אפיון תמותה באשפוז בשתי קבוצות אוכלוסייה,עם אבחנת HHS וקבוצה שניה עם אבחנת DKA

Predictors of in-hospital mortality in Hyperosmolar Hyperglycemic State (HHS) and Diabetic Ketoacidosis (DKA) patients

**Introduction:**

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) represent two extremes in the spectrum of decompensated diabetes. DKA and HHS remain significant causes of morbidity and mortality among diabetic patients, despite well-developed diagnostic criteria and treatment protocols. The rate of hospital admissions for HHS is lower than that of DKA and accounts for less than 1% of all primary diabetic admissions [1].

DKA consists of the biochemical triad of [hyperglycemia](https://www-sciencedirect-com.ezproxy.bgu.ac.il/topics/medicine-and-dentistry/hyperglycemia), ketonemia, and [metabolic acidosis](https://www-sciencedirect-com.ezproxy.bgu.ac.il/topics/medicine-and-dentistry/metabolic-acidosis) resulting from absolute or relative [insulin deficiency](https://www-sciencedirect-com.ezproxy.bgu.ac.il/topics/medicine-and-dentistry/insulin-deficiency) together with an increase in insulin [counterregulatory hormones](https://www-sciencedirect-com.ezproxy.bgu.ac.il/topics/medicine-and-dentistry/counterregulatory-hormones), such as glucagon, [catecholamines](https://www-sciencedirect-com.ezproxy.bgu.ac.il/topics/medicine-and-dentistry/catecholamine), [cortisol](https://www-sciencedirect-com.ezproxy.bgu.ac.il/topics/medicine-and-dentistry/hydrocortisone), and growth hormones [2].

HHS is most prevalent in individuals over 65 years old [3]. HHS evolves over several days to weeks, and the most common symptom is an altered mental status. In general, glucose levels are higher in HHS than in DKA. Patients with HHS often present with severe dehydration due to the chronic nature of hyperglycemia [4].

The factors responsible for the relative absence of ketogenesis in HHS are not fully understood. Patient studies have shown that HHS is associated with higher hepatic and circulating insulin concentrations and lower glucagon levels than patients with ketoacidosis. Lower glucagon levels and, therefore, a higher insulin/glucagon ratio minimize ketogenesis [5].

HHS is the initial manifestation of diabetes mellitus in 7–17% of patients. However, this complication is more often reported in patients previously diagnosed with diabetes mellitus [6]. Precipitating factors both for DKA and HHS are infection and discontinuation of, or inadequate, insulin therapy. Compromised water intake due to underlying medical conditions, particularly in older patients, can promote severe dehydration and HHS development. Myocardial infarction, cerebrovascular accidents, sepsis, and inadequate treatment are also common reasons for HHS development [7].

Up to 20% of adults with diabetes who arrive at the emergency department (ED) are diagnosed with DKA. HHS is less likely to be found in diabetes ED patients, and there is no U.S. national data for HHS incidence. A recent study reported a 55% increase in the rate of DKA hospitalizations from 2009 to 2014. However, questions remain about national HHS trends and DKA and HHS trends in ED settings [8]. The mortality rate for patients with HHS is 10-20%, approximately ten times higher than that for DKA [5]. Combined DKA-HHS is associated with higher mortality compared with DKA or HHS alone. Severe hypokalemia and severe hypoglycemia are associated with higher hospital mortality in patients with hyperglycemic crises [11].

There is increasing recognition that a large percentage of patients admitted with diabetic ketoacidosis are at high risk for other life-threatening events, mortality, and hospital readmission [10]. Developing a method that considers individual risk factors and uses a scoring system based on objective predictors of recurrent DKA and HHS admission could be of tremendous value in identifying patients with high readmission risks. Patient identification would allow interventions to be targeted more effectively to reduce readmission rates, associated morbidity, and mortality [9].

In this retrospective study, we examined records of patients diagnosed with either DKA or HHS for mortality, length of hospital stays, and ICU admission rates. We focused on the clinical and treatment options in the different outcomes. The findings presented here are inconclusive.

**Research hypothesis:**

Our research hypothesis is that patients with HHS have a higher mortality risk than patients with DKA, both in the long and short term.

**Research goals:**

**Primary Outcome:** Compare the factors associated with in-hospital mortality in DKA and HHS patients.

**Secondary outcomes:** Analyze 30-day and one-year mortality, hospital stay length, ICU admission rate, recurrent hospitalization, and a composite of the outcomes in DKA vs. HHS patients.

**Research methods:**

1. **Research type:** This is a retrospective cohort study. We will compare two groups of patients, diagnosed with either HHS or DKA, according to the clinical characteristics and outcomes. The primary outcome will be in-hospital mortality. The secondary outcomes will be 30-day and one-year mortality, hospital stay length, ICU admission rate, recurrent hospitalization, and a composite of the outcomes mentioned above. We will use discharge diagnoses (ICD-9) to identify subjects with DKA (code 250.1) and HHS (code 250.2).
2. **Research population:** 214 older adult patients with HHS or DKA hospitalized in internal departments and the ICU, from January 2015 to December 2019 at the Soroka University Medical Center, the only tertiary hospital in the southern region of Israel (Negev).
3. **Inclusion criteria:** Patients over 60 years old hospitalized in Soroka Medical Center’s Internal Medicine units with an ICD-9 diagnosis of HHS or DKA. Data was taken from the hospital’s computerized database.
4. **Exclusion criteria:** Patients presenting with a hyperglycemic state without HHS or DKA. Patients younger than 60 years old with HHS or DKA were also excluded from this study since HHS is a rare diagnosis in young patients.
5. **Power calculation:** Based on a previous epidemiological study in the Clinical and Epidemiological Characteristics of Diabetic Ketoacidosis in Older Adults by the "WinPepi" application. Since we estimated 16.7% in-hospital mortality, in order to achieve p < 0.05 and statistical power > 80%, we need to include 214 patients [12].

**Statistical analysis:**

1. **Dependent variables:** Patient's hospitalization and mortality with DKA or HHS diagnosis. DKA will be defined according to the American Diabetic Association (ADA) criteria. Patients will be divided into groups according to DKA severity (mild, moderate, and severe) using ADA classifications including:
   1. Plasma glucose (>250 mg/dl for all DKA groups)
   2. Arterial pH (mild: pH 7.25-7.30, moderate: pH 7.00-7.24, severe: pH < 7.0)
   3. Serum bicarbonate levels (mild: 15-18 mEq/l, moderate: 10-15 mEq/l, severe: < 10 mEq/l).
   4. Serum or urine ketones (positive for all groups)
   5. Anion gap (mild: 10-12, moderate and severe: >12)
   6. Alteration in sensoria or mental status (mild: altered, moderate: altered/drowsy, severe: stupor/coma) [1]

For the HHS definition, we will use the ADA criteria including:

1. Plasma glucose > 600 mg/dl (frequently exceeding 1000 mg/dL)
2. pH ≥ 7.3
3. Serum bicarbonate ≥ 18 meq/l
4. Low levels or absence of ketones in the urine and serum
5. Serum beta-hydroxybutyrate < 0.6 mmol/l
6. Calculated serum osmolality > 320 mOsm/kg (may reach 380 mOsm/kg)
7. Variable anion gaps.
8. Severe alteration in sensoria or mental obtundation exhibited by a stupor or coma [1].
9. **Independent variables:**
   1. Demographic features: age, gender, race, bedridden, belonging group, risk factors.
   2. Clinical co-morbidity features will be measured using the Charlson co-morbidity index (CIA) and include diabetic mellitus with organ damage, chronic ischemic heart disease, peripheral vascular disease, congestive heart disease, chronic kidney disease, dementia, alcohol abuse, abdominal pain, and neurological symptoms.
   3. Biochemical and laboratory tests upon presentation, including blood pressure, pulse, body temperature, blood count, glucose, urea, creatinine, pH, electrolytes, serum osmolality, and positive ketones in blood/urine.
   4. Etiology for DKA or HHS, including infection, insulin omission, MI, pump dysfunction, acute pancreatitis, and drugs affected carbohydrate metabolism.
   5. Hospitalization characteristics include recurrent hospitalization, duration, ICU admission, and mortality within 30 days or one year.
   6. Medication characteristics of study population: long or short-acting insulin during follow-up time and PO anti-diabetic medication.
10. **Statistical methods****:** Analysis will compare dependent and background characteristics between the two study groups. The results will be presented as means ± standard deviation or as medians and IQR-interquartile ranges (25th; 75th percentile), for continuous variables and as the percentage of the total patient for categorical data. A Chi-square test will be used for comparing categorical variables. A t-test will compare continuous variables with normal distributions, and a Mann-Whitney test can analyze variance by ranks, to compare variables with a non-normal distribution. We will conduct multivariate logistic analysis for the primary and secondary outcomes. A two-sided p-value < 0.05 will be considered statistically significant. Information will be collected from "Camilion" and the data will be organized in Excel. Statistical analysis will be performed using SPSS software (version 25.0). At the end of the study, the final report will be prepared as a research paper ready for publication.

**Research Limitations:**

This research has several limitations. First, the data collected includes only DKA or HHS complications. Since many diseases can be diagnosed in patients over 60 years old, it will be challenging to determine whether DKA or HHS is the primary health concern. However, focusing on hospitalization emphasizes the more severe and resource-demanding morbidities. The second limitation, which holds true in all retrospective studies, is the inability to pinpoint a causative difference between DKA and HHS outcomes. Thirdly, the research takes place at Soroka University Medical Center, the only hospital in the southern region of Israel (Negev), serving the entire population in this region. Though the study is based on the non-selective population of the Negev, it may represent both average Israeli and other countries’ populations.

**Student work schedule:**

1. Prepare an extensive up-to-date review of the literature and write a research proposal and paper - January 2021
2. Collect data from the hospital's archives and perform statistical analysis of the results – March 2021
3. Summarize the research results – May 2021
4. Write the research paper – June 2021