic ketoacidosis (DKA). Despite the severity of this condition, no prospective, randomized studies have determined best treatment strategies in patients with HHS, and its management has largely been extrapolated from studies of patients with DKA. There are many unresolved questions that need to be addressed in prospective clinical trials regarding the pathogenesis and treatment of pediatric and adult patients with HHS.

The hyperosmolar hyperglycemic state (HHS) is a syndrome characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of ketoacidosis. The exact incidence of HHS is not known, but it is estimated to account for <1% of hospital admissions in patients with diabetes (1). Most cases of HHS are seen in elderly patients with type 2 diabetes; however, it has also been reported in children and young adults (2). The overall mortality rate is estimated to be as high as 20%, which is about 10 times higher than the mortality in patients with diabetic ketoacidosis (DKA) (3–5). The prognosis is determined by the severity of dehydration, presence of comorbidities, and advanced age (4,6,7). Treatment of HHS is directed at replacing volume deficit and correcting hyperosmolality, hyperglycemia, and electrolyte disturbances, as well as management of the underlying illness that precipitated the metabolic decompensation. Low-dose insulin infusion protocols designed for treating DKA appear to be effective; however, no prospective randomized studies have determined best treatment strategies for the management of patients with HHS. Herein, we present an extensive review of the literature on diabetic coma and HHS to provide a historical perspective on the clinical presentation, diagnosis, and management of this serious complication of diabetes.

History of Diabetic Coma and HHS

In 1828, in the textbook *Versuch einer Pathologie und Therapie des Diabetes Mellitus*, August W. von Stosch gave the first detailed clinical description of diabetic coma in an

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adult patient with severe polydipsia, polyuria, and a large amount of glucose in the urine followed by progressive decline in mental status and death (8). Several case reports followed this publication, describing patients with newly diagnosed or previously known diabetes presenting with drowsiness or coma, most of them with a peculiar breath odor resembling acetone (9). In 1857, Petters (10) detected a substance in the urine of a fatal case of diabetic coma that resembled acetone in its reaction with sulfuric acid and caustic alkalis and was later recognized as acetoacetic acid, also called diacetic acid (11,12). Acetone was then recognized as an important outcome marker warning physicians about serious diseases, including diabetes (13,14). In 1874, Kussmaul reported several fatal cases of diabetic coma preceded and accompanied by severe dyspnea (15,16). Kussmaul breathing, as this condition came to be known, quickly became one of the hallmarks in the diagnosis of diabetic coma, along with the presence of positive urine ketones (14,17). In the 1880s, Stadelmann (18), Külz (19), and Minkowski (20) reported that the urine of most patients with diabetic coma contained, in addition to acetoacetic or diacetic acid, the presence of considerable quantities of β-oxybutyric acid (Table 1). The discovery of high concentrations of acetoacetic acid and β-hydroxybutyric acid led clinicians and researchers in the late 1890s to conclude that diabetic coma was a "self-intoxication" due to an excess of acids in the body (12,13).

The first reports of HHS are attributed to von Frerichs (21) and Dreschfeld (14). In the 1880s, they reported patients presenting with an unusual type of diabetic coma characterized by severe hyperglycemia and glycosuria but without Kussmaul breathing, fruity breath odor, or a positive urine acetone test. Dreschfeld (14) described a case series of patients with "diabetic collapse" presenting after age 40 years, who were well nourished at the time of the attack, and with fatty infiltration of the liver and the heart. Shortly after these reports, several authors (14,21) reported cases of diabetic coma in well-nourished adult patients with known diabetes, and the term "diabetes of stout people" was coined. In the early 1900s, others reported the presence of two distinct types of patients with diabetic coma, noting that not all cases presented with the characteristic Kussmaul respiration or positive urine acetone or diacetic acid (22–26). These reports created confusion and were taken with skepticism, as the source of ketone bodies and the role of acetoacetic acid in the pathogenesis of diabetic coma were not known at the time. Many physicians were against accepting that adult patients could progress to diabetic coma in the absence of ketonuria. For example, in the 1930s, Elliot P. Joslin (17) and others (27) stated that the presence of acetone or diacetic acid in the urine was requisite for the diagnosis of diabetic coma. It was later hypothesized that diabetic coma with negative urinary ketones was the result of impaired renal excretion, liver dysfunction, and the presence of other acids, such as β-hydroxybutyric acid, rather than diacetic acid or acetone (25,26,28).

HHS syndrome received little attention and remained poorly understood until the reports by de Graeff and Lips (29) and Sament and Schwartz (30) in 1957. They reported that severe hyperglycemia resulted in osmotic diuresis, polyuria, and progressive water deficit. They discussed the relevance of measuring sodium and chloride levels to estimate extracellular hypertonicity and cellular dehydration, and they proposed that patients with severe hyperglycemia and diabetic coma should be treated with large quantities of water (29). Sament and Schwartz (30) suggested that some comatose patients with severe hyperglycemia and negative or trace ketonuria could be treated successfully with the administration of fluids and lower amounts of insulin compared with regular acidotic patients with diabetic coma.

Pathophysiology

HHS is characterized by extreme elevations in serum glucose concentrations and hyperosmolality without significant ketosis (Fig. 1). These metabolic derangements result from synergistic factors including insulin deficiency and increased levels of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) (31–33). Hyperglycemia develops because of an increased gluconeogenesis and accelerated conversion of glycogen to glucose (glycogenolysis) and by inadequate use of glucose by peripheral tissues, primarily muscle. From the quantitative standpoint, increased hepatic glucose production represents the major pathogenic disturbance responsible for hyperglycemia in DKA (34). As the glucose concentration and osmolality of extracellular fluid increase, an osmolar gradient is created that draws water out of the cells. Glomerular filtration is initially increased, which leads to glucosuria and osmotic diuresis. The initial glucosuria prevents the development of severe hyperglycemia as long as the glomerular filtration rate is normal. However, with continued osmotic diuresis, hypovolemia eventually occurs, which leads to a progressive decline in glomerular filtration rate and worsening hyperglycemia.

Higher hepatic and circulating insulin concentration as well as lower glucagon are present in HHS compared with patients with ketoacidosis (32,33). The higher circulating ratio of insulin/glucagon in patients with HHS prevents ketogenesis and the development of ketoacidosis. This concept is supported by clinical studies both in animals and in humans, which have shown that the half-maximal concentration of insulin for antilipolysis is lower than for glucose use by peripheral tissues (35). Finally, a direct role of hyperosmolarity by inhibiting lipolysis and free fatty acid release from adipose tissue has been shown in experimental animals (36).

Severe hyperglycemia is associated with a severe inflammatory state characterized by an elevation of proinflammatory cytokines (tumor necrosis factor-α, interleukin (IL)β, IL6, and IL8) and reactive oxygen species, with insulin secretion and action. Hyperglycemia causes an increase in oxidative stress markers such as membrane lipid peroxidation (37). The degree of lipid peroxidation is directly proportional to the glucose concentrations in diabetic patients. This is thought to occur via several well-studied mechanisms, including increased polyol pathway flux, increased intracellular formation of advanced glycation end products, activation of protein kinase C, or overproduction of superoxide by the mitochondrial electron transport chain (37,38). By interest, elevations of circulating proinflammatory cytokines are reduced to normal levels promptly

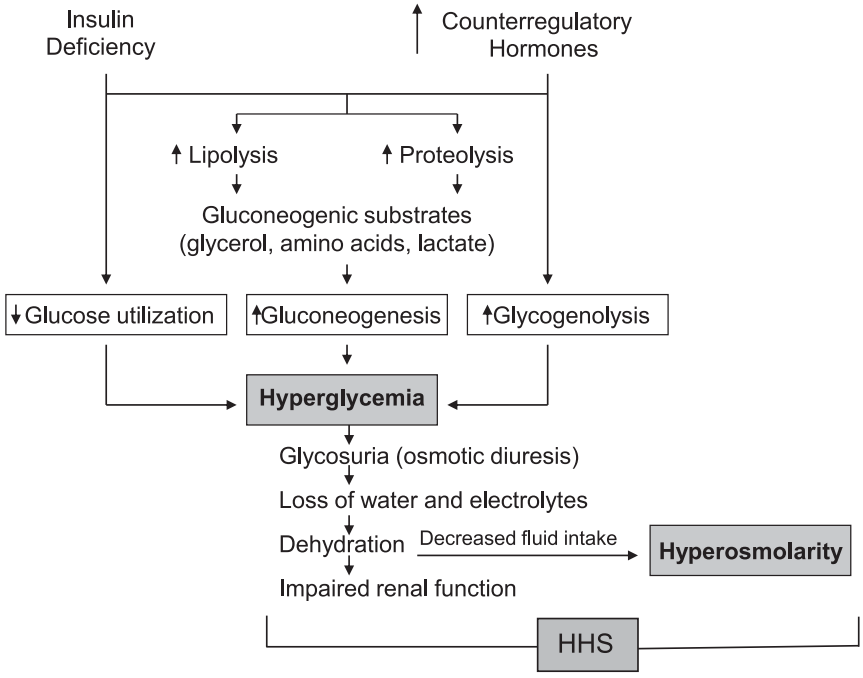

Figure 1—Pathogenesis of HHS.

in response to insulin therapy and normalization of blood glucose concentration (39).

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%) (40–42). Up to 20% do not have a previous diagnosis of diabetes (7). Underlying medical illness, such as stroke, myocardial infarction, and trauma, that provokes the release of counterregulatory hormones and/or compromises 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

Table 1—From diabetic coma to HHS

Years	Authors (reference nos.)	Comment
1828	von Stosch (8)	Initial descriptions of diabetic coma
1857	Petters (10)	Discovery of acetone in the urine of patients with diabetes
1865	Gerhardt (91)	Discovery of acetoacetic acid in the urine of patients with diabetes
1874	Kussmaul (15)	First extensive description of diabetic coma
1878	Foster (11)	Cases of diabetic coma and acetonemia
1883–1884	Stadelmann (18)/Külz (19)/Minkowski (20)	Discovery of β-hydroxybutyric acid in patients with diabetes
1884–1886	von Frerichs (21)/Dreschfeld (14)	Description of a nonketotic diabetic coma
1922	Banting et al. (83)	Insulin discovery
1909–1923	Lépine (92)/Revillet (93)/McCaskey (94)/Bock et al. (95)	Case series of diabetic coma without ketonuria
1930–1935	Lawrence (84)/Joslin (17)	Initial recommendations for the management of diabetic comas
1957	Sament and Schwartz (30)/de Graeff and Lips (29)	Detailed case reports of diabetic coma without ketones and hyperosmolality
1962	Singer et al. (85)	Linking osmolality and hyperglycemia
1971	Arieff and Carroll (55)/Gerich et al. (54)	Case series of HHS; initial criteria
1973	Arieff and Kleeman (77)	Mechanisms leading to cerebral edema
1976–1977	Alberti and Hockaday (60)/Kitabchi et al. (70)	Low-dose insulin protocols
2004–2009	Kitabchi et al. (4,86,87)	Position Statement, American Diabetes Association: management of hyperglycemic crises
2011	Zeitler et al. (59)	Guidelines for the management of HHS in children

medications associated with metabolic decompensation and HHS include glucocorticoid, thiazide diuretics, phenytoin, β-blockers, and more recently atypical antipsychotics (43–49).

Recent case reports and series suggest an increasing incidence of this disorder in children and adolescents (50,51). In children, most common precipitating causes are diseases of the circulatory, nervous, and genitourinary systems (52). In addition, some children with T1DM may present with features of HHS (severe hyperglycemia) if high-carbohydrate–containing beverages have been used to quench thirst and replace urinary losses prior to diagnosis (53).

Diagnostic Criteria of HHS

The modern definition and diagnostic criteria of HHS derived from case series reported by Gerich et al. (54) and Arieff and Carroll (55) in 1971 (Table 2). They also provided insights into the pathophysiology of the syndrome they called "hyperglycemic hyperosmolar nonketotic coma" (HHNK). Arieff and Carroll's diagnostic criteria included a blood glucose level >600 mg/dL, a total serum osmolarity level >350 mOsm/L, and a serum acetone reaction from 0 to 2 pluses when the serum was diluted 1:1 with water (55). The selection of a glucose concentration >600 mg/dL was based on the observation that above this level, serum osmolality is >350 mOsm/kg (56). Arieff and Carroll also reported that patients with HHNK coma had a mean plasma osmolarity of ~380 mOsm/L, compared with the ~320–330 mOsm/L osmolality observed in conscious patients (54,55,57). In addition, they reported that patients with HHNK coma had an admission plasma bicarbonate level of 17.0 ± 6 mEq/L, a mean arterial pH of 7.31, and an average plasma glucose level of 1,076 ± 350 mg/dL (range 650–1,780 mg/100 mL). Current diagnostic criteria of HHS recommended by the American Diabetes Association (ADA) and international guidelines include a plasma glucose level >600 mg/dL, plasma effective osmolarity >320 mOsm/L, and an absence of significant ketoacidosis (Table 2) (4,58,59). The term HHNK was replaced with "hyperglycemic hyperosmolar state" to reflect the fact that many patients present without significant decline in the level of consciousness (less than one-third of patients present with coma) and because many patients can present with mild to moderate degrees of ketosis (32,60). In some studies, up to 20% of patients with severe hyperglycemia and hyperosmolarity were reported to have combined features of HHS and DKA (7,32).

In contrast with the original formula proposed by Arieff and Carroll (55) to estimate total serum osmolality [2(Na) +18/glucose + BUN/2], recent reports and consensus guidelines have recommended the use of effective serum osmolality [2(Na) +18/glucose] not taking into consideration urea, as the osmotic contribution of urea is not significant compared with the effects of sodium and glucose levels (32,61,62). Urea is distributed equally in all body compartments, and its accumulation does not induce an osmotic gradient across the cell membranes. Symptoms of encephalopathy are usually present when serum sodium levels exceed 160 mEq/L and when the calculated total and effective osmolality are >340 and 320 mOsm/kg, respectively (32,63).

Evolution of HHS treatment

In the 19th century and preinsulin era, a large number of treatment modalities were recommended to treat diabetic coma. Kussmaul tried blood transfusions with only temporary results. Reynolds (64) published two cases of recovery with castor oil followed by 63 grains of citrate of potassium. In the late 1900s, the most common therapeutic regimen was the administration of subcutaneous and intravenous saline solutions with 3% sodium carbonate (13). Chadbourne (65) reported that among 17 cases of diabetic coma, only one case was treated successfully, and seven patients showed a temporary improvement in consciousness.

Before the discovery of insulin, diabetic coma was regarded as an inevitable culmination of life, as it was exceedingly rare for a diabetic individual to live for more than a few months after an episode of diabetic coma (17). After the discovery of insulin in 1922, the development of diabetic coma became much less frequent in patients with diabetes, and when acquired, patients had better treatment options. After the 1930s, <10% of hospital admissions for diabetes were due to diabetic coma (17).

Shortly after the introduction of insulin, patients with diabetic coma were treated with 20–100 units s.c. soluble insulin every 30 min on a sliding scale according to the Benedict test for glucosuria (17). The total insulin dose for treatment of diabetic coma was increased in the 1940s after the reports by Root (66) and Black and Malins (67), who recommended an initial bolus dose

Table 2—Diagnostic criteria of HHS first reported by Arieff and Carroll and current ADA criteria

	Arieff and Carroll (56)	ADA (4)
Plasma glucose, mg/dL	>600	>600
Arterial pH	N/A	>7.30
Serum bicarbonate, mEq/L	N/A	>18
Urine or serum ketones by nitroprussiate test (acetoacetate)	0 to 2 pluses	Negative or small
Serum β-hydroxybutyrate, mmol/L	N/A	<3 mmol/L
Total serum osmolality, mOsm/kg*	>350	N/A
Effective serum osmolality, mOsm/L**	N/A	>320
Anion gap, mEq/L	N/A	Variable
Mental status	N/A	Variable; most patients present with stupor, coma

*Total serum osmolality formula = 2(Na) + 18/glucose + BUN/2. **Effective serum osmolality formula = 2(Na) + 18/glucose.

of 200–400 units i.v. soluble insulin depending on the severity of the mental status. Three arbitrary stages were used to guide initial bolus doses: stage 1, drowsy but easily rousable; stage 2, rousable with difficulty; and stage 3, unconscious on admission. These researchers suggested giving an initial injection of 200 units to patients in stage 1, 300 units to patients in stage 2, and 400 units to patients in stage 3, followed by boluses of 50 units i.v. injected into drip tubing every 30 min until the urine became free of acetone bodies (67). From 1950 to the 1970s, most experts in the field recommended an initial bolus dose of 20–80 units intramuscularly (i.m.) or i.v. followed by 20–80 units i.m. or i.v. every 1–2 h (68). It was recognized that patients with HHS required lower doses of insulin than patients with DKA, who were given ~50–100 units i.m. or i.v. every hour (68).

In 1973, Alberti et al. (69) were the first to report the successful treatment of patients with diabetic coma using small intramuscular doses of regular insulin. They treated 14 patients with ketoacidosis, one patient with hyperosmolar nonketotic coma, and two cases of hyperglycemic nonketotic state with an initial mean dose of 16 ± 2 units followed by 5 or 10 units i.v. or i.m. every hour. The patients' plasma glucose rates fell at a regular rate of 90 mg/h (69). The authors reported a cumulative insulin dose of <100 units per day, which was a significant reduction from previous reports that used 400–500 units per day. These studies were later confirmed by two randomized, controlled trials conducted by Kitabchi and colleagues (70,71), who compared treatment using low-dose intramuscular with treatment using large-dose intravenous and subcutaneous regular insulin (Table 3). Unfortunately, no prospective, randomized studies have been conducted in patients with HHS, and those patients are treated following the protocols designed to treat DKA. Low-dose insulin infusion protocols have been shown to be effective, with resolution of hyperglycemia in ~9 ± 2 h and resolution of HHS in 11 ± 1 h (7).

The importance of hydration and electrolyte replacement has been recognized in the management of patients with HHS (32,72). Isotonic saline (0.9% NaCl) is recommended at 15–20 mL/kg during the first 1–2 h, followed by 250–500 mL/h until resolution of the hyperglycemic crisis. Fluid replacement alone has been shown to reduce glucose concentration by 75–100 mg/h, due to a reduction in counterregulatory hormones and improvement of renal perfusion (73). In addition, many patients with HHS have high serum potassium despite total body potassium deficit due to insulin deficiency and hyperosmolality,

Table 3—Evolution of treatment regimens for patients with diabetic coma and HHS

Years (reference nos.)	Insulin therapy	Fluids	Other
Preinsulin era (13,14)	—	NS/3% NS (s.c.)	Alcohol, laxatives, alkalies, salicylate, oxygen inhalations, castor oil and citrate of potassium, camphor and ether, caffeine, circulatory stimulants
1930–1950 (17,27)	20–100 units i.v. or s.c. bolus followed by 20 units s.c. every 30–60 min depending on glucosuria	NS (s.c. or i.v.) at variable rates	Routine gastric lavage, cleansing enema, blood transfusion
1950–1970s (29,88,89)	2 units/kg bolus of crystalline insulin; up to 920 units in the first 7 h	NS followed by hypotonic solution ~30 mL/kg or 600–800 cc × m^2	Gastric aspiration
Early 1970s (54,68,90)	50 units i.v. bolus followed by 50–80 units/h i.v. or s.c.	NS at 1–1.5 L over the first 2 h, followed by hypotonic solution at ~100 mL/h	Add 20 mEq potassium to the second or third liter of fluid when potassium level is <6.0 mEq/L
Late 1970s (60,71)	Low-dose insulin regimens. Regular insulin 0.1 units/kg i.v. followed by 0.1–0.3 units/h i.v., s.c., or i.m.	NS at 1–2 L over the first 2 h, followed by NS or half NS. Add dextrose-containing solutions when glucose ~250 mg/dL	Risk of hypokalemia during insulin treatment identified. Early potassium replacement when serum potassium <5.5 mEq/L
1990s (7)	0.1 units/kg i.v. bolus, then 0.1 units/kg/h as continuous infusion until glucose level <13.8 mmol/L (250 mg/dL)	0.9% saline, 500–1,000 mL/h for 2 h, then switch to 0.45% saline at 250–500 mL/h. Add dextrose-containing solutions when glucose ~250 mg/dL	No gastric lavage or gastric suction recommended
2004–2009 (4,87): ADA consensus for treatment of DKA and HHS in adult patients	Initial bolus (0.1 units/kg i.v.), followed by 0.1 units/kg/h until glucose <250 mg/dL, then reduce insulin by 50%	NS at 500–1,000 mL/h for 2–4 h, then 0.45% saline at 250–500 mL/h	
2011 (59): Pediatric Endocrine Society guidelines for treatment of HHS in children	In HHS: no intravenous insulin bolus, start at 0.025–0.05 units/kg/h when no decline in glucose with fluids alone; in hyperosmolar DKA: start 0.05–0.1 units/kg/h	20 mL/kg NS bolus until adequate tissue perfusion	Dantrolene*

NS, normal saline (0.9% NaCl). *If a malignant hyperthermia-like syndrome is suspected.

which cause a shift of potassium from the intracellular compartment into plasma (74,75). During insulin treatment and hydration, serum potassium levels rapidly fall; therefore, it is recommended that potassium replacement should be initiated when serum levels fall <5.5 mEq/L, with the goal to maintain a serum potassium concentration in the range of 4–5 mEq/L.

Arieff and colleagues (56,76,77) first reported the development of brain edema, a feared complication of treatment after rapid correction of hyperglycemia and hyperosmolality. They reported that cerebral edema developed during diabetic coma treatment after a rapid lowering of plasma glucose levels in nondiabetic animals. Hyperglycemia was induced by infusing 50% glucose to maintain the plasma glucose level at ~60 mmol/L (1,080 mg/dL) for periods of 1–4 h. After 4 h of hyperglycemia, brain osmolality (343 mOsm/kg H20) was similar to that of cerebrospinal fluid (340 mOsm/kg). The authors proposed that during glucose infusion and the development of extracellular hyperosmolality, the brain protects against changes in volume by increasing osmolality, largely through a gain in unidentified solutes (idiogenic osmoles). They also observed that rapid normalization of plasma glucose due to insulin and hypotonic fluid administration resulted in gross brain edema as a result of an osmotic gradient between brain and plasma (77). Although such observations have not been demonstrated in humans, it is believed that rapid changes in plasma and brain osmolality after the administration of hypotonic fluids could result in brain edema. Thus, it is recommended that glucose levels be kept at ~300 mg/dL when managing patients with HHS in order to prevent brain edema (68,77).

Future Areas of Research

Several unresolved questions regarding the pathogenesis and treatment of HHS in adults and children need to be addressed in prospective clinical trials.

A major question is the cause of the lack of ketosis in HHS patients compared with DKA patients. Some studies have indicated that HHS patients have higher circulating insulin concentration levels, sufficient to prevent lipolysis and generation of ketone bodies; however, levels of free fatty acids and counterregulatory hormones are comparable between patients with DKA and HHS. Additional studies are also needed to determine the role of inflammatory and oxidative stress markers and clinical outcomes in patients with hyperglycemic crises. Elucidating the roles of these pathways might provide valuable information for reducing the high cardiovascular and thrombotic morbidity rates associated with hyperglycemic emergencies.

Hospitalizations for HHS in children and adolescents have increased significantly in recent reports. Population rates for HHS hospitalizations in children between 1997 and 2009 increased by 52.4%, with a reported yearly increase of 4.4% (52). Clinical programs are needed for early detection and management to reduce the development of hyperglycemic crises in the pediatric population.

The frequency and pathogenesis of cerebral edema in adults and children with HHS needs to be determined in well-designed prospective studies. Similarly, prospective studies are needed to settle the long-term controversy regarding the use of anticoagulant therapy in patients with hyperglycemic crises. Several case reports have indicated an increased risk of thrombosis, which is greater in HHS than in ketoacidosis (78,79). Severe dehydration and hypertonicity may result in osmotic disruption of endothelial cells, leading to a release of tissue thromboplastins and elevated vasopressin caused by the fluid status, which may contribute to enhanced coagulation (80). However, uncomplicated diabetes has never been shown to be an independent risk factor for venous thromboembolism (81). In a retrospective review of 426,831 cases of venous thromboembolism, the overall incidence among patients with hyperosmolarity was 1.7%, which is only modestly lower than the incidence in patients undergoing orthopedic surgery (82). The risk benefit of anticoagulation therapy in patients with HHS and DKA has not been evaluated prospectively.

The most recent ADA Position Statement on the management of hyperglycemic crises in adult patients proposed a single treatment algorithm for the management of DKA and HHS. Low-dose insulin infusion protocols for treating DKA appear to be effective, but the mortality rate is about 10 times higher in HHS patients than in DKA patients (5,7). Thus, prospective studies are needed to determine effective and safe insulin and hydration strategies, as well as to determine glucose targets during intravenous insulin infusion and during the transition to subcutaneous insulin therapy in patients with HHS.

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