Protocol

TITLE:
Starvation in the Treatment of Diabetic Ketoacidosis: Is there enough evidence to support this practice?

INVESTIGATORS:
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Abstract/Project Summary
Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are common, but serious metabolic disorders are often encountered in intensive care. In the intensive care setting, it is common to withhold food from patients during treatment of DKA. However, there is no evidence or current literature supporting this practice. The following proposed research investigates the initiation of an early diet versus withholding food during the treatment of diabetic ketoacidosis.

OBJECTIVE:
To investigate the effect of initiating an early diet in the management of diabetic ketoacidosis

INTRODUCTION / BACKGROUND / SIGNIFICANCE:
Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are common, but serious metabolic disorders are often encountered in intensive care.(1) These disease states occur due to an elevated blood glucose and a lack of insulin. DKA is associated with over 500,000 hospitalization days per year with an estimated cost of 2.4 billion USD. (2) Due to this prevalence and estimated costs, understanding the proper management of DKA is essential in the practice of critical care medicine.

Current guidelines by the American Diabetes Association include treatment with insulin, intravenous fluids, and electrolyte management. However, there is no current guidance on when to initiate feeding in the management of DKA. (2) It is common for hospital protocols and current practice to keep patients NPO (nothing by mouth) during the treatment of DKA. This is not currently backed by any evidence. In fact, an initial retrospective study has suggested that early feeding within 24 hours of hospitalization leads to shorter MICU and hospital durations without increasing rates of complications.(3) However, there have not been further investigations into this practice.

Lack of literature on this topic has led to a common practice that is not substantiated by evidence. The literature that is available for this topic is limited to a retrospective observational study, thus confounders are not controlled for. This study aims to investigate dietary management of DKA through a prospective, randomized design, which is the gold standard in

investigating intervention efficacy. Our goal in this study is provide an evidentiary standard in the dietary management in patients with DKA.

HYPOTHESIS:
Early feeding in the management of DKA decreases duration of DKA and length of stay in the medical intensive care unit.

METHODS:
Using electronic medical records from University Medical Center (UMC), we will identify patients admitted to the medical intensive care unit with an ICD-10 diagnosis code of diabetic keto acidosis who meet the following commonly accepted criteria: blood glucose greater than 250 mg/dL, arterial pH less than 7.3, serum bicarbonate less than 15 mEq/L, and the presence of ketonemia or ketonuria. (4)

After consent is obtained, participants will be randomized 1:1 to one of two arms: a control arm and a treatment arm. The current protocol for treatment of DKA in the UMC MICU includes keeping all patients N.P.O until their anion gap is less than 12 on two consecutive metabolic panels. At the time of the second anion gap being less than 12, a non-standardized diet is ordered for the patient. Participants in the control arm will be treated per this routine protocol. ~~the routine protocol of being kept N.P.O. until their anion gap closes (anion gap and closed anion gap defined below).~~ Participants in the treatment arm will be initiated on a clear liquid diet on day 1 of medical ICU admission. Diet will be progressed on day 2 to full liquid diet or diabetic diet as patient tolerates based on which diet the patient would prefer.

Data will be obtained per the data sheet.

Type of study:
Prospective, randomized, controlled trial.

Subjects/Recruitment:
To determine which patients are eligible to participate in the study, we will identify patients admitted to the medical intensive care unit at the University Medical Center with the following criteria on admission lab work done as standard of care: blood glucose greater than 250 mg/dL, arterial pH less than 7.3, serum bicarbonate less than 15 mEq/L, and the presence of ketonemia or ketonuria.

Subjects will then be asked to participate in the study and sign a consent form if agreeable.

We aim to recruit at least 88 participants based on statistical significance with a maximum recruitment of 1500 participants.

Inclusion criteria:
1. Males and females with the diagnosis of diabetic ketoacidosis (defined as blood glucose greater than 250 mg/dL, arterial pH less than 7.3, serum bicarbonate less than 15 mEq/L, and the presence of ketonemia or ketonuria)
2. Age between 18-89
3. Admission to the Medical Intensive Care Unit

4. Able to provide informed consent

Exclusion criteria:

1. Pregnant and breast-feeding women
2. Institutionalized patients or prisoners
3. Patients unable to eat by mouth, including intubation, presence of any tube used for enteral feeding (nasogastric tube, orogastric tube, PEG tube, etc.), medical conditions requiring parenteral feeding, and a history of a medical condition that prevented oral intake prior to admission, including achalasia, esophageal cancer, stroke with residual deficits preventing oral intake, amyotrophic lateral sclerosis, or head and neck trauma.

Site of study: University Medical Center Hospital and Texas Tech University Health Sciences Center, Lubbock, TX.

Design:
This study will be a prospective, randomized study in the UMC Medical Intensive Care Unit. It will measure the effect of early dietary intervention in patients in DKA, including days until resolution of DKA, length of stay in the MICU, and length of stay in the hospital. Intervention includes initiating a diet on hospital day 1. Participants will be followed throughout their hospitalization until discharge.

Roles of subjects: See appendix on page 5.

Materials, instruments or measurements: Electronic medical records, biostatics, lab values, including hemoglobin A1C, complete blood count, complete metabolic panel, arterial blood gas, ketone level, serum osmolarity, lipid panel, and urinalysis, Charlson Comorbidity Index, and APACHE II scores.

Data Sheet: See attached**.**

Outcomes: Primary outcomes: days until resolution of DKA (defined as a closed anion gap. Adjusted Anion Gap defined as (Blood Sodium – Blood Chloride – Blood Bicarbonate) + 0.25 x ((normal albumin (4.0)) x (observed albumin)); Elevated Anion Gap is >12) and length of stay in the medical intensive care unit (in days). Secondary outcomes: length of stay in the hospital (in days) and mortality.

Independent Variables: Age, biological sex, race, insurance, height, weight, type of diabetes

Possible Confounders: DKA Severity, initial creatinine level, evidence of infection, elevated Charlson Comorbidity Index or APACHE II score

Analysis: This will be a prospective study with a biostatistician consulted. If this study has insufficient subjects, it will be sent to a biostatistician for design analysis.

All data management and analyses will be conducted using STATA statistical software version 13.0. For all hypothesis testing, statistical significance will be determined at an alpha level of 0.05.

We will examine the distribution of variables by conducting descriptive analysis. This will include frequency and percentage for categorical variables and mean and standard deviation for continuous variables. Normality of the continuous outcomes will be assessed using tests of normality. This will be followed by bivariate analysis of the exposure (early feeding) and each of the outcomes (days until DKA resolution, ICU length of stay, hospital length of stay, and mortality) as well as with each of the possible confounders using chi-square tests for categorical outcomes and independent t-tests for continuous outcomes. The association between the outcomes and each of the possible confounders will also be assessed using similar methods.

To control for potential confounding, multivariable regression models will be used to estimate the effect of early feeding on each outcome, adjusting for the possible confounders. Factors associated with both the outcomes and the exposure (p-value<0.2) will be controlled for in the regression analyses. Unadjusted and adjusted odds ratios (ORs) and their 95% confidence intervals will be estimated by logistic regression (outcome: mortality) adjusting for the possible confounders. While unadjusted and adjusted mean differences and their 95% CI will be estimated by Poisson or negative binomial regression (outcomes: days until DKA resolution, ICU length of stay, hospital length of stay) adjusting for the possible confounders.

Justification for Sample size: We conducted power analysis using G*Power software with an alpha level of 0.05 and power=0.8. The effect size included was 0.18 based on previous literature. A sample size of 88 patients was determined necessary to achieve statistical significance.

Risks: Risks can include hyperglycemia and longer duration of DKA to patients in the diet group. To minimize this risk, blood glucose will be routinely monitored on an hourly basis, as is the standard in typical DKA protocol. Additional risk includes loss of confidentiality. To minimize this risk, all subjects will be represented by a study ID number on the data collection sheet.

Benefits: Participants receiving a diet might benefit in comfort if they are able to eat sooner. While all subjects may not directly benefit, this study aims to benefit the general population by establishing evidence-based data regarding when to initiate a diet in the management of DKA. This data allows providers to provide better care to patients in DKA in an evidentiary manner.

Confidentiality: All data collected will be entered into a password protected, TTUHSC computer or in TTUHSC Box, which is HIPAA compliant per TTUHSC IT. Study documents will be kept at least 3 years after IRB closure, and then destroyed.

Monitoring Plan:
To ensure compliance with the study protocol, GCP guidelines, and TTUHSC Human Research Protection Program research policies and procedures during the conduct of the study, as well as quality data, a monitor in the Clinical Research Institute will conduct the monitoring of the study. The first monitoring visit will be conducted within two weeks after the first subject has been enrolled into the study. The succeeding monitoring visits will be scheduled periodically, but no less than every 2 months when there is an active study participant, at a mutually agreed timeframe by the PI and study monitor. All data collected will be 100% source document verified. The study monitor may inspect and audit all study documents, i.e. data collection forms, and medical records within the applicable confidentiality regulations.

Reimbursement: Participants will not be paid.

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Acknowledgments: Clinical Research Institute at Texas Tech University Health Sciences Center

References:

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3. Lipatov K, Kurian KK, Shaver C, White HD, Ghamande S, Arroliga AC, et al. Early vs late oral nutrition in patients with diabetic ketoacidosis admitted to a medical intensive care unit. World J Diabetes. 2019;10(1):57-62. doi: 10.4239/wjd.v10.i1.57. PubMed PMID: 30697371; PubMed Central PMCID: PMC6347656.
4. Lizzo JM GA, Gupta V. Adult Diabetic Ketoacidosis StatPearls: StatPearls Publishing; 2023 [updated 2022 Jul 122023 Mar 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560723/.

Appendix:

Roles of Subject:

Day of Admission to MICU:

- Informed consent will be obtained to participate in the study
- Subjects will be randomized to the control group versus the intervention group.
- Data collected at this time includes age, biological sex, race, insurance, height, weight, type of diabetes.
- Collect data on the results of vital signs, urinalysis, hemoglobin A1C, complete metabolic panel, including albumin and electrolytes, arterial blood gas, ketone level, serum osmolarity, lipid panel, and a complete blood count. Collect Charlson co-morbidity score and the APACHE II score on admission to document the overall health status of each participant.

Subsequent Days in MICU

- Blood will be collected daily, per the normal standard of care in the intensive care unit. This will be sent for a complete blood count and complete metabolic panel, including albumin and electrolytes, and results collected for the study. The APACHE II score will be monitored.
- During hospitalization, depending on which group patients are randomized to, patients will be given a diet on hospital day 1 or a diet once the anion gap has closed on two complete metabolic panels as per the current DKA protocol

Discharge Day from MICU

- Data will be collected including total hours in DKA, total days in the MICU, total days in the hospital, and if the patient died because of DKA

Discharge Day from the Hospital

- Data will be collected including total days in the hospital and mortality data