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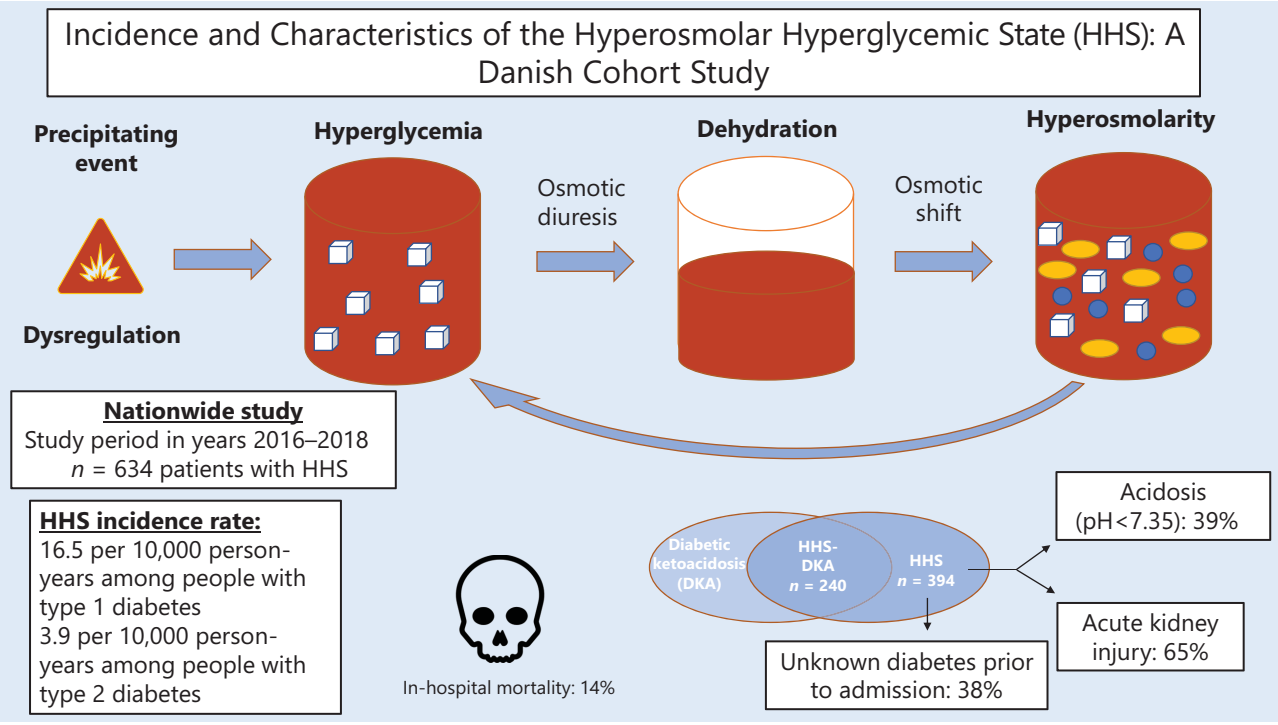

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  We performed this study because the hyperosmolar hyperglycemic state (HHS) is a rare condition and knowledge of patient characteristics and the epidemiology is limited.
- **What is the specific question(s) we wanted to answer?**
  We wanted to estimate the incidence of HHS in patients with diabetes and identify the characteristics of patients acutely admitted to the hospital with HHS.
- **What did we find?**
  We identified 634 patients with HHS. The incidence rates of HHS among people with type 1 and 2 diabetes were 16.5 and 3.9 per 10.000 person-years, respectively. One-third of the patients were not diagnosed with diabetes beforehand.
- **What are the implications of our findings?**
  The epidemiology and characteristics of patients with HHS may facilitate better treatment of this life-threatening disease.

Incidence and Characteristics of the Hyperosmolar Hyperglycemic State: A Danish Cohort Study

Emilie V. Rosager,[1] Amalia Lærke K. Heltø,[1] Cathrine U. Fox Maule,[2] Lennart Friis-Hansen,[3,4] Janne Petersen,[2,5] Finn E. Nielsen,[1] Steen B. Haugaard,[4,6] and Rasmus Gregersen[1,2,5]

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ORIGINAL ARTICLE

OBJECTIVE

The hyperosmolar hyperglycemic state (HHS) is a rare and life-threatening complication of diabetes. We aimed to estimate the incidence of HHS and describe the clinical and biomarker profiles of patients with HHS, including subgroups with acidosis and acute kidney injury.

RESEARCH DESIGN AND METHODS

This nationwide, descriptive cohort study used Danish registry data during years 2016–2018 to identify acutely admitted patients fulfilling the hyperglycemia and hyperosmolarity criteria of HHS (glucose ≥33 mmol/L and osmolarity [2 × sodium + glucose] ≥320 mmol/L).

RESULTS

We identified 634 patients (median age, 69 years (first quartile; third quartile: 58; 79) who met the criteria of HHS among 4.80 million inhabitants aged ≥18 years. The incidence rates were 16.5 and 3.9 per 10,000 person-years among people with known type 1 (*n* = 24,196) and type 2 (*n* = 251,357) diabetes, respectively. Thirty-two percent of patients with HHS were not previously diagnosed with diabetes. Patients were categorized as pure HHS (*n* = 394) and combined HHS and diabetic ketoacidosis (HHS-DKA; *n* = 240). The in-hospital mortality rate for pure HHS was 17% and 9% for HHS-DKA.

CONCLUSIONS

The incidence of HHS was higher among patients with type 1 diabetes compared with type 2 diabetes. HHS is a spectrum of hyperglycemic crises and can be divided in pure HHS and HHS-DKA. In one-third of patients, HHS was the debut of their diabetes diagnosis.

The hyperosmolar hyperglycemic state (HHS) is an acute, rare, and life-threatening complication of diabetes mellitus (1). HHS is defined by plasma glucose ≥33 mmol/L, effective plasma osmolarity (2 × sodium [mmol/L] + glucose [mmol/L]) ≥320 mmol/L; clinical dehydration; absence of significant ketoacidosis; and a degree of encephalopathy (2). Previously, HHS was termed hyperosmolar nonketotic coma, but this definition has changed because most patients with HHS present with altered mental status, focal neurological symptoms, or blurred sensorium, rather than outright coma (3,4). Therefore, HHS covers hyperglycemia and hyperosmolarity in a spectrum from none to mild ketosis, and alterations in sensoria, and ultimately, a state of coma (5). Diagnostic guidelines of HHS from the United Kingdom and Denmark include additional criteria of

[1]Department of Emergency Medicine, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark
[2]Center for Clinical Research and Prevention, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark
[3]Department of Clinical Biochemistry, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark
[4]Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[5]Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
[6]Department of Endocrinology, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark

Corresponding author: Emilie V. Rosager, emilie.vangsgaard.rosager.02@regionh.dk

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pH >7.3 and serum bicarbonate >15 mmol/L (5,6). These criteria are often evaluated secondarily to the clinical symptoms because people with HHS may have metabolic acidosis (pH <7.3, low bicarbonate, and increased anion gap) for other reasons than ketosis, such as concomitant renal failure and progression of the disease, which increases risk of lactic acidosis (3,6,7).

HHS is often initiated by a precipitating event such as infection or acute myocardial infarction, lack of treatment adherence, or a dysregulated or unrecognized diagnosis of diabetes mellitus (4). In contrast to diabetic ketoacidosis (DKA), people with HHS still secrete enough insulin to prevent increased lipolysis and notably ketogenesis (7). Some individuals present with a combined condition of HHS and DKA, featuring severe hyperosmolarity and hyperglycemia with ketosis. However, a definition of this combined condition is yet to be established (2,8–11).

Only a few studies have examined renal impairment in patients with HHS (9,12). One study examined the development of acute kidney injury (AKI) during hospitalization, but data on the prevalence of AKI at the time of admission were missing in that study (8).

The exact incidence of HHS is unknown (4). Denmark has comprehensive national patient registries on public health care suitable for population-based epidemiological research (13). Using these nationwide Danish health registries, we aimed to estimate the incidence of HHS among people with type 1 diabetes and people with type 2 diabetes, separately. Further, we aimed to characterize patients with HHS, regardless of previously established diabetes diagnoses, and to describe subgroups of patients presenting with acidosis and AKI.

RESEARCH DESIGN AND METHODS

Design, Study Population, and Data Sources

We conducted a nationwide, register-based cohort study including all patients ≥18 years of age meeting the HHS criteria of glucose and osmolarity among all Danish acute hospital contacts in 2016–2018 (see flowchart in Supplementary Fig. 1). The HHS criteria were defined as glucose ≥33 mmol/L and effective plasma osmolarity ≥320 mmol/L in blood samples taken from 2 h before until 6 h after hospital admission (2). For glucose measures, we used plasma glucose or converted blood glucose corresponding to plasma glucose (14). It was not possible to determine other diagnostic criteria of HHS (namely, clinical dehydration, altered mental status, and lack of ketosis) at the time of admission because this information was not available. If a person fulfilled the criteria of HHS several times during the study period, only the first hospitalization was included. To separate patients with a combined condition of HHS and DKA (HHS-DKA) and patients with pure HHS, we used the Danish National Patient Register (DNPR) (15) to identify whether the patients had an ICD10 diagnosis code of DKA (i.e., E10.1, E11.1, E13.1, E14.1) during the hospitalization, hereby defined as combined HHS-DKA and otherwise as pure HHS.

We retrieved data from an established database (16) combining information from the DNPR (15), the Register of Laboratory Results for Research (RLRR) (17), the Danish National Prescription Register (NPR) (18), the Central Person Register (19), the Income Statistics Register (20), and the Danish Education Register (21), on all adults (≥18 years of age) in Denmark. Data from these registries were available from 2003 onward except for the RLRR, in which data only were available from 2016 to 2018. During the study period, the DNPR comprised 4.80 million adult inhabitants and data from all of the hospital organizations in Denmark (15,22). Laboratory data are available in the RLRR from all public hospitals and general practitioners in Denmark. Point-of-care tests such as blood glucose, urine test strips, and ketone tests were often not registered in the electronic laboratory information systems and, consequently, were not reported to the RLRR and, therefore, not available for this study (17). The unique Danish personal identification number was used to link patients across registries.

Ethics Approval and Informed Consent

According to Danish law, there is no need for ethical approval of registry-based studies. This project was approved by Statistics Denmark (project no. 707838), the Danish Health Data Authority (FSEID-00004732 and FSEID-00005777), and the Data Protection Agency (P-2019-616).

Characteristics

Age, sex, comorbidities, prescribed drugs, diabetes status at admission, in-hospital mortality, length of stay, and socioeconomic factors including marital status, educational level, housing type, and income were analyzed. Comorbidities were assessed by the total M3 multimorbidity score and by the following selected comorbidities (defined by the M3 index), which were expected to be clinically relevant to describe the HHS population: diabetes, cerebrovascular disease, chronic renal disease, cancers, dementia, and alcohol use disorder (23). The M3 index is a validated multimorbidity score, including 55 chronic conditions, developed to predict 1-year mortality (23). We defined three M3 levels: 0, 0 to <1, and ≥1, indicating no, low to moderate, and high morbidity, respectively (23). The total number of prescribed drugs was counted as different redeemed medications from the NPR dispensed to each patient up to 365 days prior to admission. The medications were differentiated at the fourth level of the Anatomical Therapeutic Chemical classification code, except for antibiotics, which were differentiated at the second level. Furthermore, we assessed whether the patients had redeemed prescriptions of antidiabetic medications, diuretics, antihypertensives, glucocorticoids, and benzodiazepines (Supplementary Table 1). We also retrieved data on dispensed prescriptions of antibiotics for each patient within 14 days before the hospital admission with HHS. Treatment with vasopressor or inotropes was identified by procedure codes.

We examined the prevalence of type 1 diabetes and type 2 diabetes at the time of admission. Type 1 diabetes was defined as a type 1 diabetes diagnosis (E10) registered in the DNPR and a prescription of insulin as the only antidiabetic medication registered in the NPR. Individuals with a type 2 diabetes diagnosis (E11) or prescriptions of other antidiabetic medications were defined as having type 2 diabetes (Supplementary Table 1). If people treated only with insulin already had a diagnosis of type 2 diabetes, they kept that diagnosis. An ICD10 code of type 1 diabetes overruled an ICD10 code of type 2 diabetes in the cases where patients had registered both. Metformin prescriptions for polycystic ovarian syndrome were not considered. The first date of registration of either a diagnosis or the

dispensing of a diabetes medication was defined as the start date of the diagnosis.

We assessed the registration of selected and grouped diagnoses within the fields of endocrinology and infectious diseases, and within the circulatory system during the hospitalization with HHS. The grouping followed previously presented methods (16,24). For ICD10 codes of diagnoses, see Supplementary Table 2.

We assessed laboratory results, which were a part of a typical standard blood test panel collected upon arrival at Danish emergency departments. The highest value of the blood tests for each patient from 2 h before until 6 h after hospital admission was selected for analysis, except for pH, bicarbonate, hemoglobin, and estimated glomerular filtration rate (eGFR), from which the lowest value was selected. The most recent HbA_{1c} value obtained 14 to 365 days before hospital admission was compared with the HbA_{1c} at the time of admission.

Subgroups

The patients with pure HHS were divided into subgroups of no acidosis versus acidosis (pH $<$7.35) and no AKI versus AKI (defined by the Kidney Disease Improving Global Outcome [KDIGO] guidelines as serum creatinine increase of 26.5 μmol/L from baseline or 1.5 times greater than baseline) (25). The baseline creatinine level of each patient was assessed as the latest creatinine result from 14 to 365 days before hospital admission and compared with the creatinine level at the time of admission. The subgroups of acidosis and AKI were not mutually exclusive.

Statistical Methods

Data management and statistical analyses were performed using SAS, version 9.4 software (SAS Institute, Cary, NC) on Statistics Denmark's remote server. Because of rules of protection of microdata at Statistics Denmark, rows with data of fewer than five individuals were censored.

To estimate the incidence of HHS among individuals with type 1 and type 2 diabetes, we calculated time at risk for all Danish citizens with either type 1 or type 2 diabetes, aged ≥18 years, who were alive and living in Denmark on 1 January 2016. We followed these individuals from 2016 to the end of 2018, or until they experienced one of the following events: hospitalization with HHS, death, or emigration (see flowchart in Supplementary Fig. 2). The incidence of HHS was calculated as an incidence rate with 95% CIs, using the normal approximation to the Poisson distribution.

Categorical variables were presented as percentages and analyzed by estimating a risk difference with 95% CI. Continuous variables followed a nonnormal distribution and were presented as medians (first quartile [Q1]; third quartile [Q3]), and results were analyzed by the Hodges–Lehmann estimation of location shift and 95% CIs (26). The Hodges–Lehmann estimation is related to the Wilcoxon rank test, and it provides a median of all paired differences between observations in the two groups (27).

Data and Resource Availability

Because the data are protected by Danish legislations, they cannot be made available publicly or privately. Approved Danish research institutions can apply for equivalent data material through Statistics Denmark and the Danish Health Data Authority.

RESULTS

From a population of 4.80 million adult inhabitants in Denmark in 2016–2018, we identified 634 patients acutely admitted with HHS (Table 1). During the 3-year period, 19 of these patients had more than one admission with HHS. A total of 24,196 and 251,357 adults from the Danish population were diagnosed with type 1 and type 2 diabetes before year 2016, respectively. Among these, 114 with type 1 diabetes and 277 with type 2 diabetes developed HHS over the 3-year period. This corresponds to incidence rates of 16.5 (95% CI, 13.5, 19.5) per 10,000 person-years in people with known type 1 diabetes (total 69,193 person-years) and 3.9 (95% CI, 3.4, 4.4) per 10,000 person-years in people with known type 2 diabetes (total 710,645 person-years).

Of the total HHS population, 394 patients had pure HHS and 240 patients had HHS-DKA (Table 1). Because data on ketones were missing, it was not possible to determine the degree of ketosis among patients with pure HHS and HHS-DKA. Among patients with pure HHS 16 (extrapolated n = 16 of 134 [12%]) had a bicarbonate level $<$18 mmol/L and pH $<$7.3 (missing data, n = 260). Among patients with HHS-DKA, 25 (extrapolated n = 25 of 97 [26%]) had a bicarbonate level ≥18 mmol/L and pH ≥7.3 (missing data, n = 143).

The in-hospital mortality rate was significantly higher for patients with pure HHS (17%) compared with those with HHS-DKA (9%) (risk difference: 8%; 95% CI, 3.3%, 13.7%) (Table 1). In both groups, there were more male than female patients. The pure HHS group was older than the HHS-DKA group; the median age was 73 and 62 years, respectively. More patients with pure HHS had a high score of comorbidities (35%) compared with the patients with HHS-DKA (20%). No significant difference in the median M3 score was found between the groups. Patients were more likely to be unmarried, divorced, or widowed (64%) than married (36%), and 54% were living alone (Table 2). Most patients had a primary or lower secondary education (46%), and an income level in the second or third quintile (34% and 33%, respectively). Significant differences in socioeconomic factors between patients with pure HHS and patients with HHS-DKA were observed for marital status and first quintile income.

Complicated and uncomplicated diabetes defined by the M3 index were significantly more prevalent in the HHS-DKA group (23). Cerebrovascular disease was prevalent both in the pure HHS group (19%) and in the HHS-DKA group (9%). The median number of prescribed medications was 11 (7,14) for pure HHS and 7 (4,11) for HHS-DKA. The use of metformin (31%), other antidiabetics (23%), diuretics (45%), antihypertensives (62%), glucocorticoids (17%), and benzodiazepines (17%) was all more frequent in patients with pure HHS compared with those with HHS-DKA. Conversely, insulin (62%) was more frequently used and the most common medication used by patients with HHS-DKA. More patients from the pure HHS group (20%) had redeemed a prescription of antibiotics within 2 weeks before admission than those in the HHS-DKA group (11%).

From the total HHS population, 211 (33%) had a new diabetes diagnosis at admission, when the proportion of patients with pure HHS (38%) was higher than that of patients with HHS-DKA (26%). The overall median duration of the diabetes diagnosis among people registered in the DNPR was 12 years (7,15).

A total of 222 individuals (35%) of the total HHS population received a diagnosis

Table 1—Patient characteristics of acutely admitted patients with HHS (plasma glucose ≥33 mmol/L and osmolarity ≥320 mmol/L), stratified as pure HHS or combined HHS-DKA

	Total	Pure HHS	HHS-DKA	RD/HL estimation (95% CI)
Total, *n*	634	394	240	
Sex				
Female	243 (38.3)	145 (36.8)	98 (40.8)	−4.0 (−11.9; 3.8)
Age (years)				
Median (Q1; Q3)	69 (58; 79)	73 (63; 81)	62 (48; 73)	11 (8; 13)
M3				
Median (Q1; Q3)	0.5 (0.1; 1.2)	0.6 (0.1; 1.3)	0.3 (0.1; 0.8)	0.1 (0; 0.3)
0	137 (21.6)	82 (20.8)	55 (22.9)	−2.1 (−8.8; 4.5)
>0	310 (48.9)	173 (43.9)	137 (57.1)	−13.2 (−21.2; −5.2)
>1	187 (29.5)	139 (35.3)	48 (20.0)	15.3 (8.4; 22.2)
Comorbidities‡				
Diabetes, uncomplicated	88 (13.9)	44 (11.2)	44 (18.3)	−7.1 (−13.0; -1.4)
Diabetes, complicated	241 (38.0)	137 (34.8)	104 (43.3)	−8.5 (−16.4; -0.7)
Cerebrovascular disease	95 (15.0)	74 (18.8)	21 (8.8)	10.0 (4.8; 15.3)
Chronic renal disease	37 (5.8)	28 (7.1)	9 (3.8)	3.3 (−0.1; 6.9)
Cancer	82 (12.9)	55 (14.0)	27 (11.3)	2.7 (−2.6; 8.0)
Dementia	35 (5.5)	*	*	
Alcohol use disorders	36 (5.7)	21 (5.3)	15 (6.3)	−1.0 (−4.7; 2.9)
Number of medications				
Median (Q1; Q3)	10 (5; 13)	11 (7; 14)	7 (4; 11)	3 (2; 4)
Medications†				
Metformin	166 (26.2)	121 (30.7)	45 (18.8)	11.9 (5.2; 18.7)
Insulin	244 (38.5)	96 (24.4)	148 (61.7)	−37.3 (−44.8; −29.8)
Other antidiabetics	123 (19.4)	89 (22.6)	34 (14.2)	8.4 (2.4; 14.5)
Diuretics	243 (38.3)	176 (44.7)	67 (27.9)	16.8 (9.3; 24.3)
Antihypertensives	368 (58.0)	245 (62.2)	123 (51.3)	10.9 (3.0; 18.9)
Glucocorticoids	77 (12.1)	65 (16.5)	12 (5.0)	11.5 (6.9; 16.1)
Benzodiazepines	83 (13.1)	66 (16.8)	17 (7.1)	9.7 (4.8; 14.6)
Antibiotics (within 2 weeks from admission)	105 (16.6)	79 (20.1)	26 (10.8)	9.3 (3.6; 14.8)
Vasopressor or inotropes during admission	9 (1.4)	*	*	
Diabetes status at admission**				
Known type 1 diabetes	116 (18.3)	23 (5.8)	93 (38.8)	−32.9 (−39.5; −26.3)
Known type 2 diabetes	307 (48.4)	222 (56.3)	85 (35.4)	20.9 (13.1; 28.7)
New diabetes diagnosis	211 (33.3)	149 (37.8)	62 (25.8)	12.0 (4.7; 19.3)
In-hospital mortality rate	89 (14.0)	68 (17.3)	21 (8.8)	8.5 (3.3; 13.7)
Length of stay (days)	7 (4; 11)	7 (4; 10)	8 (4; 13)	−1 (−2; 0)

Categorical variables are presented as *n* (%) and an estimated RD with 95% CI. Continuous variables are presented as medians (Q1; Q3) and analyzed by the HL estimation of location shift and 95% CI. HL, Hodges–Lehmann estimation; M3, M3 multimorbidity score. ‡Comorbidities follow the M3 index definitions. *Data censored due to rules of protection of Statistics Denmark. †For Anatomical Therapeutic Chemical classification and procedure codes, see Supplementary Table 1. **Defined by having a registered diabetes diagnoses (E10/E11) or a prescription of diabetes medication prior to hospitalization.

of infectious disease. Pneumonia (16%) and sepsis (13%) were more common than urinary tract infections (7%) (Table 3).

Subgroups

Thirty-nine percent (*n* = 132) of the patients with pure HHS with pH results available had an acidosis (pH <7.35) at the time of admission (Table 4). There was a significant difference in the distribution of sexes between the acidosis (44% female) and the nonacidosis group (32% female), but in both groups, there were still more men than women. Significantly fewer patients with pure HHS with acidosis had cerebrovascular disease and cancer (95% CI, −16.1%, −0.2% and −15.2%, −1.0%, respectively) compared with patients without acidosis. The use of diuretics and antihypertensives was significantly lower in the acidosis subgroup (95% CI, −23.6%, −2.3% and −22.3%, −1.1%, respectively), though, these still were the two most used drugs for both subgroups. More patients without acidosis (23%) had redeemed a prescription of antibiotics before hospital admission.

A total of 210 (65%) of the patients with pure HHS with baseline creatinine data available (*n* = 324) had AKI according to the KDIGO guidelines at the time of admission (Table 4) (25). There was only a significant difference in the moderate M3 score between patients with and without AKI.

Patients with pure HHS had a median glucose level of 48 mmol/L (Q1; Q3: 40; 60), and a median sodium level of 144 mmol/L (Q1; Q3: 139;151) (Supplementary Table 3). Median levels of lactate, potassium, C-reactive protein,

Table 2—Socioeconomic factors of patients with HHS (plasma glucose ≥33 mmol/L and osmolarity ≥320 mmol/L), stratified as pure HHS or combined HHS-DKA

	Total	Pure HHS	HHS-DKA	RD (95% CI)
Total, *n*	634	394	240	
Marital status				
Married	228 (36.0)	146 (37.1)	82 (34.2)	2.9 (−4.8; 10.6)
Divorced	140 (22.1)	87 (22.1)	53 (22.1)	0 (−6.7; 6.7)
Widow	115 (18.1)	85 (21.6)	30 (12.5)	9.1 (3.2; 14.9)
Unmarried or data missing	151 (23.8)	76 (19.3)	75 (31.3)	−12 (−19.0; −4.9)
Education level				
Primary or lower secondary	290 (45.7)	186 (47.2)	104 (43.3)	3.9 (−4.1; 11.9)
Upper secondary or postsecondary, nontertiary	220 (34.7)	127 (32.2)	93 (38.8)	−6.6 (−14.2; 1.2)
Short-cycle tertiary or above	97 (15.3)	62 (15.7)	35 (14.6)	1.1 (−4.6; 6.9)
No primary education or data missing	27 (4.3)	19 (4.8)	8 (3.3)	1.5 (−1.6; 4.6)
Housing type				
Living with others	292 (46.1)	173 (43.9)	119 (49.6)	−5.7 (−13.7; 2.3)
Living alone or data missing	342 (53.9)	221 (56.1)	121 (50.4)	5.7 (−2.3; 13.7)
Income quintile†				
First, or data missing	71 (11.2)	33 (8.4)	38 (15.8)	−7.4 (−12.8; −2.1)
Second	215 (33.9)	136 (34.5)	79 (32.9)	1.6 (−6.0; 9.2)
Third	212 (33.4)	142 (36.0)	70 (29.2)	6.8 (−0.6; 14.3)
Fourth	79 (12.5)	44 (11.2)	35 (14.6)	−3.4 (−8.9; 2.0)
Fifth	57 (9.0)	39 (9.9)	18 (7.5)	2.4 (−2.1; 6.8)

Data reported as *n* (%) except where indicated otherwise. RD, risk difference. †Income quintiles are based on the quintiles in the Danish population.

leukocytes, creatinine, and urea were elevated, whereas eGFR levels were lower, compared with reference levels (Supplementary Table 4) (>17,28). The median HbA_{1c} level at admission was 96 mmol/mol (Q1; Q3: 78;115), and the median HbA_{1c} prior to admission was 56 mmol/mol (Q1; Q3: 47;74). Missing HbA_{1c} results were common both during and before hospital admission (*n* = 262 and *n* = 193, respectively).

The acidosis subgroup had significantly higher levels of potassium, lactate, leukocytes, and creatinine, and lower eGFR compared with the subgroup without acidosis (Supplementary Table 3). The AKI subgroup had significantly higher levels of sodium, C-reactive protein, and leukocytes compared with the subgroup without AKI. In patients with AKI, pH levels were lower than in patients without AKI, but they still were within the normal reference level.

Table 3—Diagnostic groups and specific diagnoses patients received during hospitalization with HHS

Diagnosis	*n* (%; 95% CI)
Endocrinology (all)	545 (86.0; 83.3–88.7)
Hyperosmolality or hypernatremia	65 (10.3; 7.9–12.6)
Ketoacidosis	240 (37.9; 34.1–41.6)
Type 1 diabetes mellitus	167 (26.3; 22.9–29.8)
Type 2 diabetes mellitus	285 (45.0; 41.1–48.8)
Dehydration	41 (6.5; 4.5–8.4)
Infectious diseases (all)	222 (35.0; 31.3–38.7)
Sepsis	85 (13.4; 10.8–16.1)
Pneumonia	104 (16.4; 13.5–19.3)
UTI	47 (7.4; 5.4–9.5)
Cardiology and the circulatory system (all)	154 (24.3; 21.0–27.6)
AMI	15 (2.4; 1.2–3.5)
Heart failure	10 (1.6; 0.6–2.6)
Stroke	24 (3.8; 2.3–5.3)

AMI, acute myocardial infarction; UTI, urinary tract infection.

CONCLUSIONS

Knowledge of the incidence of HHS is scarce (4,7). Here, we describe the incidence and characteristics of all acutely admitted patients with HHS in Denmark during years 2016–2018. The condition is rare, with a total of 634 cases among the entire adult population in Denmark. The incidence rate of HHS was higher among individuals with type 1 diabetes (16.5 per 10,000 person-years) compared with type 2 diabetes (3.9 per 10,000 person-years). From the total HHS population, 33% did not have an established diabetes diagnosis prior to hospital admission, and their diabetes diagnosis debuted with HHS. For patients with pure HHS, the proportion of unknown diabetes at admission was higher (38%) than in the patients with combined HHS-DKA (26%). In comparison, another study identified 20% of study patients without a diabetes diagnosis before the presentation of HHS (29). Patients with type 1 diabetes are at risk for developing HHS or, more likely, a combination of HHS-DKA, because 39% of patients with HHS-DKA had type 1 diabetes. Benoit et al. (30) estimated that 10–12% of patients with HHS have type 1 diabetes. This highlights that HHS does not occur exclusively in people with type 2 diabetes, and the condition has a higher

Table 4—Patient characteristics of subgroups of acidosis and AKI in patients with pure HHS

	Acidosis* (Data missing, *n* = 53)		RD/HL estimation (95% CI)	AKI† (Data missing, *n* = 70)		RD/HL estimation (95% CI)
	Yes	No		Yes	No	
Total, *n* (%)	132 (38.7)	209 (61.3)		210 (64.8)	114 (35.2)	
Sex						
Female	43.9	32.1	11.8 (1.3; 22.5)	36.2	40.4	−4.2 (−15.3; 7.0)
Age (years)						
Median (Q1; Q3)	71 (61; 82)	73 (65; 82)	−2 (−5; 1)	74 (65; 83)	74 (64; 82)	1 (−2; 4)
M3						
Median (Q1; Q3)	0.4 (0.1; 1)	0.7 (0.1; 1.5)	−0.2 (−0.3; 0.0)	0.6 (0.3; 1.2)	1.1 (0.3; 1.9)	−0.4 (−0.6; 0.2)
0	22.0	21.1	0.9 (−3.5; 9.9)	14.8	9.6	5.2 (−2.0; 12.4)
0 to <1	53.8	38.8	15.0 (4.2; 25.8)	50.5	37.7	12.8 (1.6; 24.0)
≥1	24.2	40.2	−16.0 (−25.9; −6.1)	34.8	52.6	−17.8 (−29.0; −6.6)
Comorbidities‡						
Diabetes, uncomplicated	8.3	12.4	−4.1 (−10.6; 2.4)	§	§	
Diabetes, complicated	35.6	33.5	2.1 (−8.3; 12.5)	36.2	42.1	−5.9 (−17.1; 5.2)
Cerebrovascular disease	12.9	21.1	−8.2 (−16.1; −0.2)	19.0	23.7	−4.7 (−14.2; 4.8)
Chronic renal disease	§	§		6.2	13.2	−7.0 (−14.0; 0.0)
Cancer	9.1	17.2	−8.1 (−15.2; −1.0)	§	§	
Alcohol use disorders	§	§		§	§	
No. of medications						
Median (Q1; Q3)	10 (6; 13)	11 (7; 15)	−1 (−2; 0)	11.5 (8; 14)	12 (9; 17)	−1 (−2; 0)
Medications‖						
Metformin	24.2	34.0	−9.8 (−19.5; 0.0)	33.8	36.8	−3.0 (−14.0; 7.9)
Insulin	24.2	23.4	0.8 (−8.5; 10.1)	23.8	34.2	−10.4 (−7.9; 0.0)
Other antidiabetics	20.5	23.9	−3.4 (−12.5; 5.5)	§	§	
Diuretics	36.4	49.3	−12.9 (−23.6; −2.3)	46.7	51.8	−5.1 (−16.5; 6.3)
Antihypertensives	55.3	67.0	−11.7 (−22.3; −1.1)	67.6	67.5	0.1 (−10.6; 10.8)
Glucocorticoids	14.4	19.1	−4.7 (−12.8; 3.3)	§	§	
Benzodiazepines	17.4	14.8	2.6 (−5.5; 10.7)	15.2	21.1	−5.9 (−14.7; 3.1)
Antibiotics (2 weeks before admission)	14.4	22.5	−8.1 (−16.3; −0.2)	22.9	18.4	4.5 (−4.7; 13.5)

Categorical variables are presented as *n* (%) and an estimated RD with 95% CI. Continuous variables are presented as medians (Q1; Q3) and were analyzed by the HL estimation of location shift and 95% CI. HL, Hodges-Lehmann; M3, M3 multimorbidity score. *Acidosis: pH <7.35. †AKI is defined by the KDIGO guidelines: serum creatinine increase of 26.5 μmol/L from baseline or 1.5 times greater than baseline. ‡Comorbidities follow the M3 index definitions. §Data censored due to rules of protection of Statistics Denmark. ‖For Anatomical Therapeutic Chemical classification codes, see Supplementary Table 1.

incidence among patients with known type 1 diabetes. One-third of the patients debuted with diabetes when admitted with HHS, and 149 of these had pure HHS. It is expected that these might be diagnosed with type 2 diabetes.

The in-hospital mortality rate was 17% in patients with pure HHS and 9% in patients with HHS-DKA. Patients with pure HHS were older, had more comorbid conditions, and took more prescribed medications compared with patients with HHS-DKA. Other studies have suggested a mortality rate of 10–20% (1,31). Pasquel et al. (8) reported a lower mortality rate than we detected in patients with combined HHS-DKA (8%) and patients with pure HHS (5%).

For this study, we identified HHS patients solely based on the biochemical criteria of HHS within 6 h of an acute admission. In this registry-based study, it was not possible to access validated data on encephalopathy and clinical dehydration, which are important additional diagnostic criteria of HHS besides hyperglycemia and hyperosmolarity (5). Because data on ketone bodies from blood or urine samples are thus far not reported consistently to the national registries, we could not separate patients with or without ketosis. Instead, we identified patients with a DKA diagnosis during hospitalization and defined those as having a combined condition of HHS-DKA (38%). Patients with DKA can achieve extreme hyperglycemia and concurrently develop hyperosmolarity, though this patient group still remains rather unexplored (8). Patients with HHS-DKA were younger, had fewer comorbidities, more often had type 1 diabetes, which was treated with insulin. Opposingly, patients with pure HHS were more likely to have type 2 diabetes and prescriptions for metformin and other antidiabetic medications, although patients with type 1 diabetes and type 2 diabetes were present in both groups. Patients with pure HHS and acidosis were not excluded from this study, because we were not able to determine the etiology of the acidosis. The late disease progression and the expectation of delayed medical seeking behavior of patients with HHS are likely to increase the risk of acidosis, due to the pathophysiology of HHS whereby lactate levels increase and renal impairment increases (4).

Among the patients with pure HHS who did not receive a DKA diagnosis during hospitalization, 39% still had an acidosis. Those with pure HHS with acidosis had more abnormal blood results, with

high levels of potassium, lactate, leukocytes, and creatinine, and low levels of eGFR compared with patients with pure HHS without acidosis. This finding supports the importance of finding the underlying cause of the acidosis in patients with HHS, because the disease can present both with a combined condition of HHS-DKA and pure HHS with acidosis. In this study, 65% of the patients with pure HHS had AKI at hospital admission, but among these patients, few had chronic renal disease (6.2%). AKI is expected to develop in individuals with HHS, considering the pathophysiology of the condition, with osmotic diuresis and dehydration leading to a decline in glomerular filtration (4). Comparisons with other studies are limited by other definition criteria of AKI. One study defined AKI as a 0.5 mg/dL increase (corresponding to a 44 μmol/L increase) in the creatinine level during hospitalization for those patients admitted with creatinine <5 mg/dL (<442 μmol/L) (8). They found that 8% of the patients with HHS developed AKI. Other studies showed that patients with HHS had a degree of impairment in renal functions with increased levels of creatinine at admission (9,12). Acidosis and AKI often co-occurred; patients with AKI had significantly lower pH, and patients with acidosis had higher levels of creatinine.

The elevated level of HbA_{1c} at hospital admission and the increase in HbA_{1c} compared with the baseline HbA_{1c} level indicate that pure HHS may be facilitated by impaired glycemic control. Most patients presented with a plasma glucose level markedly greater than 33 mmol/L (the diagnostic criterion of HHS) but normal sodium levels. Hyperglycemia causes hyponatremia due to an osmotic shift of water from the intracellular space to the extracellular space, also known as translocational hyponatremia (32). Sodium will decrease by approximately 0.4 mmol/L for each 1 mmol/L increase in glucose above normal. When taking into account the sodium translocation caused by the high blood glucose level, the corrected sodium level for our pure HHS population should be perceived as elevated (33). However, the normal sodium level shown in this study could also be caused by osmotic diuresis (7).

HHS has been reported to develop over many days and frequently caused by precipitating factors (4,7). In this study, 17% of the HHS population had redeemed a prescription of antibiotics up to 14 days prior to hospital admission, indicating that these patients had been seeking medical attention before an HHS admission and received treatment for an infection. Thirty-five percent received a diagnosis of infectious disease during hospitalization, pneumonia and sepsis being the most frequent causes. This is in agreement with other studies that reported infections to be the most common precipitating cause of HHS, with pneumonia occurring in 40–60% of the patients (4).

Glucocorticoids and benzodiazepines were more frequently used by patients with pure HHS. This suggests that, in some cases, glucocorticoids and benzodiazepines may play a role as possible precipitating factors in the development of pure HHS. Another study found an association between the intake of benzodiazepines and development of HHS; benzodiazepines were also positively associated with death (34). Glucocorticoids induce diabetes mellitus by increasing insulin resistance and can also exacerbate hyperglycemia in patients with diabetes (35,36).

Strengths and Limitations

Epidemiological research in HHS is challenged by its low incidence, but the comprehensive Danish national registries allowed us to identify a relative large study population and thereby characterize phenotypes and estimate the incidence rate of HHS among individuals with type 1 and 2 diabetes.

In Denmark, public health care services are universal and paid for by taxes, thus Danish citizens have access to health services regardless of income or social status (13). Using data from national registries, it was possible to identify HHS cases for this study by assessing the glucose and hyperosmolarity criteria of HHS. We evaluated blood samples from 2 h before until 6 h after admission, which allowed us to take possible delays at emergency departments into account. Previous studies have stated that evaluating the diagnosis of HHS solely as hyperosmolarity and hyperglycemia is insufficient, but available data sources did not allow for clinical data of the patients nor data on ketone bodies (5,7). Additional diagnostic criteria of HHS that are based on pH values and bicarbonate levels are imprecise because of the various possible causes of acidosis other than ketosis. Identifying patients with HHS by biomarkers can limit selection bias from misregistration. However, this study might be biased due to misclassification of patients with pure HHS and HHS-DKA, because of missing data on ketone bodies and bicarbonate levels. These data could be used to confirm a diagnosis of potential DKA among patients with pure HHS.

This study, therefore, describes the characteristics and incidence of patients on a spectrum of acute hyperglycemic states where the pathophysiology and management of the conditions overlap (2,11,37). If blood or urine ketone bodies data were to be reported consistently to RLRR, it would allow for the examination of patients with HHS in even more detail without relying on clinicians registering a correct diagnosis. Validation studies performed on the DNPR of diabetes diagnosis codes conclude there is generally high validity with positive predictive values from 64–96.3%, although a low reporting of HHS diagnosis codes in this study indicates poor sensitivity for this subgroup (13).

Perspective

HHS is a rare, but severe, disease with a high mortality rate. This study confirms some findings from other studies (2,4,7) and adds new knowledge on the incidence of HHS, mortality, and subgroups of patients with acidosis and AKI. Characteristics of HHS are important to help clinicians realize and act upon this acute condition so that timely and efficient treatment can be initiated at hospital arrival. Studies are needed to establish significant risk factors and prognosis of HHS.

In summary, 634 adult individuals were acutely admitted to Danish hospitals during 2016–2018 with a condition of HHS based on glucose and sodium concentrations in plasma at admission. The incidence rate of HHS among patients with a known type 1 (n = 24,196 individuals) and type 2 (n = 251,357 individuals) diabetes diagnosis was 16.5 and 3.9 per 10,000 person-years, respectively. One-third of the individuals were debuting with diabetes when admitted with HHS. Individuals who received a DKA diagnosis during hospitalization were categorized with a combined condition of HHS-DKA. The in-hospital

mortality rate among patients with pure HHS was 17%.

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