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 important 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 the rate for diabetic ketoacidosis (DKA) and accounts for less than 1 percent 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) in the presence of an increase in [counterregulatory hormones](https://www-sciencedirect-com.ezproxy.bgu.ac.il/topics/medicine-and-dentistry/counterregulatory-hormones) (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 hormone) [2].

HHS most commonly develops in individuals older than 65 years [3]. The evolution of HHS is over several days to weeks, and the most common presentation is altered mental status. In general, glucose levels in HHS are higher than the ones for DKA. Patients with HHS present with severe dehydration due to the chronic nature of hyperglycemia [4].

The mortality rate for patients with HHS is between 10 and 20 percent, which is approximately 10 times higher than that for DKA [5].

 The factors responsible for the relative absence of ketogenesis in HHS are incompletely understood. Studies in humans have demonstrated higher hepatic and circulating insulin concentration as well as lower glucagon are present in HHS compared with patients with ketoacidosis. Less marked elevation of glucagon levels and therefore a higher insulin/glucagon ratio minimizes ketogenesis [5].

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

Up to 20% of adults present in Emergency Department at diabetes diagnosis in DKA. HHS is less likely to be found at diabetes diagnosis. No U.S. national data exist for HHS incidence. A recent study reported a 55% increase in the rate of DKA hospitalizations from 2009 to 2014. However, questions remain about trends in HHS as well as DKA and HHS trends in emergency department (ED) settings [8].

Consideration of individual risk factors and the use of a scoring system based on objective predictors of recurrent DKA, and HHS admission could be of value in helping identify patients with high readmission risk, allowing interventions to be targeted most effectively to reduce readmission rates, associated morbidity, and mortality [9]. There is increasing recognition that a large percentage of patients who are admitted with diabetic ketoacidosis are a group at high risk for other life-threatening events, mortality, and hospital readmission [10].

Combined DKA-HHS is associated with higher mortality compared with isolated DKA or HHS. Severe hypokalemia and severe hypoglycemia are associated with higher hospital mortality in patients with hyperglycemic crises [11].

In this study we chose a diagnosis of DKA or HHS, to assessmortality rate, length of hospital stays and rate of admission to ICU. We are focusing on the clinical and treatments options according to the different outcome. These findings are inconclusive and have not been studied in similar populations to ours.

**Research hypothesis:**

Our research hypothesis is that patients with HHS have higher risk for mortality rate for the long and the short term more than patients with DKA.

 **Research goals:**

**Primary Outcome:** To compere the factors that associated with in hospital mortality in DKA VS HHS patients.

**Secondary outcomes:**

To analyze 30-day mortality, one-year mortality, length of hospital stays, rate of admission to ICU, 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 with HHS and DKA according to the clinical characteristics and outcomes. The primary outcome will be in-hospital mortality. The secondary outcomes will be 30-day mortality, one-year mortality, length of hospital state, rate of admission to ICU, 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 and DKA hospitalized in internal departments and ICU between January 2015 until December 2019 at the Soroka University Medical Center the sole tertiary hospital in the southern region of Israel (Negev).
3. **Inclusion criteria:** Patients over 60 years old, who hospitalized in Soroka units of Internal Medicine with ICD-9 diagnoses in HHS and DKA from the hospital computerized database.
4. **Exclusion criteria:** Hyperglycemic state without the diagnosis of HHS or DKA. Also, patients younger than 60 years old with HHS or DKA. HHS is a rare diagnosis in young patients so they will be excluded from the study.
5. **Power calculation:** Based on previously epidemiological study in the Clinical and Epidemiological Characteristics of Diabetic Ketoacidosis in Older Adults by "Win- Pepi" application. We estimated 16.7% in hospital mortality to achieve p< 0.05 and statistical power > 80%, we need to include 214 patients [12].

**Statistical analysis:**

1. **Dependent variable:** Patient's hospitalization and mortality with DKA or HHS diagnosis. DKA will be define according to the criteria of the American Diabetic Association (ADA). Patients will be allocated to groups according to severity of DKA (mild, moderate and severe) using ADA classifications included: plasma glucose (more 250 mg/dl for all groups of DKA), arterial pH (7.25-7.30- for mild DKA, 7.00-7.24 for moderate DKA and less than 7.0 for severe DKA), serum bicarbonate levels (15-18 mEq/l for mild DKA, 10-15 mEq/l for moderate DKA and less than 10 mEq/l for severe DKA), serum or urine ketones (positive for all groups of DKA), anion gap (more than 10 for mild DKA, and more than 12 for moderate and severe DKA) and alteration in sensoria or mental status (alter for mild DKA, alter/drowsy for moderate DKA and stupor/coma for severe DKA) [1].

For HHS definition we will use the criteria of the ADA included: plasma glucose more 600 mg/dl (frequently exceeds 1000 mg/dL), pH 7.3 and more, serum bicarbonate 18 meq/l and more, urine and serum ketones- small or not, or serum beta-hydroxybutyrate [N less 0.6 mmol/l] less 0.6 mmol/l, calculated serum osmolality more than 320 mosm/kg (may reach 380 mosmol/kg), anion gap- variable, alteration in sensoria or mental obtundation- stupor/coma [1].

1. **Independent variable:** Demographic features: age, gender, origin, bedridden, belonging group, risk factors. Clinical comorbidity features measured by Charlson co morbidity index (CIA), diabetic mellitus with organ damage, chronic ischemic heart disease, peripheral vascular disease, congestive heart disease, chronic kidney disease, dementia, alcohol user, abdominal pain, neurologic symptoms. Biochemical and laboratory features on presentation: blood pressure, pulse, temperature, blood count, glucose, urea, creatinine, PH. Electrolytes, serum osmolality, positive ketones blood/ urine. Etiology for DKA or HHS such as infection, insulin omission, MI, pump dysfunction, acute pancreatitis, drugs affected carbohydrate metabolism. Hospitalization characteristics such as recurrent in hospitalization, duration, admission to ICU, mortality within 30 days or 1 year. Medication characteristics of study population: long or short acting insulin during time, PO anti diabetic medication.
2. **Statistical methods****:** Analysis will be performed to compare dependent and background characteristics between the two study groups. The results are presented as the mean ± standard deviation or as median and IQR- interquartile range (25th; 75th percentile) for continuous variables and as the percentage of total patient for categorical data. Chi-square test will be used for comparison of the categorical variables. T-test will be used to compare data of continuous variables with normal distribution and Mann-Whitney test for analysis of variance by ranks will be used to compare data of variables with abnormal distribution. We will conduct multivariate logistic analysis for the primary and secondary outcomes. A two-sided p-value<0.05 will be considered as statistically significant. The student will collect the information from " Camilion ". The data will be organized in Excel. The statistical analysis will be performed with SPSS software (version 25.0) by the student. In the end of the analysis, the student will author the final report, hopefully prepared as a research paper ready for publication.

**Research Limitations:**

This research has several limitations. First, data is collected only for DKA or HHS complication. Since many diseases can be diagnosed in patients older than 60 years old, it would be difficult to determine if DKA or HHS are the main problems. However, focusing on hospitalization emphasizes the more severe and resource-demanding morbidities.

Second, stems from the retrospective type of the research, which cannot point to a causative difference between DKA and HHS outcomes.

Third, if the research takes place at Soroka University Medical Center, the sole hospital in the southern region of Israel (Negev), serving the entire population in this region. Though the study is based on non-selective population of the Negev, it may represent both average Israeli and variety of countries populations.

**Student’s work and schedule:**

1. Preparing an extensive up-to-date review of the literature and writing a research proposal and a research paper- January 2021
2. Data collection from the hospital's archives, processing the information statistical analysis of the results– March 2021.
3. Summarize the research results – May 2021.
4. Writing the research paper. – June 2021