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Iatrogenic Complications Of Diabetes Mellitus: An Examination Of Hospital-Acquired Diabetic Ketoacidosis And Severe Outpatient Hypoglycemia

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Iatrogenic Complications of Diabetes Mellitus: An Examination of Hospital-Acquired Diabetic Ketoacidosis and Severe Outpatient Hypoglycemia

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Abstract

Patients with diabetes mellitus are at risk for two acute metabolic complications: severe hyperglycemia and hypoglycemia. These acute complications are costly and associated with significant morbidity and mortality, but are preventable with delivery of high-quality care. The purpose of this work is to focus on a subset of these complications which are iatrogenic, i.e., caused by medical treatment. Hospital-acquired diabetic ketoacidosis (DKA) is an iatrogenic complication as it occurs when a patient with known diabetes experiences DKA while hospitalized for other reasons. Hypoglycemia is an adverse effect of treatment and thus, by definition, all hypoglycemia resulting from the use of glucose-lowering medications in the outpatient setting is iatrogenic. Reducing the occurrence of these iatrogenic complications of diabetes can improve patient health outcomes and reduce costs. However, prevention requires targeted interventions based on a detailed understanding of precipitating factors. In order to address these iatrogenic complications, we performed two analyses to examine factors driving their occurrence.

The first analysis is a retrospective chart review of hospitalized adults with diabetes who developed DKA during a hospital admission at a single local hospital. Twenty-seven patients were included in this analysis over 5 years. The patients were predominantly White (70.4%) and middle-aged (average age 53.4 years). Most had a documented diagnosis of type 1 diabetes (59.3%) and all but 1 patient were on insulin at home. At the time of DKA, 51.9% were on medicine or neurology services, 33.3% on surgery or ob/gyn, and 14.8% on podiatry. Using common cause analysis, the most prevalent reason for DKA was a problem with insulin dosing, including missed doses of insulin (n=7, 25.9%) and insulin dose reductions of 50% or greater (n=8, 29.6%). The remaining cases were caused by steroids (n=4, 13.8%), infection (n=4, 13.8%), and acute stress associated with surgery or shock (n=4, 13.8%).

The second analysis is a retrospective analysis of factors that mediate severe hypoglycemia requiring an ED visit or hospitalization in an insured population in California. A total of 305,310 adults with diabetes were included in this analysis. Among the full cohort, the rate of severe hypoglycemia requiring an ED visit or hospitalization was 7.4 per 1,000 person-years, but this varied significantly by race. Among Black vs White patients, the rates were 13.64 vs 9.27 per 1,000 person-years, respectively. Given the significance of these racial disparities, factors mediating these disparities were further explored. Differences in insulin use by race were not significant, and racial disparities persisted among patients on insulin. Rates of hypoglycemia among Black vs White patients on insulin were 34.72 [95% CI 30.09, 38.87] vs 27.14 [25.38, 28.98] per 1000 person-years, respectively. Factors mediating the racial differences in ED visits and hospitalizations for severe hypoglycemia were investigated using literature review and clinical expert input and a directed acyclic graph (DAG) was created to depict the causal relationships of the proposed mediator variables. Analytic work for this project is ongoing. To analyze our DAG, we plan to assess the causal impact of each proposed mediator variable by using inverse probability weighting to estimate counterfactual disparity measures.

Together, these projects demonstrate the importance of thorough analysis of factors that mediate and precipitate iatrogenic complications. In the case of hospital-acquired DKA, interventions targeting inappropriate insulin dosing among hospitalized

patients with diabetes could potentially prevent over 50% of cases. For severe outpatient hypoglycemia, quantifying the causal impact of each proposed mediator variable in the DAG will reveal high-yield opportunities to address disparities in hypoglycemia. Ongoing work on both projects continues to improve understanding of these problems and will ultimately facilitate implementation of targeted prevention strategies.

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Introduction

Diabetes and its Complications

More than 10% of US adults have diabetes mellitus.[1] People with diabetes are more than three times as likely to be hospitalized as people without diabetes, and they make up 25-30% of all hospitalized adults in the US.[1-5] In 2014 alone, this resulted in 7.4 million discharges from US hospitals with diabetes listed as a diagnosis.[6] In addition to more frequent admissions and readmissions, patients with diabetes stay in the hospital longer.[7,8] As a result, costs associated with diabetes in the US are substantial. In 2017, diabetes cost the US $327 billion, including $237 billion in direct medical expenses.[9] The burden of diabetes on the health and economy of the US continues to increase year after year as the US population with diabetes increases.[9] A large proportion of the morbidity, mortality, and cost associated with diabetes is attributable to diabetic complications, which can be long-term or acute.[9,10]

Most long-term complications of diabetes result from chronic elevations in blood glucose levels due to a relative or absolute insulin deficiency. Chronic hyperglycemia can cause accumulation of advanced-glycation end products and reactive oxygen species as well as activation of inflammatory pathways.[11,12] These processes cause tissue damage and result in peripheral neuropathy, retinopathy, nephropathy, micro and macrovascular disease. Over 55% of US patients with diabetes are affected by at least one of these chronic diabetic complications and 7.6% are affected by four or more.[13] The knowledge that chronic hyperglycemia is the cause of these complications has led to the development of over 60 different glucose-lowering medications and widespread implementation of evidence-based guidelines that recommend glycemic control,

preventive screenings for microvascular complications, and cardiovascular risk reduction strategies for all diabetic patients.[14] Together, these strategies target long-term complication risk and the associated morbidity and mortality.

Despite guidelines on diabetes care, maintaining glycemic control in diabetic patients is challenging and medical intervention is not without risk.[15,16] Medical providers, treatments, and procedures can all cause complications. These complications are known as iatrogenic. Unlike the long-term complications discussed above, iatrogenic complications of diabetes tend to be acute. Two important examples of iatrogenic diabetic complications are hospital-acquired diabetic ketoacidosis and severe outpatient hypoglycemia. These complications deserve special attention because they are potentially avoidable and are an example of unintended consequences of medical care.

Hospital-Acquired Diabetic Ketoacidosis

Patients with diabetes are at risk for poor glycemic control both in and outside of the hospital. Poor control of blood glucose levels in hospitalized patients with diabetes is associated with increased morbidity and mortality.[17-20] Despite this evidence and well-established guidelines on inpatient glucose management, hyperglycemia among hospitalized patients remains prevalent.[21-23] Studies have shown that close to one third of all blood glucose measurements in the hospital are above the recommended threshold of 180mg/dL and one fifth of patients have sustained hyperglycemia.[21,22]

The most acute and serious consequence of severe, sustained hyperglycemia is diabetic ketoacidosis (DKA). DKA is defined by hyperglycemia, ketonemia, and metabolic acidosis.[24] It occurs due to a relative or absolute deficiency of insulin and a

corresponding increase in counter-regulatory hormones, including glucagon. This imbalance leads to impaired glucose utilization resulting in severe hyperglycemia. The hyperglycemia itself can increase tonicity and cause glucose-induced osmotic diuresis, leading to volume depletion and electrolyte disturbances. Inability to use glucose for fuel also causes increased proteolysis, lipolysis, and ketogenesis resulting in ketoacidosis. These processes together can cause life-threatening volume depletion, cerebral edema, and electrolyte abnormalities and require prompt treatment with an insulin infusion and fluid and electrolyte repletion.

Hospital-acquired DKA is DKA that occurs during a hospitalization and was not present on admission. It can be life-threatening, but can be prevented through appropriate management of patients with diabetes with insulin, a medication that is readily available in the hospital. Therefore, it is considered a "never event" by the Centers for Medicare and Medicaid Services.[25] This means that hospitals do not receive additional payment for cases of hospital-acquired DKA.

Few data on hospital-acquired DKA are available. One study in the UK found that approximately 7.8% of all DKA cases are hospital-acquired.[26] Another study of hospitalized patients with diabetes in California found that hospital-acquired poor glycemic control (including DKA, hyperglycemic hyperosmolar state, and severe hypoglycemia) resulted in a significantly increased length of stay (14 vs 7 days), increased cost of hospitalization ($26,125 vs $18,233), and mortality rate (16% vs 9%) compared to matched controls.[27]

The consequences of hospital-acquired DKA are serious for patients, hospitals, and healthcare systems. However, little is known about what factors precipitate the

development of DKA in hospitalized patients. An understanding of the patient population, clinical context, and precipitating factors of hospital-acquired DKA is an essential first step in reducing its occurrence.

Severe Outpatient Hypoglycemia

Hypoglycemia is also a common, costly, and preventable problem among patients with diabetes. It is an adverse effect of diabetes treatment and can either be mild (self-treated) or severe (requiring assistance of a third party to administer glucagon or carbohydrates). Severe hypoglycemia event rates are estimated at 115 per 100 person-years among patients with type 1 diabetes and 35 per 100 person-years for patients with type 2 diabetes.[28-30]

Severe hypoglycemia is detrimental to patient health and has been associated with an increased risk of cognitive impairment, cardiovascular events, falls/fractures, and death.[31-36] It is also costly, with direct medical costs in the United States estimated at $1.84 billion per year.[37] Due to growing concerns about the significant adverse impact of severe hypoglycemia on both patients and the healthcare system, considerable efforts are now being made to prevent it.

The first step in prevention is identifying patients at risk. Not all patients with diabetes are at elevated risk for severe hypoglycemia requiring an ED visit or hospitalization. Approximately 5% of patients with diabetes account for >50% of severe hypoglycemia events.[38] Previous studies have identified many patient-level risk factors for SH, including both clinical and demographic characteristics.[39-43] Many of these risk factors make clinical sense such as use of certain glucose-lowering medications (e.g., insulin or sulfonylureas), older age, and chronic kidney disease.[44] However, several

studies have also demonstrated that Black patients with diabetes have a consistently higher risk of severe hypoglycemia than White, Asian, or Latino patients.[39-42]

Rates of hospitalization for hypoglycemia are nearly four times higher among Black patients compared to White patients and studies have shown that this difference has remained unchanged for over 10 years.[41] Similarly, the incidence of severe hypoglycemia resulting in an ambulance call, ED visit, or hospitalization is close to two times higher among Black patients compared to White patients.[44] These racial differences persist among patients with uniform access to care and among those treated with insulin or sulfonylureas.[39] Recent data demonstrate that the observed racial difference is increasing due to increasing incidence of severe hypoglycemia among Black patients and relatively stable incidence in other racial and ethnic groups.[39]

Although there is a history in the medical community of consideration of racial differences in pathophysiology and treatment of disease, there is no scientific evidence that racial disparities in severe hypoglycemia are caused by inherent biological differences between races.[45] This means that the observed racial disparities in severe hypoglycemia are likely to be secondary to other unexplored differences in clinical, social, or environmental factors. Prevention of severe hypoglycemia in diabetic patients therefore requires further examination of the factors driving the observed racial disparities.

Implications of this Research

Iatrogenic complications in general have a significant impact on morbidity, mortality, and spending in all healthcare settings. Medical errors alone are estimated to account for

over 400,000 deaths annually, making them the 3rd leading cause of death in the US.[46] They cost the US approximately $19.5 billion per year including $17 billion in direct medical expenses.[47] Additional morbidity, mortality, and healthcare dollars associated with other types of iatrogenic complications such as medication side effects and negligence are more difficult to quantify, but are likely to be equally costly. Therefore, iatrogenic complications are important opportunities to improve patient care and reduce healthcare costs.

Among diabetic patients, hospital-acquired DKA and severe outpatient hypoglycemia are examples of acute iatrogenic complications that are life-threatening and costly, but preventable. Reducing the incidence of hospital-acquired DKA could not only reduce the associated morbidity and mortality, but also shorten hospital stays and healthcare costs. Similarly, reducing the incidence of severe outpatient hypoglycemia would reduce morbidity and mortality as well as the number of unnecessary hospitalizations for diabetic patients. Investigating and addressing factors that drive racial disparities in hypoglycemia will focus prevention efforts on the most vulnerable patient populations and ultimately work to close the observed racial gap.

Preventing iatrogenic complications requires understanding of the context in which they occur. Assessing the relative causal contributions of patient factors, clinical settings, and institutional environments is necessary in order to develop effective interventions. There are different methodological approaches to the study of iatrogenic complications and the choice of methods depends upon the goal of the project, the scientific question, and the context of the study. This project uses two methods that are explained in detail in the methods section below. Common cause analysis is applied to investigate hospital

acquired DKA in the first study aim. Mediation analysis of directed acyclic graphs using inverse probability weighting is applied to investigate racial disparities in severe outpatient hypoglycemia in the second study aim. Both methodologies are effective, efficient, and well-suited for the question and type of data in each project.

Statement of Purpose and Hypotheses

The overall goal of this project is to examine the factors driving iatrogenic complications of diabetes, including hospital-acquired DKA and severe outpatient hypoglycemia. This overall goal has two specific aims:

Aim 1: Hospital-Acquired DKA

To characterize cases of hospital-acquired DKA in a large teaching hospital by retrospective chart review using common cause analysis:

a. To describe clinical and demographic characteristics of patients who develop DKA during a hospital admission
b. To identify common causes of hospital-acquired DKA
c. To propose solutions to common causes of hospital-acquired DKA

Hypothesis: We expect that the majority of hospital-acquired DKA will occur in patients with type 1 diabetes because they are more likely to experience ketoacidosis than patients with type 2 diabetes. Based on clinical experience and one previous study, we expect that the majority of hospital-acquired DKA will occur due to inappropriate insulin dosing.[48] We also anticipate that the majority of cases will occur on surgical or specialty services since general medical providers have more experience managing diabetic patients and will therefore be less likely to omit or inappropriately dose insulin. In addition, surgical patients have frequent diet changes, including periods in which they are NPO for procedures. These changes may necessitate frequent adjustments in insulin dose and knowledge of appropriate glycemic control in patients with no oral intake, which may be challenging when diabetes is not the primary reason for admission.

Aim 2: Severe Outpatient Hypoglycemia

To identify factors mediating racial disparities in severe hypoglycemia requiring an ED visit or hospitalization in a large insured population of adults with type 1 and type 2 diabetes:

a. To quantify racial and ethnic disparities in rates of severe outpatient hypoglycemia overall and by insulin use
b. To use literature review and expert clinical knowledge to identify potential factors that may mediate racial disparities
c. To use directed acyclic graphs (DAGs) to depict the causal relationships between mediator variables, the exposure (race), and the outcome (ED visits and hospitalizations for severe hypoglycemia)
d. To quantify the causal effect of each mediator variable proposed in the DAG using inverse probability weighting to estimate the counter factual disparity measure[1]

Hypothesis: We expect that Black patients will have higher rates of severe outpatient hypoglycemia requiring ED visits and hospitalizations than White, Asian, and Latino patients in the overall cohort and in the subgroup of insulin users.[39] We anticipate that our proposed DAG based on literature review and expert clinical knowledge will include multiple factors potentially mediating these disparities. We expect that the most important mediators will be the use of urgent vs preventative care (which may be, in turn, mediated by neighborhood deprivation and measures of low socioeconomic status) and the presence of established long-term diabetic complications and comorbidities, including

[1] These analyses are ongoing and results are not presented in this thesis

chronic kidney disease, which are more common among Black compared with White patients with diabetes.[49]

Methods

Aim 1: Hospital-Acquired DKA

Overall Design: Root Cause vs Common Cause Analysis

One common way to examine preventable iatrogenic complications is by using root cause analysis. Root cause analysis is a structured method of analysis that aims to identify a problem, determine the root cause of the problem, and design an intervention to prevent future occurrences of the same problem. In 2015, The Joint Commission released an article titled "Root Cause Analysis in Healthcare: Tools and Techniques," which detailed the types of problems that can be addressed by RCA and step-by-step guidelines on using RCA to address them.[50] The Joint Commission now requires hospitals to perform RCA for all sentinel events and develop appropriate interventions to prevent their reoccurrence.[50] Therefore, RCA is used routinely in healthcare across the US.

Despite its widespread use, there is little evidence that RCA is effective in improving patient safety or reducing adverse events.[51] In part, this may be due to how it is performed. Many healthcare professionals report that limitations in time, resources, and feedback as well as difficulty collaborating with RCA team members and managers impact their ability to perform thorough and effective RCAs.[52] Even when RCAs are completed, less than 10% of the resulting recommendations are found to be effective and sustainable.[53] In addition, RCA is impractical to use for events that occur more than once because each intervention is targeted for one individual case. As a result of these problems, many hospitals have reported reoccurrences of events after RCAs.[51]

One proposed solution to the problems with RCA is common cause analysis (CCA). CCA is based closely on RCA, but instead of focusing on one event, it uses aggregate

data from multiple cases. Using multiple cases, it is possible to identify factors that contribute to multiple events. Interventions targeting these common causes have the potential for greater impact than interventions addressing the cause of one isolated event.[54,55]

Setting and Participants

Our study included adult patients who developed DKA during a hospital admission at Yale New Haven Hospital (YNHH) between Feb 1 2013 and Nov 1 2018. YNHH is a non-profit teaching hospital that serves residents of Connecticut. It has approximately 1.4 million outpatient encounters and 76,000 inpatient admissions annually.

At YNHH, the majority of inpatient diabetes care is provided by patients' primary teams. However, there are several exceptions. One is on the podiatry service, where all patients with diabetes are followed by a medicine consult team for diabetes management. Another exception is when the primary service is unable to manage a patient's diabetes. In this case, the primary team can call the inpatient diabetes management team or the endocrinology service for consultation. The inpatient diabetes management team consists of nurse practitioners who specialize in inpatient hyperglycemia.[56] The endocrinology service is available for consultation on all endocrine-related issues and is staffed by physicians. Both consult services see patients daily. Of note, per YNHH guidelines, all inpatients with an insulin pump should be followed by the endocrinology service.

All inpatient admissions for adults over age 18 years with a discharge diagnosis of DKA were identified from the electronic medical record using ICD-9-CM and ICD-10

codes. The codes for DKA were 250.10 – 250.13 and E10.10, E10.11, E11.00, and E 11.01.[57] Patients were excluded if any of these codes were present on admission or if DKA was documented in the admission note. After this list of admissions was selected, the diagnosis of DKA was confirmed by the following criteria: blood glucose >250 mg/dL and bicarbonate <18 mEq/L and one of the following two criteria: anion gap >16 or B-Hydroxybutyrate >3 mmol/L.[58] All values had to occur within a 12-hour period. The date of DKA was the first time during the admission that the patient met all DKA criteria. The mean and range of values of DKA criteria for all included patients can be found in Appendix A.

All data were obtained by chart review performed by the author. Date of death was determined by chart review or by first missed appointment due to death through the end of the study period (Nov 1 2018). This study was deemed exempt from continuing review by the Yale University Human Investigations Committee (HIC).

Main Outcome Measures

DKA etiology in each case was determined using the following criteria for mutually exclusive categories that were determine a priori (based on prior literature and clinical experience):

1. Insulin dose reduction – Dose of basal insulin reduced within 24 hours prior to DKA by at least 50% of the outpatient dose.
2. Missed insulin dose – At least one missed dose of basal insulin for any reason in prior 24 hrs.

3. Infection – Patient met criteria for sepsis (defined as a suspected source of infection plus two of the following: temperature >38° or <36°, heart rate >90, respiratory rate >20 or $PaCO_2$ < 32mm Hg, WBC >12,000/mm^3, <4,000/mm^3, or >10% bands).[59] Of note, one patient who did not meet sepsis criteria, but had a suspected source of infection and was on antibiotics was categorized as having a "suspected infection" and was included in this category.
4. Steroids – Patient did not meet any DKA criteria before initiation of steroids and did meet criteria after initiation of steroids (at any dose) with no insulin dose reduction or missed doses of insulin.
5. Other – Patients who did not fall into any of the categories above were classified as "other" and the reason for DKA was determined by progress notes from the primary team or endocrine consult service if available.

Statistical Analysis

Demographic and clinical variables were described using frequencies and means for categorical and continuous variables, respectively. DKA etiology was determined by chart review and the frequencies for each category were reported. In addition, ten charts were also reviewed by Kasia Lipska, MD and the rate of agreement (kappa) for the chief reason for DKA was assessed. Kappa statistic was 70% (for this analysis, the missed vs. reduced insulin dose categories were combined).

Data were entered into a Microsoft Excel spreadsheet and analyzed using JMP V13.0. All analyses were performed by the author (CZ).

Aim 2: Severe Outpatient Hypoglycemia

Overall Design: Directed Acyclic Graphs and Mediation Analysis

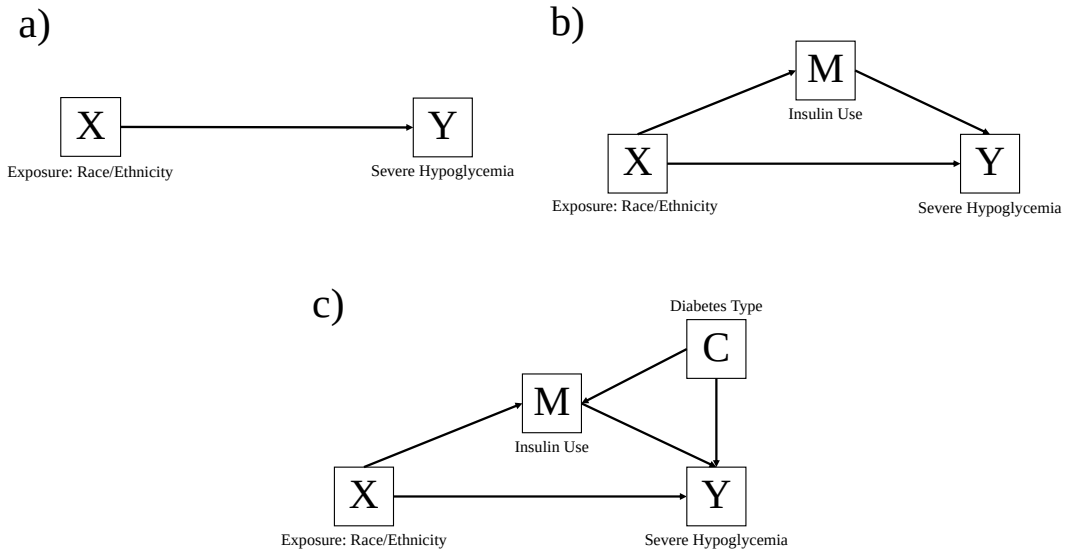
While common cause analysis is an effective tool for analyzing iatrogenic complications on a small scale, it is not feasible to perform on a large scale because it requires analysis of individual cases. An alternative method for examining causal factors for iatrogenic complications on a larger scale is mediation analysis using directed acyclic graphs (DAGs). This process allows for causal analysis of many cases simultaneously while minimizing confounding bias.

DAGs are visual representations of relationships between variables that are used to model causality. They are useful in observational trials to identify confounders and determine ways to resolve them based on explicit assumptions. DAGs consist of variables connected by arrows. Each arrow represents the causal effect of one variable on another. Following the path of arrows from one variable to the next is a visual representation of a series of cause and effect relationships. Each pathway through a DAG is called a directed path. No directed path in a DAG will lead back to its starting point because the cause and effect relationships are unidirectional and acyclic.

A simple example of a DAG is shown in Figure 1a. In this figure, the exposure (X) influences the outcome (Y) directly. The arrow from X to Y represents the direct causal relationship between the exposure and the outcome. In our examination of severe hypoglycemia, the exposure (X) is race and the outcome (Y) is an ED visit or hospitalization for severe hypoglycemia. This simplified DAG represents our hypothesis based on previous research that race influences the rate of ED visits and hospitalizations for severe hypoglycemia. However, the purpose of our analysis is to investigate which

variables mediate this relationship between race and severe hypoglycemia. To answer that question, we need to represent these variables in our DAG.

Figure 1: Simplified Theoretical Directed Acyclic Graph



In Figure 1b, there is an additional variable (M) between our exposure and outcome. This is a mediator variable because it is affected by the exposure and in turn affects the outcome. The addition of M creates an indirect pathway between X and Y. It does not erase the effect of X on Y directly, because we do not believe that all of the impact of X on Y goes through this mediator, M. In fact, by adjusting for the mediator (M) in our model we can determine how much of the effect of X on Y is a result of the mediator. For example, if M is insulin use, examining the racial disparities in severe hypoglycemia after controlling for insulin use will allow us to assess the impact of insulin use on the relationship between race and severe hypoglycemia.

In addition to mediators, confounder variables can impact the causal relationships represented in DAGs. Confounders are variables that affect both the exposure or mediator

and the outcome. Therefore, they limit our ability to assess the effect of the exposure or mediator on the outcome by creating a "back-door path." In Figure 1c, a confounder variable (C) is added to the DAG that causes both the mediator (M) and the outcome (Y). This confounder could be diabetes type. Patients with type 1diabetes are more likely to be prescribed insulin than patients with type 2 diabetes and are also more sensitive to insulin, meaning they are more likely to develop severe hypoglycemia. Therefore, it is difficult to assess the effect of insulin on the relationship between race and hypoglycemia without controlling for diabetes type.

Although this example DAG is simplified, it demonstrates the importance of identifying causal relationships between variables that impact the exposure and outcome of interest. This process is based on a priori knowledge, which is most often a combination of literature review and expert clinical input. When all relevant variables and relationships are represented, it is possible to identify both direct, indirect, and confounding interactions. These interactions can be used to develop statistical models that minimize bias in data interpretation.

In summary, the process of creating and analyzing a DAG minimizes bias in mediation analysis particularly when using data from observational studies in which bias cannot be minimized by randomization. As such, DAGs are a useful tool for mapping out potential causal mediator variables, such as the factors mediating the racial disparities in severe outpatient hypoglycemia.

Mediator Variable Selection

Mediator variables for the DAG were selected based on a combination of literature review, unpublished data, and expert opinion. The literature search was performed in PubMed and limited to articles published from 1999-2019 in English. Two areas were explored to create a comprehensive list of factors that may mediate racial disparities in hypoglycemia including (with search terms listed in parentheses):

1. Risk factors for hypoglycemia ((“hypoglycemia”[Title] OR “hypoglycaemia”[Title]) AND “severe” AND (“risk” OR “predict”) AND “diabetes”) – 692 results, 10 included plus 4 from cross-reference
2. Factors mediating racial disparities in diabetes and other diabetic complications ((“race”[Title/Abstract] OR “ethnic”[Title/Abstract]) AND “diabetes”[Title/Abstract] AND (“disparities” OR “differences”)) – 4584 results, 8 included plus 7 from cross-reference

Articles were included based on relevance. After the literature search, additional mediator variables were added based on unpublished data from KPNC and expert clinical opinion from endocrinologist Kasia Lipska, MD. The DAG was created using all identified mediator variables after thorough discussion with all authors (CZ, KL, AK, MW).

Inverse Probability Weighting and Counterfactual Disparity Measures

After creating a DAG to depict the causal interactions of our proposed mediator variables, we plan to estimate the causal effects of each mediator variable by determining its counterfactual disparity measure with inverse probability weighting. The

counterfactual disparity measure for each variable is a measure of that variable's causal effect on the outcome with minimal contributions from confounding variables. Counterfactual disparity measures are especially useful in observational studies when randomization of participants to the exposure of interest is not possible. This is true of our study, in which the exposure of interest is race. Since race is an inherent characteristic of an individual (and this is an observational study), it is not possible to randomize each participant to a racial or ethnic group and observe the effect that their assigned race/ethnicity has on their risk of severe outpatient hypoglycemia. Therefore, each race or ethnic group will contain a sample of the population that is not random. As a result, it is likely that there are differences in baseline characteristics between groups.

We suspect that some of these differences in baseline characteristics are contributing to the observed racial differences in severe outpatient hypoglycemia. For example, if Black patients are more likely to use urgent care (such as the ED) for any cause instead of outpatient care than White patients, this may account for some of the racial differences in ED visits and hospitalization for hypoglycemia.

In order to estimate the effect of these baseline mediator variables, we can use inverse probability weighting to estimate the counterfactual disparity measure. Conceptually, inverse probability weighting assigns all subjects a certain value for the mediator variable. In our example, we would assign all patients to either no ED visits (for any cause) in the prior year or ≥1 ED visit (for any cause). Within each category, we would then determine the persistent racial differences (i.e. the difference in the rate of severe hypoglycemia among Black and White patients who had no ED visits and the difference in the rate of severe hypoglycemia among Black and White patients who had

≥1 ED visit). If prior ED visits accounted for 100% of the racial disparities in severe hypoglycemia, racial differences among the two groups would disappear in this analysis. Conversely, if prior ED visits did not account for any of the observed racial disparities, the racial disparity within each group would be as large as the racial disparity in the full cohort. The resulting risk difference after inverse probability weighting analysis is known as the counterfactual disparity measure (because it is not true that all patients are in one group).

In reality, we do not expect to find one mediator variable that accounts for 100% of the racial difference in severe hypoglycemia. However, using inverse probability weighting to estimate the counterfactual disparity measure for each mediator variable of interest, we can estimate the causal effects of the variables proposed in our DAG.

Given the amount of work that goes into defining variables, creating models, and running analyses, we plan to start with the variables we believe have the strongest causal effects on the observed racial differences in ED visits and hospitalizations for severe hypoglycemia based on literature review and expert clinical knowledge as described above.

Setting and Study Population

Kaiser Permanente of Northern California (KPNC) is a large, integrated managed care consortium that provides inpatient and outpatient healthcare for approximately 30% of residents in Northern California. KPNC has a diabetes registry for all patients with diabetes that is updated annually and now includes over 350,000 patients. Patients with diabetes are identified for this registry using multiple data sources including pharmacy

use, laboratory results, and diagnoses from outpatient visits, ED visits, and hospitalizations. Details on the algorithm used to identify patients are published elsewhere.[49,60] Patient race and ethnicity was determined by self-report in the Kaiser electronic medical record.

As mentioned above, the purpose of the DAG and inverse probability weighted analysis is to visually represent and accurately assess relationships between all known exposure, mediator, confounder, and outcome variables. However, we recognize that not all variables and their interactions are currently known. Therefore, in addition to DAG analysis it is important to control for as many confounding variables as possible by creating a relatively homogeneous population except for the exposure of interest. A large part of this was already completed in our choice of study population because access to healthcare at KP is relatively equal across patient demographics. To further limit unknown confounding, we restricted our study population to patients on insulin at home.

All included patients had KP membership and prescription benefits for at least one year prior to the study start period. Patients on insulin were identified by prescription records demonstrating at least 1 fill in the 6 months prior to 7/1/17. ED visits and hospitalizations for severe hypoglycemia were identified using ICD codes according to a validated definition (251.0, 251.1, 251.2, 962.3, or 250.8 modified by 259.8, 272.7, 681, 682, 686.9, 707.1-707.9, 709.3, 730.0-730.2, or 731.8).[61] Cohort identification was performed by Margaret Wharton, MPH at KP due to restrictions on data access to researchers outside of the KP system.

Statistical Analysis

The combined number of ED visits and hospitalizations for severe hypoglycemia was calculated for the study period and divided by the number of person years of follow-up to determine the event rate per 1,000 person-years. This was calculated for the full cohort as well as by race/ethnicity and insulin use. Rates are reported as mean [95% confidence interval], although confidence intervals were calculated only for subgroups by race and insulin use and not for the full cohort.

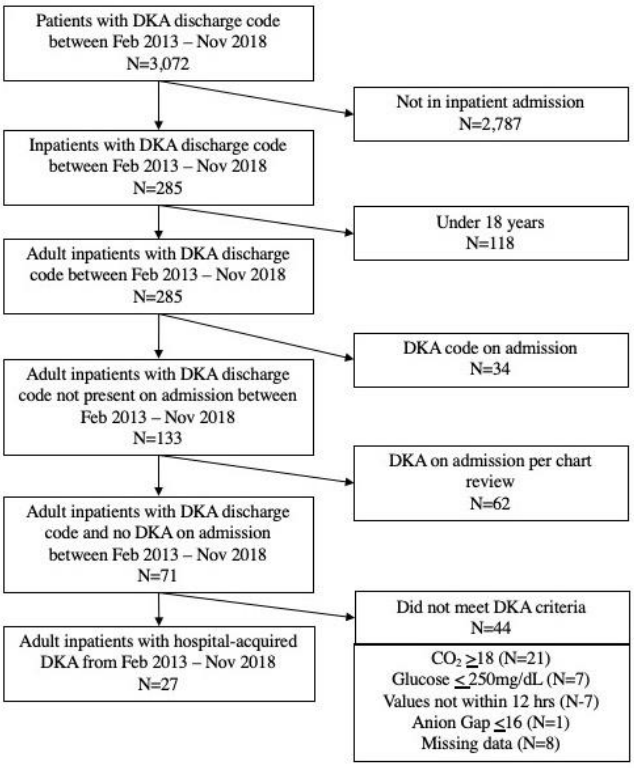
Future mediation analyses will be performed by Margaret Wharton, MPH at KPNC. Briefly, counterfactual disparity measures will be calculated for each mediator variable of interest using inverse probability weighted regression models (marginal structural models). From these models, we will get an estimate of how much of the observed racial disparities in severe hypoglycemia events requiring ED visits or hospitalizations is attributable to the mediator variable of interest.

Results

Aim 1: Hospital-Acquired DKA

Patient demographics and clinical characteristics are presented in Table 1. A total of 27 patients were included in our study of hospital-acquired DKA (Figure 2). These patients had a mean age of 53.4 years, and were predominantly female (59.3%) and white (70.4%). The majority of cases were Type 1 diabetics (59.3%), but approximately one quarter (25.9%) had an unspecified diabetes type based on ICD codes and chart review. All except one patient used insulin at home and the majority (70.4%) were on a basal bolus regimen prior to admission (details and definitions of insulin regimens are found in Appendix B). The mean HbA1c within 3 months of admission was 8.9%$\pm$2.2.

Figure 2: Inclusion Criteria for Hospital-Acquired DKA Chart Review



On admission, the mean blood glucose was 193$\pm$102. 16 patients (59%) were hypoglycemic during the admission (blood glucose <70 mg/dL). Of these, 10 were hypoglycemic before developing DKA, 13 were hypoglycemia after developing DKA, and 7 were hypoglycemic both before and after developing DKA. Twenty-one patients (77%) were on a teaching service at the time of DKA development, and 7 (25.9%) were in an intensive care (ICU) or step-down unit (SDU).

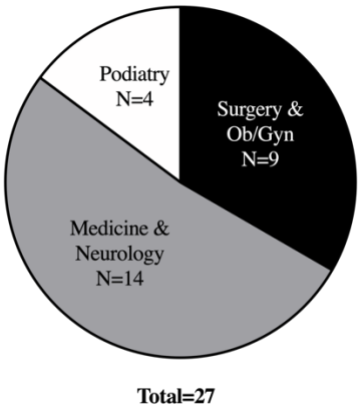
Table 1: Demographics and Clinical Characteristics of Patients with Hospital-Acquired Diabetic Ketoacidosis.

N	27
Age, years, mean (SD)	53.4 (11.5)
Female gender, n (%)	16 (59.3%)
Race/ethnicity, n (%)	
Black	3 (11.1%)
White	19 (70.4%)
Hispanic*	5 (18.5%)
Diabetes type, n (%)	
Type 1	16 (59.3%)
Type 2	4 (14.8%)
Unspecified	7 (25.9%)
Diabetes treatment at home, n (%)	
Basal bolus insulin	19 (70.4%)
Basal insulin only	1 (3.7%)
Basal bolus insulin plus orals	3 (11.1%)
Basal insulin plus orals	1 (3.7%)
Insulin pump	2 (7.4%)
Orals only	1 (3.7%)
HbA1c, mean (SD) (n=20)	8.9 (2.2)
Admission glucose, mean (SD)	193 (102)
Hypoglycemia (<70mg/dl), n (%)	
Total during this admission	16 (59%)
Before DKA only	3
After DKA only	6
Before and after DKA	7
Teaching service, n (%)	21 (77.8%)
In ICU or SDU at time of DKA onset, n (%)	7 (25.9%)

*All patients who identified as Hispanic had were listed as “unknown” race in EMR
Legend: ICU, intensive care unit; SDU, step-down unit

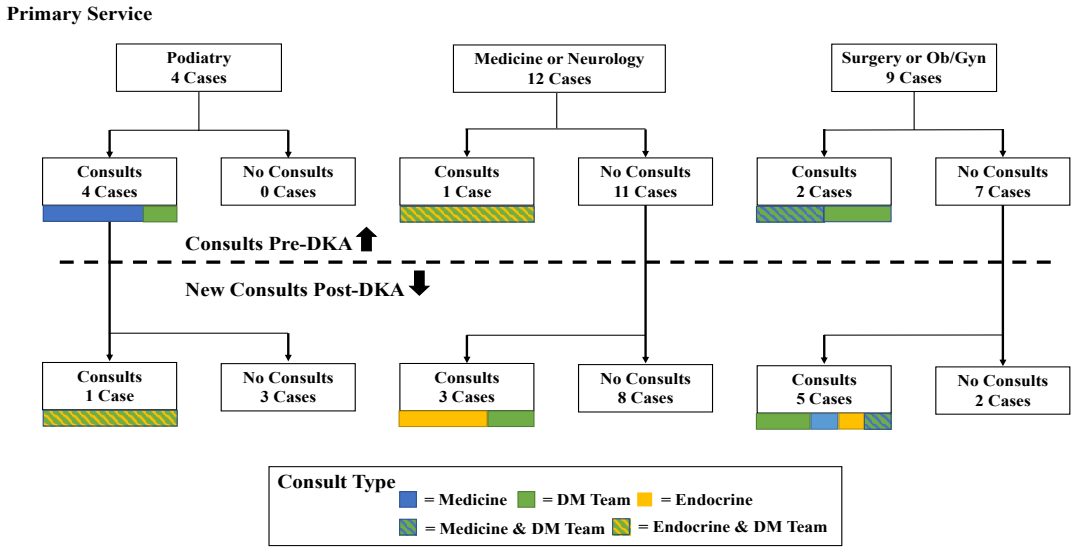
At the time of DKA development, 14 patients (51.9%) were on a medicine or neurology service (13 medicine, 1 neurology), 9 (33.3%) were on a surgery or ob/gyn service (8 surgery, 1 ob/gyn), and 4 (14.8%) were on a podiatry service (Figure 3).

Figure 3: Primary Service at time of DKA



Consults before and after DKA are depicted in Figure 4. Briefly, all patients on the podiatry service had consults to medicine regarding their diabetes (3 of 4 cases) or the diabetes team (1 of 4 cases) before the development of DKA. On medicine and surgery, rates of consults related to diabetes were lower before the development of DKA. Prior to DKA, 11 of 12 patients on medicine and 7 of 9 patients on surgery had no diabetes related consults. After DKA, 5 patients on surgery received new consults to either medicine, endocrine, or the diabetes team. On medicine, 3 patients received new consults to endocrine or the diabetes team. 10 patients had no consults before or after DKA.

Figure 4: Consults before and after DKA



Legend: DM Team – diabetes team

Of note, out of 7 cases with consultants, 4 developed DKA due to insulin dose reduction or a missed insulin dose. In 2 of these 4 cases, consultants recommended a higher or extra dose of insulin in the consult note that the patient never received.

Patients developed DKA a median of 2 days after admission with a range of 0-15 days. This did not differ across services. In the 24 hours prior to DKA, 12 patients (44.4%) received doses of basal and bolus insulin. Eight patients (29.6%) received bolus insulin only and 3 patients (11.1%) did not receive any insulin. One patient (3.6%) was on an insulin pump prior to DKA and 2 (7.4%) were on insulin infusions. Twelve patients (44%) received steroids in the 24 hours prior to DKA. Data on precipitating factors and medications in the 24 hours prior to the development of DKA are shown in Table 2.

Table 2: Treatment Characteristics of Patients with Hospital-Acquired DKA and DKA Etiology

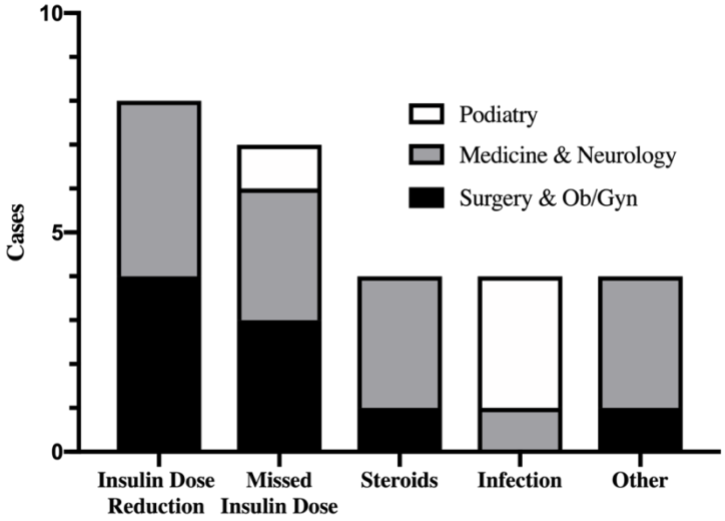
Time to DKA, days (median, range)	2 (0-15)
Insulin administered within 24 hrs prior to DKA, n (%)	
Basal and bolus insulin	12 (44.4%)
Bolus insulin only	8 (29.6%)
None	3 (11.1%)
Insulin pump	1 (3.7%)
Insulin drip	2 (7.4%)
Insulin drip and bolus insulin	1 (3.7%)
Steroids within 24 hrs prior to DKA, n (%)	12 (44.4%)
Reason for DKA, n (%)	
Missed doses of insulin	7 (25.9%)
Insulin dose reduction	8 (29.6)
Infection[+]	4 (14.8%)
Steroids	4 (14.8%)
Other*	4 (14.8%)

[+]Includes one case of suspected infection that did not meet SIRS criteria
*Per chart DKA was attributed to physiologic stress from shock, surgery

The majority of cases appeared to be caused by problems with insulin dosing, including missed doses of insulin (7 cases, 25.9%) and insulin dose reduction of 50% or greater (8 cases, 29.6%). The causes among the remaining 12 patients were evenly

distributed between steroids (n=4, 13.8%), infection (n=4, 13.8% including 1 with suspected infection), and severe stress associated with surgery and shock (n=4, 13.8%). The etiology of DKA on each primary service was variable (Figure 5). However, 3 of 4 cases attributed to infection were on the podiatry service.

Figure 5: Etiology of DKA by Primary Service



After DKA was diagnosed, 22 of 27 cases were treated with an insulin infusion for a mean duration of 43.1 hours (range 7-257). Nine of 20 eligible patients were transferred to an ICU or SDU for DKA treatment. A total of 12 patients (44.4%) died by the end of the study period (Nov 1 2018). Two of these patients died during the same hospital admission in which they developed DKA and 1 within one week of discharge. Treatment and outcomes of cases included in the study are shown in Table 3.

Table 3: Treatment and Outcomes of Patients with Hospital-Acquired DKA

Insulin drip	
Yes, n (%)	22 (81.4%)
Duration (hrs), mean (range)	43.1 (7-257)
Transfer to ICU or SDU for DKA (n=20)*	9 (45%)
Mortality	
Death by end of study period, n (%)	12 (44.4%)
Time to death from DKA, days, mean (range)	238 (3-1100)

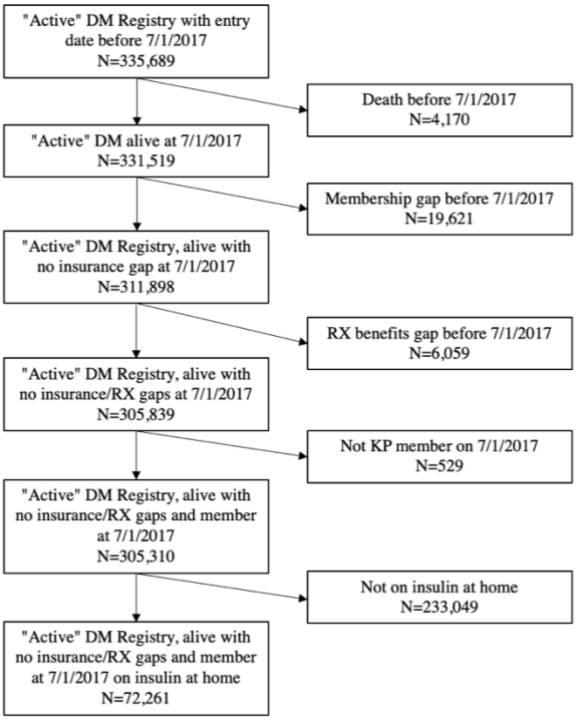
*7 patients were in an ICU or SDU at the time of DKA and were not eligible for transfer
Legend: ICU – intensive care unit, SDU – step-down unit

Aim 2: Severe Outpatient Hypoglycemia

Study Population

A total of 305,310 patients (including patients on insulin at home and patients not on insulin at home) were included in this analysis. A flowchart for inclusion/exclusion of patients is shown in Figure 6.

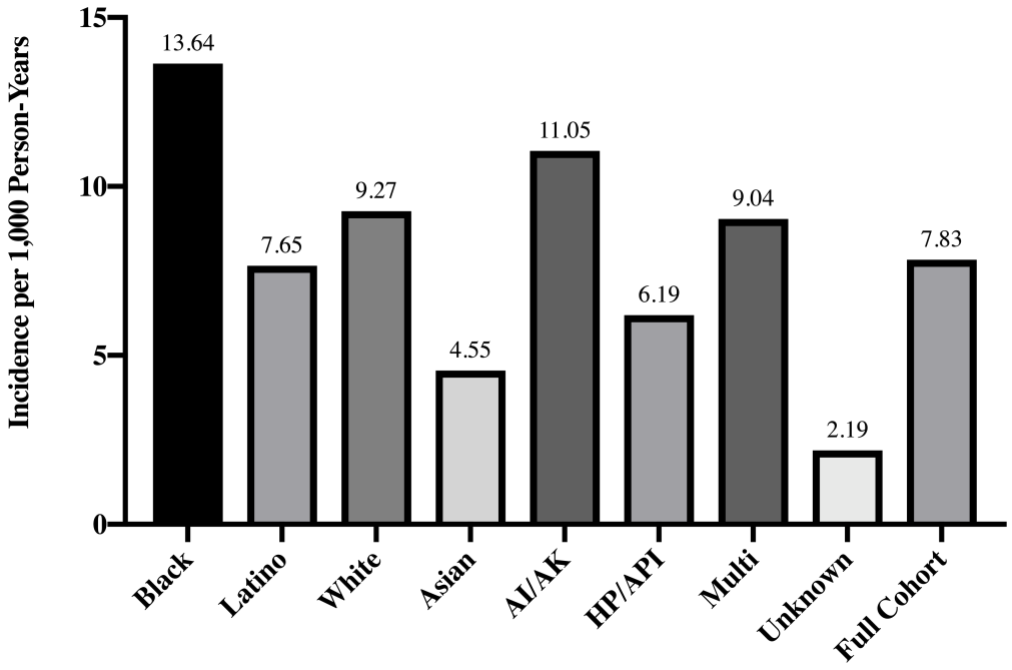
Figure 6: Inclusion Criteria for Severe Outpatient Hypoglycemia



Rate of Severe Hypoglycemia, Overall and by Race

There were a total of 2391 severe hypoglycemia events requiring an ED visit or hospitalization from July 2017 – June 2018 at KPNC. The event rate for the full cohort was 7.83 per 1000 person-years. This rate varied significantly by race. The highest rate was among Black patients at 13.64 compared to a rate of 9.27 among Whites and 7.65 per 1000 person-years among Latinos (Figure 7).

Figure 7: Unadjusted Severe Hypoglycemia Rate per 1,000 Person-Years by Race/Ethnicity Among Patients with Diabetes Mellitus at Kaiser Permanente Northern California, July 2017-June 2018



Insulin Use, Overall and by Race

For the mediation analysis, only patients on insulin will be included in order to control for variations in disease severity and duration. Of the full cohort, 23.7% of patients were treated with insulin. This did not vary significantly between races or ethnicities (Figure 8). As expected, the rate of severe hypoglycemia among patients on insulin was higher than the full cohort at 24.72 [23.37, 25.73] events per 1000 person-years (Figure 9). This rate also varied significantly by race. The highest rate was among Black patients at 34.27 [30.09, 38.87] compared with a rate of 27.14 [25.39, 28.99] among White patients and 22.14 [19.71, 24.73] among Latino patients. Rates of severe hypoglycemia among patients not on insulin were significantly lower (3.07 [2.81, 3.27] events per 1,000 person-years for the full cohort).

Figure 8: Percentage of Study Population with Baseline Insulin Use by Race/Ethnicity July 2017-June 2018

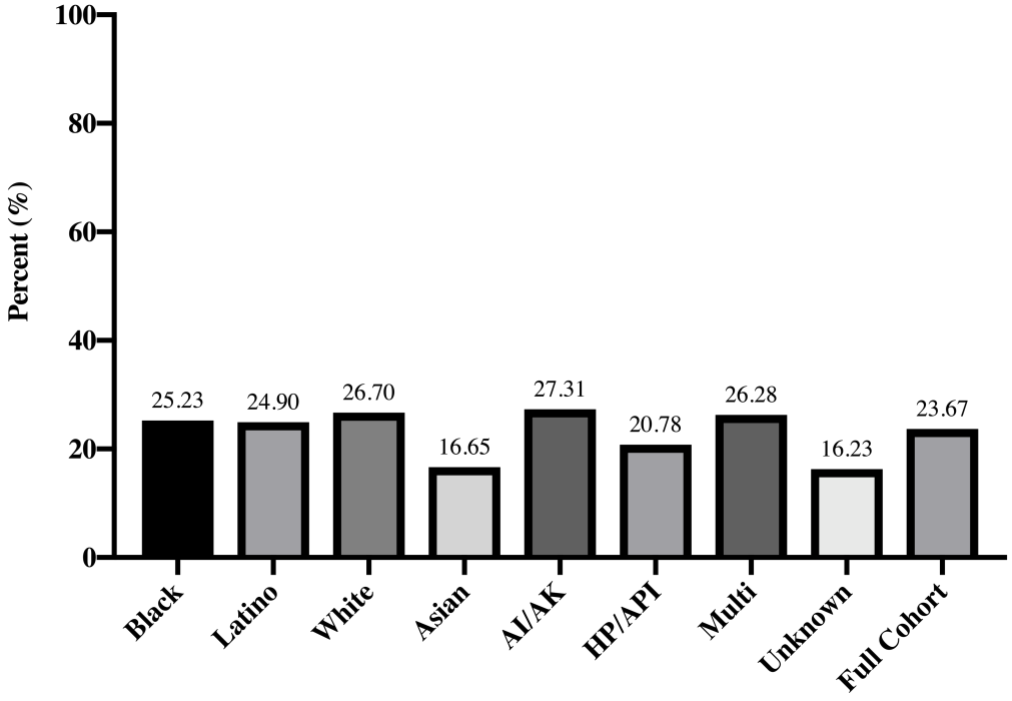
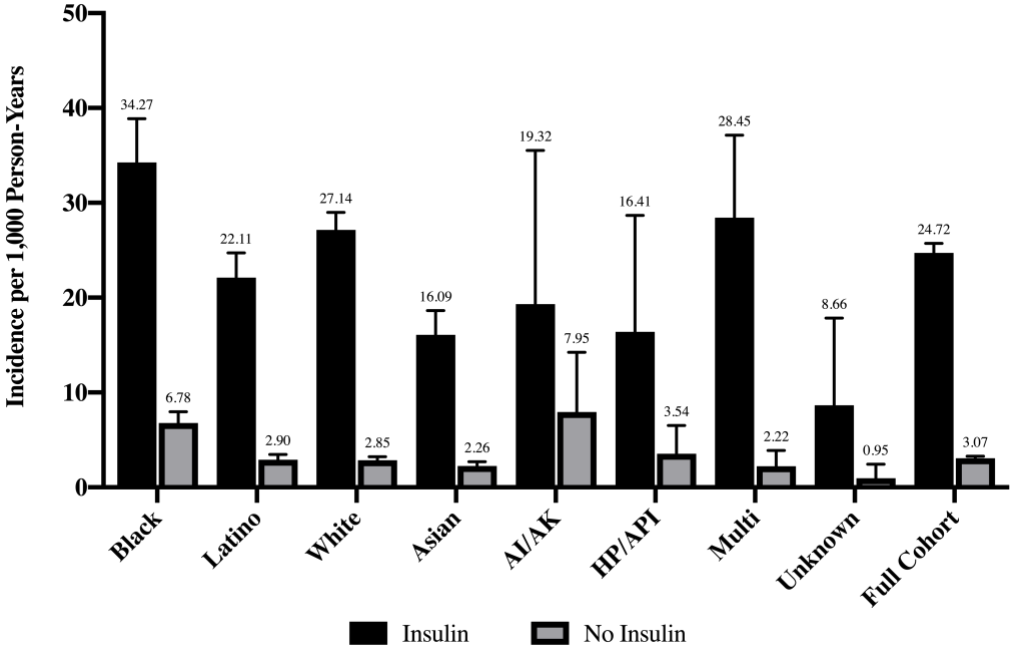


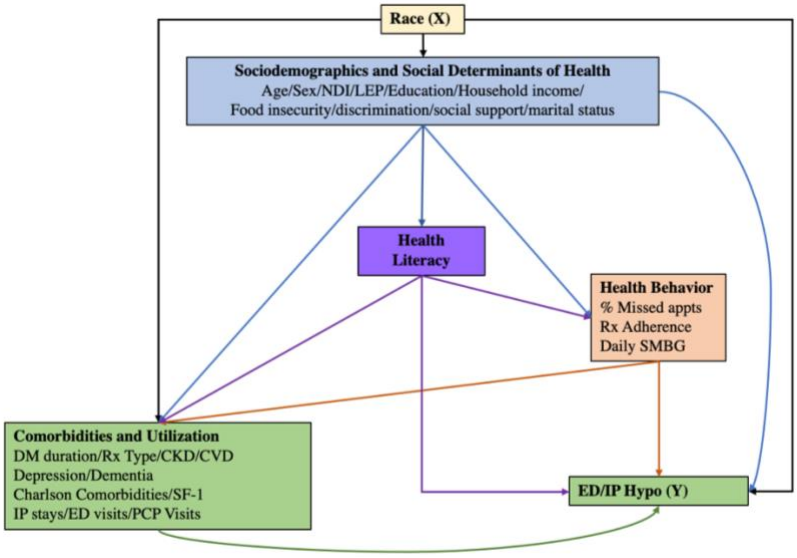
Figure 9: Unadjusted Severe Hypoglycemia Incidence per 1,000 Person-Years By Race/Ethnicity and Baseline Insulin Use July 2017-June 2018



Directed Acyclic Graphs

In order to facilitate mediation analysis, a DAG was created to visualize the relationships between the exposure of interest (race) and the outcome (ED visits/hospitalizations for severe hypoglycemia). This DAG (Figure 10) was created based on literature review and expert clinical knowledge as discussed in the methods section, and was the result of multiple discussions among all team members (CZ, KL, MW, and AK). It depicts the relationships between race and severe hypoglycemia through categories of mediator variables. These categories were created by grouping related variables identified in the literature search. They include sociodemographics and social determinants of health, health literacy, comorbidities and healthcare utilization, and health behavior. Briefly, justifications for each category of variables and their interactions in the DAG are laid out below.

Figure 10: Directed Acyclic Graph of the Race (X) Severe Hypoglycemia (Y) Relationship



Legend: NDI – Neighborhood Deprivation Index; LEP – Limited English Proficiency; CKD – Chronic Kidney Disease; CVD – Cardiovascular Disease; SF-1 Self-Rated Health Form; IP – Inpatient; PCP – primary care provider; SMBG – Self-monitoring of blood glucose

Comorbidities and Utilization

Multiple clinical factors and comorbidities are associated with increased rates of severe hypoglycemia among diabetic patients.[44,62,63] The most well studied of these risk factors include longer duration of diabetes and treatment,[30] use of sulfonylureas or insulin,[63] increasing number of antidiabetic medications,[43] cardiovascular disease,[64] dementia,[65] depression,[66] and CKD.[67] Measures of overall illness burden such as the Charlson Comorbidity Index (CCI, Appendix C) have also been shown to be significant independent risk factors for the development of severe hypoglycemia.[40,62] This is likely caused by inclusion of several of the well-studied risk factors for hypoglycemia in the CCI as well as inclusion of other risk factors for hypoglycemia that have not yet been thoroughly investigated. In addition, higher overall disease burden as measured by the CCI may decrease awareness of hypoglycemia and thus the ability to identify and treat it before it becomes severe.

Many of these clinical risk factors and comorbidities including CKD[68] and cardiovascular disease[69] are present at higher rates in African Americans.[49,70] Racial disparities in any one (or some combination) of these clinical factors may be contributing to the observed racial disparities in ED visits and hospitalizations for severe hypoglycemia.

The racial disparities observed in our data may not only be the result of increased risk of severe hypoglycemia among Black patients, but also differences in healthcare utilization patterns resulting in increased use of the ED for hypoglycemic episodes. In fact, increased use of urgent care for any reason is associated with increased risk of hypoglycemia requiring an ED visit or hospitalization.[63] This pattern of decreased use of

preventive care and increased use of urgent care (including the ED) has been previously identified in Black patients compared to White patients with diabetes in populations with access to healthcare.[71,72] Because healthcare utilization is closely related to comorbidity burden in patients with access to healthcare such as patients at KPNC, these variables were grouped together in our DAG.

Sociodemographics and Social Determinants of Health

Sociodemographic and social determinants of health together form a measure of social vulnerability, which is defined as the reduced ability of a person to respond to or withstand external adverse events. Higher social vulnerability is an independent risk factor for hypoglycemia among patients with diabetes.[73] In addition, several individual components of social vulnerability are associated with an increased risk of hypoglycemia and other diabetic complications. For example, sociodemographic characteristics including age, sex, place of birth, education, and social support have been shown to affect health outcomes such as HbA1c among diabetic patients with access to a standardized healthcare system.[74,75] Socioeconomic factors such as low household income are also associated with increased risk of hospitalization and reduced use of preventive care among insured patients with diabetes.[76,77]

Many sociodemographic factors and social determinants of health also vary by race and ethnicity. Racial disparities in self efficacy and social support at home have been observed and are thought to contribute to observed racial differences in self-management of hypoglycemia.[78] Previous studies have shown that differences in English proficiency may also account for some of the ethnic differences in preventive care use.[71]

Together, these data demonstrate the importance of careful consideration of social vulnerability in the relationship between race and ED visits and hospitalizations for severe hypoglycemia.

Health literacy

Adequate health literacy is necessary in order to understand disease, make healthcare related decisions, and follow treatment recommendations. It is especially important in managing chronic diseases such as diabetes, which require consistent and appropriate preventive care. Among patients with diabetes, lower health literacy is associated with an increased risk of hypoglycemia and poor glycemic control.[79,80] Health literacy is also thought to mediate the association between low socioeconomic status and multiple poor health outcomes such as increased rates of diabetic complications.[78,81,82]

Black patients are disproportionately affected by inadequate health literacy with approximately 24% of Black patients having below basic health literacy compared to 9% of White patients.[83] These data suggest that health literacy may be an important mediator of the relationship between race and severe hypoglycemia even though it is not directly affected by race itself.

Health Behaviors

Health behaviors include adherence to medications, attendance at healthcare visits, and daily management of health at home. For patients with diabetes, this includes regular monitoring of blood glucose, routine preventive care appointments, and consistent use of prescribed medications. Certain health behaviors, such as adherence to

appointments and medications are associated with improved glycemic control and reduced risk of hospitalizations in patients with diabetes.[84,85]

Important health behaviors such as self-monitoring of blood glucose and use of preventive care have been shown to vary across racial and ethnic groups.[71,72,86] As with health literacy, there is no evidence that race impacts health behaviors directly. The relationships between race and health behaviors may instead be mediated by social vulnerability and health literacy.[81,87]

Variable Interactions

Accurately depicting the relationships between these variables in the DAG is important in order to minimize bias and confounding in the inverse probability weighted analysis. Based on the evidence above, we created the following description of variable interactions (with direct relationships represented as arrows in the DAG in Figure 10):

1. *Relationships between mediator variables and the outcome variable.* All mediator variables directly impact the rate of ED visits and hospitalizations for severe hypoglycemia.
2. *Relationships between race and mediator variables.* Race impacts the following variable categories:
    a. Sociodemographics and social determinants of health
    b. Comorbidities and utilization
3. *Relationships between mediator variables.* Mediator variable interactions are as follows:

a. Sociodemographics and social determinants of health impact health literacy, health behaviors, and comorbidities and utilization.
b. Health literacy impacts health behaviors and comorbidities and utilization

Future Results

Inverse probability weighted modeling will result in estimates of the causal contribution of each mediator variable of interest on the observed racial disparities in ED visits and hospitalizations for severe hypoglycemia. An example of this analysis for all cause ED visits in the prior year is shown in Appendix D.

Discussion

Aim 1: Hospital Acquired DKA

In summary, we identified 27 cases of hospital-acquired DKA between Feb 1, 2013 and Nov 1, 2018 at a large teaching hospital. The majority of patients had type 1 diabetes and were on basal bolus insulin regimens at home. They were admitted to a variety of different hospital services and 7 patients had consults related to their diabetes prior to the development of DKA. Patients developed DKA a median of 2 days after admission and the majority of cases were caused by problems with insulin dosing including missed doses and dose reduction by 50% or more. In the same admission in which they developed DKA, 16 patients also experienced episodes of hypoglycemia. Of all 27 patients, 12 were deceased by the end of the study period.

These data highlight three challenges in caring for diabetic patients that may be contributing to the development of hospital-acquired DKA. The first challenge is the transition to inpatient management as demonstrated by the occurrence of many cases of hospital-acquired DKA within 48 hours of admission. The second challenge is communication between co-managing teams given the development of DKA despite the involvement of expert consultants. The third challenge is labile blood sugars as shown by the large proportion of cases with hypoglycemia during the same admission. Below, each challenge is discussed in detail.

1. *Transition to inpatient management*

In our study, hospital-acquired DKA occurred a median of 2 days after admission. This suggests that diabetic patients are especially vulnerable to hospital-acquired DKA

within the first 48 hours of admission. On average DKA takes less than 24 hours to develop, meaning that many cases began to develop shortly after hospital admission. Given that the majority of cases were caused by problems with insulin dosing, this finding likely highlights challenges providers face in determining which types of insulin to use in the inpatient setting and their appropriate doses. Inappropriate insulin orders placed on admission can cause hospital-acquired DKA within the first 48 hours.

In addition, in approximately one quarter of cases, the type of diabetes was not specified either by ICD code or in the text of the admission note. Unspecified diabetes type may hinder appropriate glycemic control (e.g. due to the absolute requirement for insulin in patients with type 1 diabetes) and could be an indicator that diabetes management was not prioritized during the hospital admission.

Challenges with documenting the correct diabetes types, choosing which insulin types to continue in the inpatient setting and selecting an appropriate dose appear to be contributing to many cases of DKA that occur within the first 48 hours of admission given that many of these cases are caused by inappropriate insulin dosing. Missed and reduced doses of insulin are common in the transition to the inpatient setting due to changes in patients' diets and environments. Assessing patients' insulin needs at the time of admission depends on knowledge of that patient's diabetes type, treatment regimen at home, and diet in the hospital. Even with this information, glycemic control requires dose adjustments based on frequent blood glucose monitoring throughout the hospitalization. Additional challenges arise when a patient is admitted for a problem unrelated to their diabetes because the reason for admission may be prioritized over glycemic control both during the admission and throughout the hospital stay.

To address the difficult transition from outpatient to inpatient management of diabetes, we propose the following:

a. Expand the admission insulin order set to provide more detailed instructions on dosing of basal and bolus insulin including suggested dosing based on outpatient regimen and hospital diet
b. EMR alerts for insulin dose reduction of >50% of outpatient dose or discontinuation of basal insulin in patients on outpatient basal regimens or those with type 1 diabetes
c. Re-categorization of diabetes in the EMR problem list and past medical history to encourage specification of diabetes type

2. Communication between co-managing teams

In 7 of 27 cases, a consult service (including medicine, endocrine, or the diabetes team) was following the patient's diabetes prior to the development of DKA. In these cases, diabetes management is typically the responsibility of the consulting specialists and problems with glycemic control caused by insulin dosing may be due to decisions made by the consultants and not the primary service. However, on further investigation it became apparent that consultant recommendations were not always communicated or carried out.

Multiple teams managing diabetes in a single patient can cause challenges in the creation, communication, and follow-through of the diabetes management plan. These challenges were evident among patients who developed DKA on the podiatry service

while being managed by a consulting medicine team and patients with endocrine or diabetes team consultants.

To address the challenges in communication between co-managing teams, we propose the following:

a. Assessment of communication barriers between consultants and primary services about diabetes management using qualitative/narrative interviews

3. Labile blood sugars

A majority of patients in our study were hypoglycemic during the same admission they developed DKA. Ten patients were hypoglycemic before the development of DKA and 6 were hypoglycemia after. Progress notes in several charts mentioned concern for hypoglycemia as rationale to lower or discontinue basal insulin. These appropriate concerns raise additional challenges – the risk of hypoglycemia needs to be balanced against the risk of DKA, each one of which can develop acutely when insulin is given in excess or when it is held or reduced, respectively.

To address the challenges in managing diabetic inpatients with labile blood glucose we propose the following:

a. Addition of dose adjustment suggestions to the EMR insulin order based on real time blood glucose levels [One proposed solution using an algorithm for insulin dosing suggestion is found in Maynard et al (Appendix E).[88] This algorithm walks providers through appropriate dosing based on the patient and their diet while in the hospital. It also includes adjustments based on hyper or hypoglycemia. An algorithm like this could be integrated into admission

orders as well as programmed to suggest dose adjustments based on real-time blood glucose results.]

b. Educational intervention for providers on the appropriate basal/bolus regimens to minimize both hyper and hypoglycemia[88]

Limitations

Although we know that hospital-acquired DKA is not unique to our hospital, the results of this study may not be generalizable across institutions because it was performed at a single site. However, the purpose of this analysis is to call attention to the existence of hospital-acquired DKA and highlight common cause analysis as a method of investigating and addressing these events. Using this approach, hospitals will be able to identify and address causes of DKA specific to their institution. This type of approach will allow for the most effective, tailored interventions. As other hospitals and individuals perform their own analyses, it is likely that some of the causes will be similar across institutions. Implementing and monitoring interventions directed at these common causes could provide useful data for hospitals across the country aiming to reduce cases of hospital-acquired DKA.

This analysis likely vastly underestimates the incidence of hospital-acquired DKA because it relies on appropriate ICD coding and uses strict criteria for DKA. Many cases of DKA are not coded as such because of errors in coding or diagnosis. Although quantifying the incidence of hospital-acquired DKA is important in order to understand the scope of the problem, that was not the aim of this analysis. The purpose was to find the most severe, unquestionable cases of hospital-acquired DKA in order to describe

patterns in precipitating factors that can lead to the development of targeted interventions. Other, less severe cases likely have similar causes that were recognized and addressed before they reached DKA that would qualify for our study. Interventions targeted at the most severe cases may also address these cases of incipient DKA.

Not only does relying on chart documentation lead to an underestimation of the number of cases of DKA, but it also may have limited our ability to understand the cases of hospital-acquired DKA that we did identify. Not all events that occur during an inpatient admission are documented in the chart. Furthermore, providers may be less likely to document adverse events especially when they are iatrogenic. When reviewing cases, we made every effort to use objective data such as records of insulin administration and sepsis criteria. We also used multiple sources of notes from primary teams, consultants, and nursing staff. However, we understand that we may still have missed important events due to a lack of documentation.

Next Steps

This analysis sought to identify the patient population and clinical context in which hospital-acquired DKA develops at a large teaching hospital using common cause analysis. Identification of patterns in causes of hospital-acquired DKA is the foundation of the development of effective and targeted interventions. At this point, we have characterized patient, clinical, and institutional factors that contributed to the most serious cases of DKA identified by ICD codes. However, there is still work to be done.

We have several ongoing and future initiatives to better understand and address hospital-acquired DKA. First, as mentioned above, we are working to address each

specific challenge identified in our study with a targeted intervention. In order to do so effectively, we are collaborating with Dr. Steven Choi, the chief quality officer of YNHH. Second, we plan to use laboratory values to identify patients with hospital acquired DKA regardless of whether or not it was coded appropriately. We can further examine these cases to understand not only why it occurred, but what prevented accurate and timely diagnosis if applicable. Finally, we are looking to share our results with other institutions. This will help us call attention to hospital-acquired DKA and identify collaborators with whom we can identify and address common causes. The manuscript based on this work will be submitted for publication (with CZ as the lead author). With these efforts, we aim to reduce cases of inpatient DKA at our hospital and others in the US.

Aim 2: Severe Outpatient Hypoglycemia

Our analyses of 305,310 patients of KPNC demonstrated racial disparities in rates of severe outpatient hypoglycemia requiring ED visits or hospitalizations. These disparities were consistent with prior studies.[41,89] We did not find significant differences in insulin use between races and ethnicities despite previous research demonstrating a higher rate of insulin use among Black patients. This may be a result of standardization of access and diabetes management in the KP system. This finding allows us to restrict our study population to patients on insulin in order to create a more homogeneous study population.

In our DAG, we proposed that the observed racial disparities in severe hypoglycemia are mediated by several categories of factors including sociodemographic factors and social determinants of health, comorbidities and healthcare utilization, health

literacy, and health behaviors. We expect each variable in the DAG to contribute to the disparities to varying degrees. However, assessing the impact of all of these variables using inverse probability weighting to determine the counterfactual disparity measure is impractical at this stage. Therefore, we plan to start with the variables we believe have the highest impact according to our literature review and expert clinical knowledge.

We expect that racial disparities in severe hypoglycemia are primarily driven by differences in healthcare utilization patterns. Severe hypoglycemia requiring an ED visit or hospital admission involves two steps: the development of hypoglycemia and the inability to manage hypoglycemia at home. Although research has demonstrated racial disparities in ED visits and hospital admissions for SH, it is not known whether these disparities arise from differences in rates of hypoglycemia or differences in ED visits for hypoglycemia or both.

We suspect that although there may be increased rates of severe hypoglycemia among Black patients compared to White patients, these differences will not be as great as the racial differences in ED visits and hospitalizations for severe hypoglycemia because of increased use of the emergency room for severe hypoglycemia among Black patients compared to White patients.[72] As demonstrated in the DAG, other factors affect healthcare utilization patterns including sociodemographics and social determinants of health, health literacy, and health behaviors. Therefore, we expect that a large portion of the causal effects of other variables may act through differences in patterns of healthcare utilization. Beginning our analysis by assessing the impact of healthcare utilization patterns on racial differences in severe hypoglycemia will allow us to work backward in order to determine the most important causal factors.

Limitations

One of the main challenges of this type of study is the identification and measurement of variables. It is not possible to identify every single variable that mediates racial disparities in severe hypoglycemia and measure it perfectly. However, that is not the aim of this study. Instead, the aim is to identify important factors that may be driving the observed racial disparities in order to understand which variables to target in interventions to reduce these disparities. Although we may not capture every mediator variable or measure the effects of each mediator precisely, our analysis will yield important information on the relative impact of key mediators. This will allow us to create interventions targeted to reduce disparities in ED visits and hospitalizations for severe hypoglycemia.

This study also uses the KPNC system, which has detailed information on a large population of patients with access to care. Racial and ethnic disparities in access to healthcare in this population are much smaller than in the general US population. Although this is helpful in identifying other factors that may be mediating disparities in healthcare outcomes, we do not want to minimize the importance of addressing disparities in access to care in the general population.

Next Steps

We are currently working to define and measure each variable proposed in the DAG in order to begin our inverse probability weighting analysis with ED visits for any cause in the prior year as the mediator variable. Subsequently, we plan to analyze each proposed variable in a similar fashion. Ultimately, understanding the factors that mediate the racial disparities in ED visits and hospitalization for severe hypoglycemia will allow

us to develop the most effective interventions. The manuscript based on this work will be submitted for publication (with CZ as the lead author).

Conclusions

Taken together, these two projects demonstrate the usefulness of thorough analysis and description of iatrogenic complications of diabetes. The process through which we examine and analyze these problems is of the utmost importance and this project demonstrates two rigorous analyses for cohorts of different sizes. In the hospital-acquired DKA analysis, common cause analysis is used on a small number of cases with extensive data on each individual case context. In the severe outpatient hypoglycemia analysis, Directed Acyclic Graphs are created to clearly depict which variables mediate the relationship between race/ethnicity and severe hypoglycemia and we describe the analytic plan using inverse probability weighting to estimate counterfactual disparity measures. These analyses minimize bias and allow for appropriate controlling for confounders. Although iatrogenic complications of diabetes can be challenging to examine due to their complex nature, their effects on patient safety are important and impossible to ignore. Understanding and describing the factors contributing to these iatrogenic complications is the first step in reducing their occurrence.

Appendices

Appendix A: DKA criteria

Glucose, mean (range)	359 (263-604)
HCO_3, mean (range)	13 (5-17)
Anion gap, mean (range)	25 (17-35)
Beta-hydroxybutyrate, mean (range) (n=16)	3.3 (0.08-8.9)
pH arterial, mean (range) (n=11)	7.35 (7.22-7.49)

Appendix B: Treatment regimens[90]

Treatment regimens for patients with diabetes mellitus vary based on diabetes type and severity. In type 1 diabetes, therapy with insulin including both basal (long-acting) and bolus (short-acting) or premixed insulin is initiated at the time of diagnosis because of the absolute insulin deficiency in type 1 diabetes. In type 2 diabetes, the choice of therapy is dependent on disease severity. After a trial of lifestyle changes, many patients with less severe disease are initially started on oral medications (often with a 3-month trial of monotherapy followed by a 3-month trial of dual therapy). If blood sugars are not well-controlled on 2 oral medications, basal insulin therapy is often initiated. Due to the progressive nature of the disease, many patients require therapy intensification including the transition to basal and bolus or premixed insulins or the use of an insulin pump later in the course of their disease.

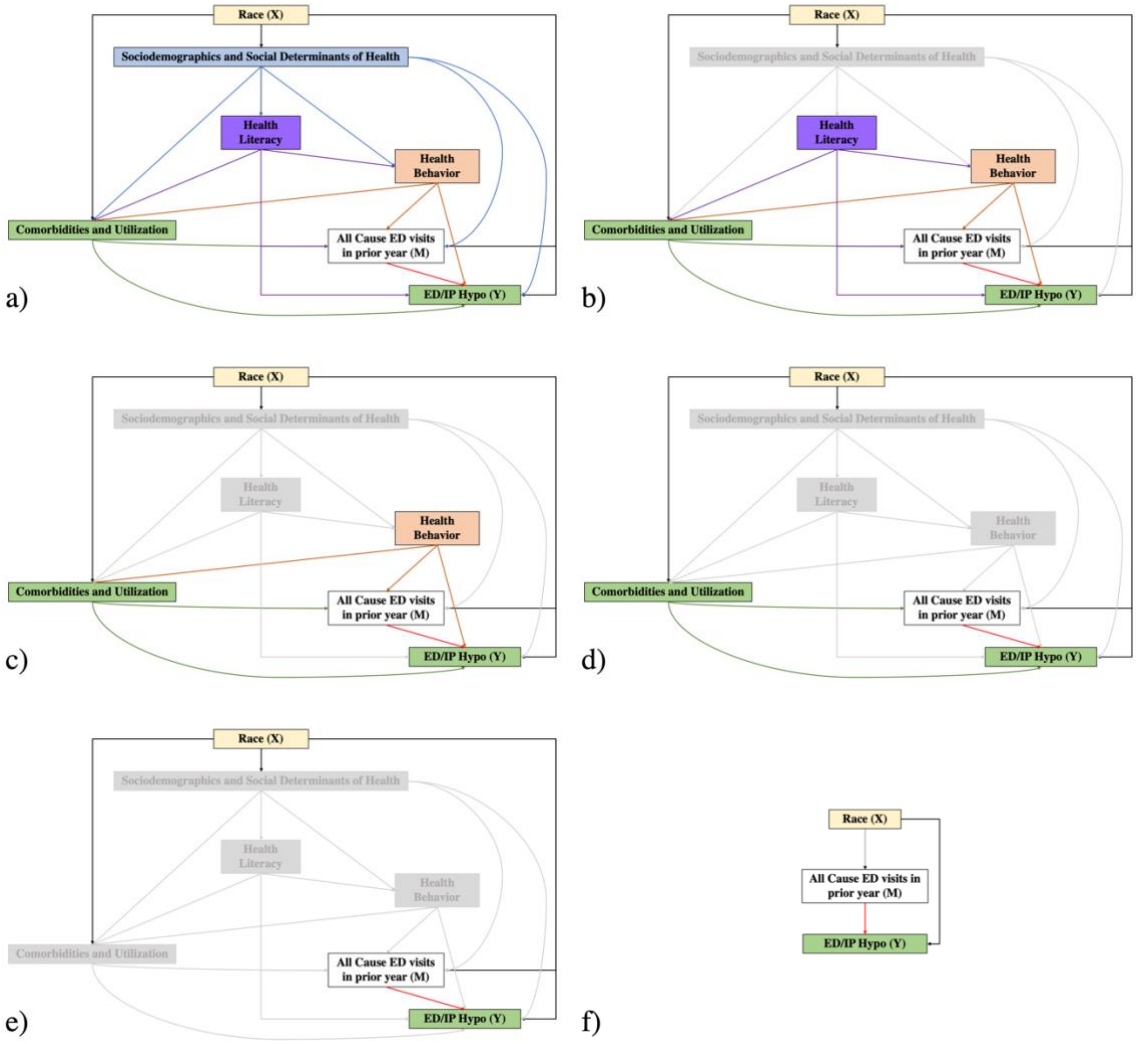
Many of the patients in our study had type 1 diabetes, and were therefore on basal and bolus or insulin pump regimens. Among patients with type 2 diabetes, the treatment regimens that include basal and bolus insulin may indicate increased disease severity compared to patients on basal insulin or oral medications only.

Appendix C: Charlson Comorbidity Index Calculation[91]

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

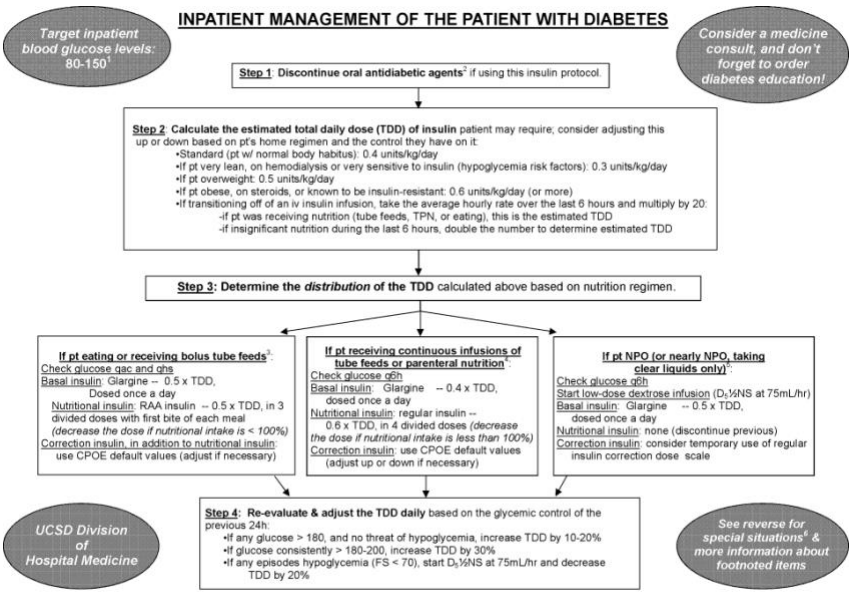
NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Appendix D: Inverse Probability Weighted Analysis for All Cause ED Visits in Prior Year



Legend:
a) Initial DAG with all cause ED visits in prior year isolated as the mediator variable (M).
b) Adjustment for sociodemographics and social determinants of health blocks the pathway between race and health literacy, health behavior, and comorbidities/utilization. It is not a collider, so no bias is introduced.
c) Adjustment for health literacy blocks the pathway between race and health behavior.
d) Adjustment for health behavior.
e) Adjustment for comorbidities and utilization removes all other alternate pathways from race to all-cause ED visits in prior year and race to ED visits/hospitalizations for severe hypoglycemia.
f) Final DAG with our exposure, outcome, and mediator of interest. Adjustment for this mediator will determine how much of the effect of race on ED/IP hypo is mediated by all caused ED visits in the prior year.

Appendix E: Sample Insulin Dosing Algorithm from Maynard et al[88]



This algorithm illustrates the preferred regimens at UCSD as of April 2005. Preferred regimens may vary among different institutions. Determir insulin, administered once or twice a day, is a suitable alternative to glargine insulin dosed q day.

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