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THE HYPERGLYCEMIC HYPEROSMOLAR SYNDROME: HISTORY AND ESSENTIAL CLINICAL INSIGHTS

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ABSTRACT

Hyperglycemic hyperosmolar state (HHS) is one of the most severe acute complications of diabetes mellitus. It is characterized by profound hyperglycemia, absence of ketoacidosis, and altered mental status. With a mortality rate that may reach up to 20%, HHS remains a critical but often underrecognized clinical entity. Historically marginalized due to its relative rarity and poorly understood pathophysiology, its clinical relevance is increasing in parallel with lifestyle changes and the global rise in type 2 diabetes prevalence.

The aim of this article was to compile key information on the history, pathophysiology, and management of HHS in order to raise awareness among all healthcare professionals involved in the care of patients with diabetes. Early recognition of HHS is essential to initiate timely treatment and improve patient outcomes.

Classic symptoms such as excessive thirst with accompanying polyuria and altered mental status particularly in patients with seemingly mild infections or those with chronic but untreated or poorly controlled diabetes - should prompt increased vigilance among medical staff.

Rapid diagnostic evaluation and prompt initiation of treatment must be prioritized in emergency settings to reduce morbidity and mortality associated with this life-threatening condition.

KEYWORDS

Diabetes, Hyperglycemic Hyperosmolar Syndrome

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Introduction.

HHS is a life-threatening complication of diabetes mellitus and is often considered alongside diabetic ketoacidosis (DKA) due to similarities in pathophysiology and treatment. However, a number of critical differences between these entities necessitate clear differentiation and, in particular, an understanding of the mechanisms underlying the development of HHS.

Historical Background

For decades, the HHS remained an enigmatic clinical entity. While DKA had been described for many years - indeed, the first references to it date back to 1828 [1] - with reports of coma in individuals presenting with polydipsia, polyuria, glycosuria, and urinary compounds later identified as ketone bodies in 1878, it was established that the cause of such comas and deaths was intoxication with ketone compounds [2].

Simultaneously, cases began to emerge of deaths in patients with diabetes that, although resembling ketoacidosis in some aspects, deviated from the typical clinical presentation. These occurred predominantly in well-nourished, often overweight adults, in whom no ketone bodies could be detected in the urine or systemically.

It was not until 1886 that the first descriptions of what would now be recognized as”diabetic coma” due to HHS were published [3]. At the time, these reports sparked considerable controversy, and despite the documentation of numerous similar cases in the following decades [4], the medical community, including both physicians and researchers, remained skeptical about their validity and the accuracy of their descriptions [1].

It was only in 1957 that electrolyte disturbances - particularly involving sodium and chloride—leading to impaired consciousness were described in the context of hyperglycemia. This marked a turning point in understanding the pathophysiology of HHS and led to the introduction of the first proposed treatment: aggressive fluid resuscitation, which remains a cornerstone of HHS therapy to this day [5][6].

The initial concepts resembling diagnostic criteria emerged around 1972. These early proposals, based on blood glucose levels exceeding 600 mg/dL, total plasma osmolality above 350 mOsm/kg, and absent or only mildly positive tests for ketone bodies [7], significantly facilitated diagnosis. Notably, these early criteria closely resemble current standards, indicating the accuracy of the original assumptions.

It was not until 2001 that the American Diabetes Association (ADA) issued formal diagnostic recommendations for HHS, establishing widely accepted criteria [8]. With only minor revisions, such as more precise and unified parameter definitions compared to the 1972 criteria, the ADA criteria emphasized effective plasma osmolality exceeding 320 mOsm/kg, hyperglycemia >600 mg/dL, pH >7.3, serum bicarbonate >15 mEq/L, and absent or only minimal ketonemia and ketonuria, typically accompanied by altered mental status.

These diagnostic criteria have remained in clinical use for years and continue to serve as the standard, with only slight modifications. According to the most recent recommendations, which emphasize four key components, a diagnosis of HHS requires: hyperglycemia >600 mg/dL; elevated effective osmolality >300 mOsm/kg or total osmolality >320 mOsm/kg; absence of significant ketone bodies; and absence of acidosis, defined as pH >7.3 or serum bicarbonate >15 mmol/L [9].

Epidemiology

The typical profile of a patient admitted to the hospital with HHS is as follows: a middle-aged individual in the fifth decade of life, with obesity, previously diagnosed but untreated type 2 diabetes, and a concurrent infection such as pneumonia or a urinary tract infection. In many cases, additional social or comorbid conditions impair the patient's ability to maintain adequate hydration [1][10][11].

The incidence of HHS is closely related to the number of individuals with type 2 diabetes [1]. This number has been steadily increasing in recent years due to lifestyle changes and a growing prevalence of obesity, which clearly explains why HHS was relatively unknown and considered a marginal problem in the early 20th century.

According to the International Diabetes Federation (IDF), approximately 589 million people aged 20–79 years are currently living with diabetes, representing over 11% of the global population. Projections estimate that this number will rise to 578 million by 2030 and may reach approximately 853 million by 2050, corresponding to 11% and 13% of the population, respectively, with the vast majority of cases being type 2 diabetes [12].

Accurate data on the incidence of HHS are difficult to obtain and interpret due to population heterogeneity and incomplete registry reporting. It is estimated that fewer than 1% of all hospital admissions are attributable to HHS [1][9].

U.S. data from 2009 to 2015 report a total of 27, 532 HHS cases, with the majority (88.1%) occurring in patients with type 2 diabetes [13]. A study conducted between 2005 and 2015 at Emory Hospital analyzed patients admitted due to life-threatening hyperglycemia. Among 1, 211 cases, DKA was diagnosed in 465 patients (38%), HHS in 421 patients (35%), and 325 patients (27%) presented with overlapping features of both conditions [14]. These figures provide a general understanding of HHS incidence in developed countries, where type 2 diabetes is a dominant health concern.

Mortality associated with HHS is difficult to quantify objectively, due to frequent multimorbidity, overlap with ketoacidosis symptoms, and differences in care standards. Available data suggest a mortality rate ranging from 5% to 20%, commonly reported as approximately ten times higher than that observed in DKA[10][15-17]. This elevated mortality is attributed to both the clinical course of HHS and the typical patient profile.

Pathophysiology

The pathophysiology of HHS has remained only partially understood for many years and continues to be incompletely elucidated [18].

HHS primarily develops in individuals with type 2 diabetes [13], who retain endogenous insulin production. However, due to insulin resistance, the available insulin is insufficient to maintain normoglycemia, yet adequate to suppress lipolysis and ketogenesis [1][18][19]. Impaired cellular glucose uptake leads to persistent hyperglycemia resulting from inadequate utilization.

In response to this relative cellular glucose deficiency, counter-regulatory hormones such as catecholamines, cortisol, and glucagon are released [1][20], further exacerbating hyperglycemia and promoting its progression. The resulting severe hyperglycemia markedly increases plasma osmolality.

Plasma hyperosmolality induces osmotic fluid shifts from the intracellular to the extracellular space [21-24], which leads to dilutional effects, including hypertonic hyponatremia due to sodium ion redistribution.

This increase in osmolality—both directly and indirectly—underpins the pathophysiological mechanisms of HHS and gives rise to its characteristic clinical manifestations.

Etiology and Clinical Presentation of HHS

The development of HHS is most commonly precipitated by infections, with bacterial pneumonia - particularly that caused by Gram-negative bacteria - being the predominant trigger. Other infectious contributors include urinary tract infections and sepsis. Certain pharmacological agents also increase the risk of HHS; second-generation antipsychotics serve as a notable example. In elderly patients, dehydration is a significant risk factor, frequently resulting from diuretic therapy. Additional contributing factors include poor adherence to diabetes treatment regimens, which accounts for approximately 21% of documented HHS cases. Furthermore, undiagnosed diabetes, intoxication with psychoactive substances, and coexisting medical conditions such as myocardial infarction, stroke, pulmonary embolism, or mesenteric artery thrombosis may also precipitate the condition [25].

The clinical manifestations of HHS typically develop gradually and include early symptoms such as polydipsia, polyuria, weight loss, weakness, and lethargy [26]. As the condition progresses, profound dehydration becomes evident, characterized by reduced skin turgor, dry mucous membranes, sunken, and soft eyeballs, cool extremities, and a rapid, thready pulse. In adult patients, low-grade fever is frequently observed. In the pediatric population, symptoms may be nonspecific and include headache, general weakness, vomiting, and abdominal pain—the latter potentially linked to gastroparesis induced by plasma hypertonicity. If abdominal distension persists despite appropriate rehydration, further investigation for alternative pathologies is warranted.[27]

Altered mental status is a common clinical feature and correlates with the degree of effective serum osmolality, ranging from full alertness to confusion, lethargy, or coma—typically occurring when osmolality exceeds 340 mOsm/kg. Seizures are observed in approximately 25% of cases and may present as either generalized or focal [25]. Notably, some seizures may be refractory to standard antiepileptic medications, necessitating further metabolic evaluation [26]. Hemiparesis is another frequent neurological manifestation, which usually resolves following correction of metabolic disturbances and fluid deficits. Neurological symptoms may closely resemble acute conditions such as stroke; thus, in the presence of significant hyperglycemia, differential diagnosis should include acute neurological pathologies [28].

Diagnostic Approach and Diagnosis of HHS

HHS is a medical emergency that requires rapid intervention and patient stabilization. The diagnostic process should begin with a comprehensive clinical assessment based on the ABCDE approach, encompassing evaluation of airway (A), breathing (B), circulation (C), neurological status (D – disability), and exposure (E) [19]. Given the most common etiologies of HHS, clinicians should actively search for potential sources of infection. If the patient's condition permits, or if relatives with relevant health information are present, a thorough medical history should be obtained, including prior diabetes management, signs of infection, comorbidities that may affect prognosis, and current medications [19].

Laboratory testing plays a pivotal role in the diagnosis of HHS. Bedside capillary blood glucose should be measured promptly, with confirmation via laboratory methods. In HHS, serum glucose levels typically exceed 600 mg/dL (33.3 mmol/L). Another critical parameter is serum osmolality, which is generally above 320 mOsm/kg (normal range: 290 ± 5 mOsm/kg) [19]. Significant elevation—particularly values above 340 mOsm/kg—may result in coma [25].

Arterial blood gas analysis allows for pH assessment and helps differentiate HHS from DKA. A normal pH (>7.3) supports the diagnosis of HHS. However, vomiting or the use of thiazide diuretics may mask underlying acidosis [25]. Measurement of serum ketone bodies is essential, although their levels are usually only mildly elevated in HHS. Laboratory evaluation should also include sodium, potassium, and other electrolytes, as appropriate fluid therapy requires ongoing monitoring and correction[19]. Creatinine levels are often elevated, indicating potential renal impairment [19], while blood urea nitrogen may serve as an independent prognostic marker for mortality in HHS [29]. Elevated lactate levels have also been associated with worse outcomes [30].

There are no universally accepted diagnostic criterion for HHS; however, the American Diabetes Association defines it by the following: glucose concentration >600 mg/dL, serum osmolality >320 mOsm/kg, absence of significant ketoacidosis, and signs of marked clinical deterioration. British guidelines propose a slightly lower glucose threshold of 540 mg/dL [31].

Management

The treatment of HHS is a complex clinical process, and a full discussion is beyond the scope of this review. This section presents the core therapeutic goals and general principles of management. It should be noted that a discussion of the underlying cause-specific treatment is deliberately omitted. Clinicians are encouraged to consult the most recent guidelines from both international and local diabetes societies, which provide detailed recommendations for the management of patients with HHS. Despite minor differences between guidelines, the core therapeutic principles remain consistent.

The 2024 guidelines jointly developed by the American Diabetes Association, European Association for the Study of Diabetes, Joint British Diabetes Societies for Inpatient Care, American Association of Clinical Endocrinology, and the Diabetes Technology Society divide the management of acute diabetes complications—including DKA and HHS—into three core components: fluid resuscitation, insulin administration, and correction of potassium imbalance. The following summary highlights selected key clinical aspects relevant to practicing clinicians [32].

The primary goal of fluid therapy in HHS is to restore adequate hydration and normalize plasma osmolality. Depending on the patient's clinical status and degree of dehydration, administration of 0.9% sodium chloride solution at a rate of 15–20 mL/kg body weight over the first 1–2 hours is recommended. Concurrently, continuous monitoring of biochemical parameters—including sodium, potassium, and effective plasma osmolality—is necessary to guide further therapeutic decisions [32].

Potassium homeostasis is of particular importance in HHS. Insulin therapy and correction of hyperglycemia lead to intracellular shifts of potassium, which may result in hypokalemia. If the serum potassium concentration is below 3.3 mmol/L, insulin administration should be withheld until potassium deficiency is appropriately corrected. Only after reaching a safe serum potassium level should insulin therapy be initiated [32].

In contrast to milder forms of DKA, where subcutaneous insulin may be considered, intravenous insulin administration is recommended in all cases of HHS. Clinical and laboratory parameters should be monitored every 1–2 hours [32].

The initial therapeutic goal in glycemic control is not to rapidly achieve normoglycemia, but rather to gradually reduce plasma glucose levels to 200–250 mg/dL. After the patient's condition is stabilized, controlled normalization of glycemia can proceed. Throughout the therapeutic process, diagnostic efforts should continue to identify the underlying cause of HHS and guide appropriate causal treatment [32].

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Author's contribution:

Conceptualization - Sebastian Iwaniuk and Ignacy Maciejewski; methodology – Szymon Szypulski; software, - Kinga Tylczyńska and Maria Michalska; check – Kinga Tylczyńska, Natalia Tylczyńska; formal analysis -Szymon Szypulski and Kinga Kowalik; investigation - Maria Michalska; resources - Zuzanna Skiba; data curation – Kinga Kowalik and Maria Michalska; writing - rough preparation - Sebastian Iwaniuk and Ignacy Maciejewski; writing - review and editing, Ignacy Maciejewski and Sebastian Iwaniuk; visualization, Kinga Kowalik; supervision - Jakub Skiba; project administration – Aleksandra Zielińska; receiving funding not applicable, All authors have read and agreed with the published version of the manuscript.

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