Predictors and Treatment Outcome of Hyperglycemic Emergencies at Jimma University Specialized Hospital, Southwest Ethiopia

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Abstract

***Background**: Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two most common life-threatening acute metabolic complications of diabetes.*

***Objective**: to assess predictors and treatment outcome of hyperglycemic emergencies (HEs) among adult and adolescent diabetic patients admitted to Jimma University Specialized Hospital (JUSH), Southwest Ethiopia.*

***Methods**: A three year retrospective review of medical records of diabetic patients admitted with HEs at JUSH was done. The information extracted included patient demographics, admission clinical characteristics, precipitants, insulin used and treatment outcomes. Statistical tests used were student's t-test, chi-square test, and binary logistic regression with α set at 0.05.*

***Results**: Complete data was available for 163 out of 421 patients admitted with HEs, 102 (62.6%) males and 61 (37.4%) females. Mean age of patients (years) was 36.6 ± 15.9 (range 15-84). The majority (63.8%) of patients had type 1 diabetes and 74 (45.4%) were newly diagnosed at admission. DKA was noted in 151 (92.6%) subjects. The most common precipitants of HEs were infections 95 (59%), non-compliance to medications 52 (32.3%), and newly diagnosed diabetes 38 (23.6%). Recurrent hyperglycemia, hypoglycemia and ketonuria (in DKA patients) occurred in 88 (54%), 34(20.9%) and 31 (20.5%) patients respectively. Mean amount of insulin used and duration of treatment till resolution of DKA were 136.85 ± 152.41 units and 64.38 ± 76.34 hours respectively. The average length of hospital stay was 9.4 days (range 1 to 59). Mortality rate of patients from HEs was 16 (9.8%). Independent predictors of HEs mortality were admission serum creatinine >1.2 mg/dl (AOR=5.86, 95%CI: 1.36-25.28, P=0.018), co-morbidity (AOR=15.26, 95%CI: 3.67-63.41, P<0.001) and sepsis (AOR=9.83, 95%CI: 1.59-60.79, P=0.014).*

***Conclusion**: DKA was the major presentation of HEs. Infections, non-compliance and new onset diabetes were the most common precipitants of HEs. Length of hospital stay and mortality from HEs were high. High use of insulin, recurrent hyperglycemia, hypoglycemia, and ketonuria were common problems noted in HEs management at the hospital. Elevated serum creatinine, sepsis and co-morbidity were independent predictors of HEs mortality. Generally, prevention, early detection and proper management of HEs at the hospital should be given due consideration.*

Key words: Hyperglycemic Emergencies, Predictors, treatment outcome, Ethiopia

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List of Acronyms and Abbreviations

BG: Blood Glucose

BUN: Blood Urea Nitrogen

DBP: Diastolic Blood Pressure

DFU: Diabetic Foot Ulcer

DKA: Diabetic Ketoacidosis

DM: Diabetes Mellitus

EDA: Ethiopian Diabetes Association

GCS: Glasgow Coma Scale

HEs: Hyperglycemic Emergencies

HHS: Hyperosmolar Hyperglycemic State

IDF: International Diabetes Federation

JUSH: Jimma University Specialized Hospital

MRN: Medical Record Number

OGLAs: Oral Glucose Lowering Agents

SD: Standard Deviation

SBP: Systolic Blood Pressure

SeCr: Serum Creatinine

SPSS: Statistical Package for Social Sciences

SSI: Sliding Scale Insulin

UTI: Urinary Tract Infection

Chapter one: Introduction

1.1. Background

Diabetes Mellitus (DM) is a metabolic disorder of multiple etiology characterized by chronic hyperglycemia due to defects in insulin secretion, insulin action, or both (1). It is classified on the basis of etiology and clinical presentation of the disorder into four types: type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types (2).

Type 1 diabetes is predominant in younger age groups with an increasing incidence in both rich and poor countries. It usually accounts for only a minority of the total burden of diabetes in a population. However, type 2 diabetes constitutes about 85 to 95% of all diabetes in high-income countries with a higher percentage in low-and middle-income countries due to rapid socio-cultural changes, ageing populations, increasing urbanization, reduced physical activity and unhealthy lifestyle and behavioral patterns (2,3).

From 1999 to 2011 prevalence and incidence of DM in Africa was 3.5 per 100,000 persons and 2.1 per 100,000 persons per year in Ethiopia (4). According to International Diabetes Federation (IDF), the greatest expected increase in diabetes is in low-income countries (92%) and the African region is expected to have the largest proportional increase by 2030 (5).

Diabetes is frequently associated with acute non-metabolic and metabolic complications. Diabetic ketoacidosis (DKA) and Hyperosmolar hyperglycemic state (HHS), commonly known as hyperglycemic emergencies (HEs), are the two most common life-threatening acute metabolic complications of diabetes (6–8).

Diabetic ketoacidosis is characterized by a triad of hyperglycemia, ketosis and acidemia and it is diagnosed when blood glucose is 250 mg/dl, arterial pH is 7.3 and bicarbonate is 15 mEq/L, and moderate ketonuria or ketonemia. Whereas HHS is characterized and diagnosed by marked elevation in blood glucose (> 600 mg/dL), elevated serum osmolarity (> 320 mOsm per kilogram of water) and a pH level > 7.30 with mild or absent ketonemia (7,9).

DKA and HHS usually occur secondary to infection (30–50% of cases), poor compliance to anti diabetic medications, intercurrent illnesses, psychological stress, alcohol/drug abuse, trauma and new onset type 1 diabetes (10–14). Mortality from HEs is often related to the underlying co-morbidities and the precipitating insult (15).

In general, DKA occurs in type 1 and most often HHS occurs in type 2 diabetes; however, each type of diabetes may be associated with DKA or HHS. Both conditions are associated with marked dehydration, electrolyte disturbances, insulin deficiency and increased counter-regulatory hormones. So treatment consists of water and electrolyte replacement and insulin administration. Recognition and treatment of precipitating factors and frequent monitoring of patients with effective standard treatment protocols are the most crucial aspects of the management affecting outcome (15–17).

1.2. Statement of the problem

According to IDF, diabetes affected at least 285 million people worldwide accounting for 12% of health expenditures in 2010 or at least $376 billion. This number is expected to reach 438 million by the year 2030 which is expected to hit $490 billion with two-thirds of all diabetes cases occurring in low- to middle-income countries (5,18).

Diabetes is one of the most challenging health problems in the 21st century. Its complications are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society (19). For example, mortality rates range from 2–5% for DKA and 15% for HHS with higher rates in the older population (20–23).

In the United States of America, 43% of the total medical costs for diabetes is spent on hospital inpatient care (24).The costs of DKA treatment are significant, with estimated mean expenses for a single hospitalization ranging from $7,470 to $20,864 (25).

In Ethiopia the prevalence of diabetes is increasing for the last two to three decades indicating that it is becoming a major economic factor in drug use and bed occupancy (26). Socioeconomic factors, particularly the cost and unreliability of insulin supplies are major obstacles to the control of diabetes and prevention of ketoacidosis in Ethiopian patients (27).

Of diabetic patients admitted at Tikur Anbessa Specialized Hospital, the average total cost of hospitalization was significantly higher than the non diabetic patients admitted to the hospital with a mean cost of 1109.7 ± 1026.4 Birr for diabetic patients and 872.9 ± 828.3 Birr for non diabetic patients respectively. A larger proportion (57%) of the total cost was utilized for treatment of acute and chronic complications of diabetes (26).

More than one-third, but only less than half, of diabetic patients in Ethiopia receives standard diabetes care (28). According to a study in Addis Ababa, access for blood glucose monitoring of diabetic patients and the emphasis given for diabetic education was low. Ninety five percent of DM patients didn't perform self-blood glucose monitoring at home, 33% didn't take their treatments regularly, 75% required admissions directly or indirectly due to uncontrolled diabetes and 25.5% of them was admitted due to DKA (29).

In at least one central hospital in Ethiopia, 3.5% of admissions to all services were of diabetics, 19.7% of bed on medical wards was used by diabetics and 18% of them died due to DM complications. Diabetes is a frequent cause of morbidity and mortality in an Ethiopian hospital because of scarce inpatient facilities and limited resources (30). The cost of inpatient diabetes management in the country is enormous and significantly higher than the cost of other inpatient managements (30). Control of hyperglycemia is commonly unsatisfactory in Ethiopian diabetic patients for reasons related to poverty, and interruption of therapy for many social and economic reasons (31). The commonest cause for diabetic admission was DKA (71.1%) resulting in a 5.8% death (32).

Among DM patients on follow up at Jimma University Specialized Hospital (JUSH), only 18.1% of patients were able to control their fasting blood sugar below 126 mg/dL (33) and DKA was the commonest acute complication and cause of hospital admission (34,35).

Generally, the overall treatment complications, precipitants, length of hospital stay and mortality of HEs in the country are not well known and hence, this study aimed to assess such problems along with mortality predictors.

Chapter Two: Literature Review

Diabetic ketoacidosis and hyperosmolar hyperglycemic state are two important causes of mortality and morbidity in patients with diabetes. Fortunately, DKA treatment is very effective; experienced centers have an estimated mortality rate from DKA of < 5% and about 15% in HHS, much of which are avoidable with appropriate management (17,25).

According to a study by Randal et al on DKA patients in USA, 22% were newly diagnosed diabetic patients with a first episode of DKA. The common precipitating factors were; insulin discontinuation (68%), new-onset diabetes (10%), infection (15%), medical illness (4%), and un-determined causes (3%) (36). In a Thailand study on incidences and outcomes of hyperglycemic crises, infections (73.5%) and non-compliance with treatments (42.2%) were the precipitating factors for HEs. Recurrent hyperglycemia and hypoglycemia during treatment were documented in 69.9% and 15.7% of patients respectively. The overall mortality rate of hyperglycemic crises was 8.4% (5.8% in DKA and 15.8% in HHS). Admission serum sodium was independently associated with mortality (AOR=1.08, 95% CI = 1.01-1.16, p = 0.03) (37).
Mortality review of DKA patients in Pakistan showed that 13.8% patients had their first presentation as DKA, the rest with known diabetes including 56.8% diabetics for less than 10 years and 11.4% diabetics for more than 10 years. Twenty (45.5%) of patients had +4 Urinary ketones. The precipitating factors were; infections 45.55%, myocardial infection 24.5%, non-compliance 11.4 %, surgery 2.3 %, unknown cause 25.0%, and 11.4 % with other causes. About 16% of patients died and 84.1% of patients were discharged (38).

In a Jamaican study DM patients with HHS were older than DKA ones (64.5 years [95% CI: 60.7-68.4] vs. 35.9 years [95% CI: 30.2-41.6]). Most DKA patients (62%) had type 2 diabetes. Only 2% of HHS patients had type 1 diabetes. Mortality from DKA was 6.7% and 20.3% from HHS. Mortality increased significantly with age, especially in patients ≥ 50 years. Significant predictors of mortality were altered mental status on admission, co-existing medical disease, increasing age, and older age at onset of diabetes, acute stressors, and DKA/HHS. In multivariate models, only altered mental status was significant (OR=3.59; 95% CI: 1.24-10.41) (39).

A study in Taiwan on prognostic factors of HHS patients showed that 72.3% cases of HHS occurred in patients with known diabetic history and 27.7% in those with no diabetic history. Most patients received oral antidiabetic drugs before HHS episodes. Death occurred in 24.4% of patients. The patients who died had shorter length of inpatient stay than did survivors (40).

In an Australian study, age at presentation for DKA patients was significantly less than HHS patients (33 ±1.2 vs. 69 ± 1.7 years, P<0.01). Age (P<0.001) and category of diabetic emergency (P<0.001) were amongst the variables that had a significant association with mortality. However, age was the only independent predictor of mortality in a multivariable analysis (P < 0.01) (41).

Zouvanis et al in South Africa reported that mortality from DKA was 6.8% and from HHS was 16.6%. Infection (39%), first presentation (23%), and noncompliance (21%) were the precipitating factors for HEs (42). In the same country Pepper et al reports showed that sepsis (36%), non-compliance with therapy (32%), and a new diagnosis of diabetes (11%) accounted for most HEs admissions. The mean duration of hospital stay was 4 days, and the overall in-hospital mortality of HEs was 7.5% (43).

In Legos, Nigeria DKA and HHS accounted for 85% and 15% of patients respectively. The mean age of the study subjects was 53.9 ± 14.4 ranging 22–86 years. Admissions due to HEs were recorded more in the 36–64 years age group while the least number of hospitalizations was found in those below 35 years of age. The overall mortality rate of HEs was 20%. Fourteen percent of the subjects with HEs were diagnosed of DM at presentation. The mean duration of DM was 6.8 (9.4) years. The common precipitants were poor drug compliance (44.1%), undiagnosed diabetes (13.5%), DFU (18%), CVA (8.1%) and sepsis (13.5%). Being elderly (OR=1.3, 95% CI: 0.3-4.1), hypokalemia (OR=0.5,95% CI: 0.2–1.6), hypertension (OR= 0.3, 95% CI: 0.1–0.9), sepsis (OR=3.2, 95%CI: 0.6-16.7) and short duration of DM (OR=1.7, 95% CI: 0.1-16) were predictors of HEs related fatality (44).

In a retrospective study on Nigerian patients with HEs, 27.38% were hypertensive. There were 41.7% cases of DKA and 58.3% cases of HHS. About 55% of all the study subjects were new diabetic patients. The mean age of subjects was 50.59 years. Patients with HHS were significantly older than DKA patients (56.98 ± 1.78 vs. 41.97 ± 2.37 years, *P*<0.001). The major

precipitants were infections and non compliance with glucose lowering drugs. Of all patients 92.86% were improved and discharged home, 3.57% died and 3.57% discharged against medical advice (45).

A five year retrospective review of diabetic admissions in Nigeria also showed that compliance to treatment was largely poor. Sixty nine percent of the subjects were non-compliant with their treatment. Length of hospital stay among died patients was higher than (31 ± 3.6 days) those discharged (18.7 ± 19.8 days) or left against medical advice (17.6 ± 9.6 days) but this difference was not statistically significant, P = 0.493 (46).

Odili and Okwuanasor (19) reported that of the total patients admitted with HEs only 5% of the patients did not have any obvious discernible comorbidity. The commonest comorbidity was hypertension (35%). Mean patient age and duration of admission were 58.4 ± 17.9 ranging 16-99 years and 8.3 ± 6.9 ranging 1–30 days respectively.

Ezeani et al reported that of the total patients admitted with HEs, 50% developed hyperosmolar hyperglycemic state, 31% DKA, 12% normo-osmolar nonketotic hyperglycemic state, and mixed hyperglycemic emergency in 7% of the subjects. The mean total duration of hospital stay in days was 24.2 ± 17.1 ranging 0.5–88; with 28.6 ± 17.65 and 20.4 ± 13.65 days for DKA and HHS respectively. The overall mortality rate from HEs was 4.8% and 4 out of the 5 patients who died were males. The mortality rate in males and females was 8% and 2% respectively. All the mortalities recorded were in subjects who had DM duration of less than 10 years prior to presentation (47).

In Sub-Saharan African patients the main precipitants of DKA are newly diagnosed diabetes, missed insulin doses and infections. Treated patients miss insulin doses for reasons like; unavailability and unaffordability of insulin, missed clinics, perceived ill-health and alternative therapies like herbs, prayers and ritual (48).

Guillermo and his colleagues reported that the amount of insulin administered until resolution of DKA and the mean duration of treatment until resolution of ketoacidosis among patients treated with regular insulin were 76 ± 46 units and 10.5 ± 6.3 hour respectively. Fourteen patients (41%) treated with NPH and regular insulin had 26 episodes of hypoglycemia and the mean total

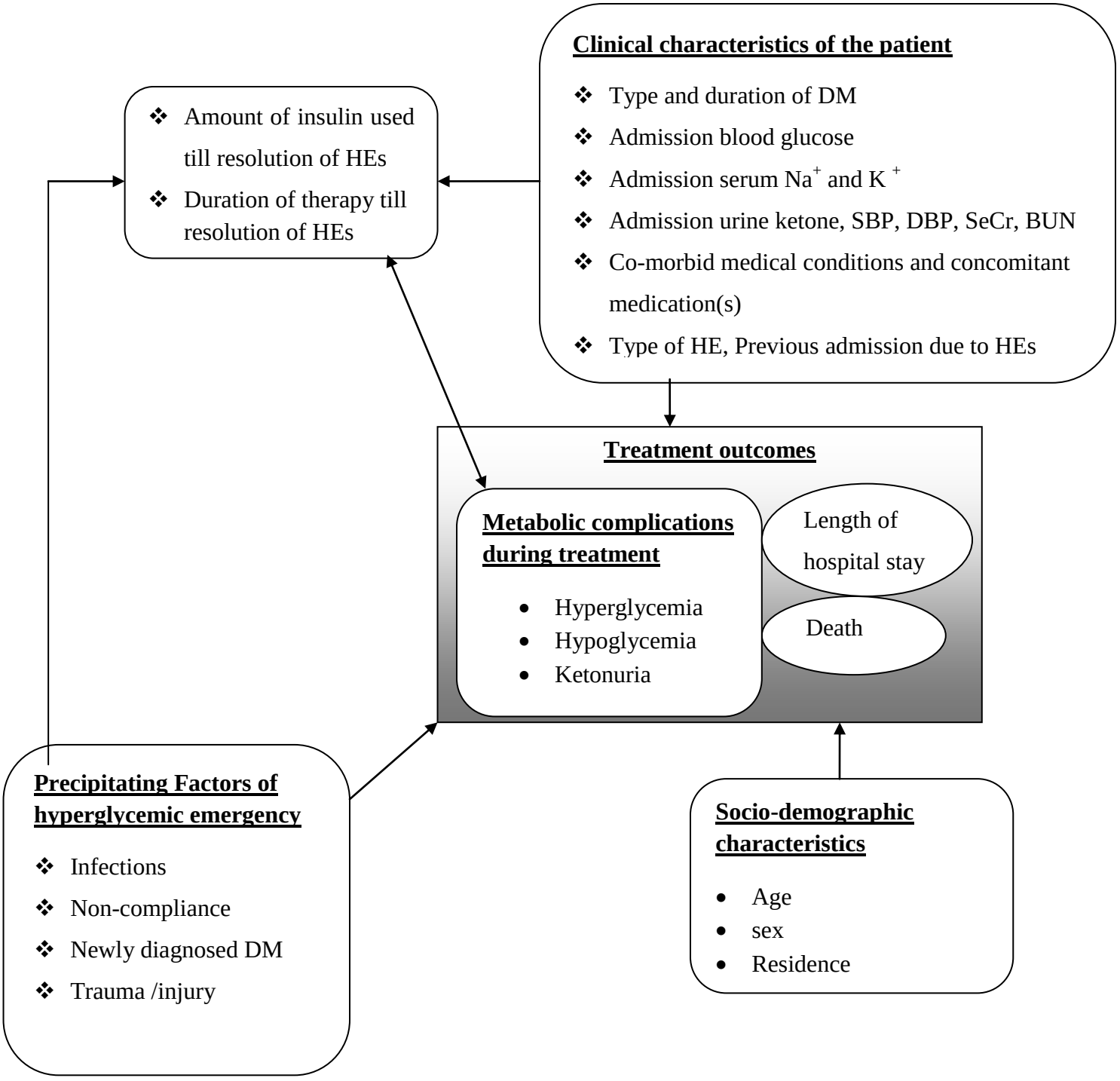
duration of insulin infusion was 20.5 ± 12 h (49). It was also reported that 98 ± 26 units of insulin and 11± 4 hours of treatment were needed until resolution of DKA with 1 (5%) developing hypoglycemic episode (50).

In another study the amount of insulin administered and the mean duration of treatment until resolution of DKA were found to be 82 ± 28 units and 11 ± 3 hours respectively(51). Jones (52) also reported that the mean time to resolution of DKA in patients treated with IV regular insulin was (10.6±7.4 hrs) and the mean amount of insulin used was 49 ± 29 units. Twelve (35%) patients had 25 episodes of mild hypoglycemia (BG < 70 mg/dL), and 2 patients (6%) had an episode of severe hypoglycemia (BG < 40 mg/dL).

Queale and his colleagues reported that sliding scale insulin regimens appear to provide no benefit; in fact, when used without a standing dose of intermediate-acting insulin, they are associated with an increased rate of hyperglycemic episodes**.** Suboptimal glycemic control is common in medical inpatients with DM which is associated with selected demographic and clinical characteristics (53).

In conclusion the majority of literatures reviewed showed that HEs are common problems experienced by diabetic patients often precipitated by infection, non-compliance to antidiabetic medication(s) and new onset diabetes. It is also shown that mortality from HEs is high in most studies attributed to different reasons. However, most of the studies conducted are limited to western countries and Nigeria and South Africa indicating lack of studies in East Africa on treatment outcome of HEs. None was reviewed in Ethiopia. Therefore, this research may produce findings that may fill these gaps.

2.1. Conceptual framework



HEs: Hyperglycemic emergencies, **DM**: Diabetes mellitus, **GCS**: Glasgow Coma Scale

Figure 1: Conceptual framework for predictors and treatment outcome of hyperglycemic emergencies.

2.2. Significance of the Study

The overall aspects of diabetes care in Ethiopian hospitals are frequently below recommended standards and the cost of inpatient diabetes management is significantly higher than the cost of other inpatient managements (28,30,34,35). Despite all these problems, to the best of the authors' knowledge, there are no adequate studies conducted on precipitants, predictors and treatment outcomes of HEs in Ethiopia. Therefore, this study will be of a paramount importance in producing important data on the magnitude of common precipitants, predictors and treatment outcomes of HEs.

The findings will also guide future directions to devise appropriate management protocol for HEs in the hospital in particular and for the country in general, and will help design effective treatment plans and interventions to improve treatment outcomes of hospitalized diabetic patients with HEs.

Chapter Three: Objectives

3.1. General objective:

To assess predictors and treatment outcome of hyperglycemic emergencies among adult and adolescent DM patients admitted to Jima University Specialized Hospital, Southwest Ethiopia.

3.2. Specific objectives:

The specific objectives of this study are:

- To identify the precipitating factors responsible for hyperglycemic emergencies related hospital admission.
- To determine treatment outcomes of hyperglycemic emergencies.
- To identify predictors of treatment outcome of hyperglycemic emergencies.

3.3. Research Questions

- What are the precipitating factors responsible for hyperglycemic emergencies related hospital admission among adult and adolescent DM patients admitted to JUSH?
- What are the treatment outcomes of hyperglycemic emergencies among adult and adolescent DM patients admitted to JUSH?
- What are the predictors for poor treatment outcome of HEs among adult and adolescent DM patients admitted to JUSH?

Chapter Four: Methods and Participants

4.1. Study setting

The study was conducted at Jimma University Specialized Hospital (JUSH). The hospital is one of the oldest public hospitals in the country which was established in 1937 during Italian occupation to serve as military hospital and rehabilitation. Geographically, it is located in Jimma city 352 km Southwest of Addis Ababa. Currently it is the only teaching and referral hospital in Southwest Ethiopia with 523 beds and a total of more than 1000 staffs of both supportive and professional. It serves approximately 20,000 admissions and 140, 000 outpatient visits a year with a catchment population of about 15 million people. Diabetes clinic at the hospital provides twice weekly outpatients services to over 100 diabetic patients a week. Antidiabetic medication(s) dose adjustment and regimen change is made based on patient fasting blood glucose readings on subsequent visits as the hospital does not use glycated hemoglobin (HbA1C) test for regular glucose monitoring of adolescent and adult diabetic patients.

4.2. Study design

A retrospective review of the medical records of diabetic patients admitted with hyperglycemic emergencies at JUSH.

4.3. Study period

The study was conducted from February 24/2014 to March 24/2014

4.4. Population

4.4.1. Source population

All diabetic patients with hyperglycemic emergencies admitted to JUSH from January 01/2011 to December 31 /2013.

4.4.2. Study population

Diabetic patients with HEs admitted to JUSH from January 01/2011 to December 31 /2013 who fulfilled the inclusion criteria.

4.4.3. Inclusion and exclusion criteria

Inclusion criteria

- Age ≥15 years old.
- All DM patients with HEs whose medical records contained complete pertinent data (Demographics, Admission laboratory tests, Treatment interventions and outcomes).

Exclusion criteria

- Pregnant mothers admitted with HEs.

4.5. Sample size and Sampling procedures

All diabetic patients with HEs admitted to JUSH over a three year period (January 01/2011 to December 31 /2013) were taken (with a convenient sampling method) and patients that met the inclusion criteria were included in the study. Over this period, a total of 421 patients were admitted with HEs of which only 163 patients' medical records contained complete information and studied.

4.6. Study Variables

4.6.1. Dependent variables

- **Primary outcome**
  - In hospital mortality due to HEs
- **Secondary outcomes**
  - Episodes of hypoglycemia during treatment
  - Episodes of hyperglycemia after resolution of HE
  - Episodes of ketonuria after resolution of DKA
  - Length of hospital stay

4.6.2. Independent variables

- Age
- Sex
- Residence
- Type of DM
- Duration of DM and antidiabetic treatment
- Admission blood glucose
- Admission blood pressure (BP)
- Admission serum sodium, potassium and Chloride (Cl^-) levels
- Admission serum creatinine (SeCr), Blood Urea Nitrogen (BUN),
- Precipitating factors for HEs
    - Infection , non-compliance, newly diagnosed DM and injury/trauma,
- Co-morbidities
- Concomitant medications
- Amount of insulin used (units) till resolution of HE
- Duration of treatment (hours) till resolution of HE

4.7. Data collection process

Five data collectors (Medical Interns) were trained for a day on the data collection tools, and data extraction procedures together with practical demonstration of the data collection from sample medical records. Then after, medical record numbers (MRNs) of patients along with treatment outcomes were traced and recorded retrospectively in a reverse chronological order from inpatient logbook. At last, the medical records were drawn from card room using MRNs extracted from inpatient logbooks, patient records that fulfill the inclusion criteria were filtered, coded and finally data was extracted.

Data extracted included sociodemographic characteristics, type of diabetes, duration of diabetes and duration of treatment, admission blood pressure, laboratory investigations (admission blood glucose, serum electrolytes, Blood Urea Nitrogen, and Serum Creatinine at presentation), antidiabetic and concomitant medications, precipitants, co-morbidities, amount of insulin used, duration of therapy till HEs resolution and treatment outcomes.

Patients with incomplete data such as demographics, results of laboratory investigations, amount of insulin used and treatment outcome were excluded. Selection of medical records for sampling was based on the physician's confirmed diagnosis registered on patient logbooks.

4.8. Data processing and analysis

Data was entered into Statistical Package for Social Sciences (SPSS) for windows Version 16.0 (Chicago, SPSS Inc.) for analysis. Data cleaning was done at several steps; prior to entry to SPSS, during entry and after entry. T-test was used for comparison of means of continuous variables. To see the association between categorical variables, chi-square test was used. To examine predictors of mortality, first a bivariate binary logistic regression (LR) between independent variables and death was done. Then variables with p-value <0.25 were entered into a multivariate logistic regression model and variables with p-value <0.05 were considered statistically significant.

4.9. Ethical considerations

Ethical clearance was obtained from Jimma University Collage of Public Health and Medical Sciences Ethical Review Committee Prior to data collection and official permission was obtained from JUSH to access data. Since data was collected from patient medical records, no consent and ascent issue was present. However, the medical records of patients were handled appropriately during data abstraction and returned to card room for documentation.

4.10. Data quality assurance

The data abstraction tool was pretested prior to data collection. Training was given for data collectors and they were being closely supervised during data collection. Meeting was being held on each day of data collection. Data had been checked during and post data collection for completeness and appropriateness and any ambiguity during data collection was being discussed on the spot. Only complete and accurate data were handed over from the data collectors as per the agreement set prior to data collection.

4.11. Strengths and Limitations of the study

- **Strengths**

Strengths of this study were:

All most all the studied samples contained complete data and data abstraction was done by medical professionals who have a good clinical experience.

- **Limitations**

Notable limitations of our study were:

First it was a retrospective Medical Records Review which limited us from getting all the necessary data to establish a causal association; Second the samples size is small as the majority of medical records had incomplete data; Third the diagnosis of type 1 DM and type 2 DM was based on simple clinical and laboratory parameters as c-peptide levels was not done; Fourth, blood glucose > 600mg/dl was not measured. Lastly, urine dipstick tests were used to check ketone clearance and serum osmolarity was not measured.

4.12. Operational definitions and Definitions of terms

1. **Co-morbidity**: the co-occurrence of one or more medical problems with diabetes.
2. **Concomitant medications:** one or more drugs used with antidiabetic medications concurrently.
3. **DKA**: refers to blood glucose >=250 mg/dL and urine dipstick ketone level >= +2.
4. **HHS:** refers to marked elevations in blood glucose (> 600 mg/dL), alteration in mental status and mild or absent ketonuria.
5. **Hyperglycemia**: An elevation of random plasma glucose greater than 200 mg/dL (54).
6. **Hyperglycemic emergencies**: refer to acute metabolic complications of diabetes (DKA and HHS) (54).
7. **Hyperkalemia**: referred to serum potassium levels of >5.2 mEq/L.
8. **Hypernatremia**: referred to serum sodium levels of >145 mEq/L.
9. **Hypoglycemia**: is defined as a blood glucose level <70 mg/dL (54).
10. **Hypokalemia**: referred to serum potassium levels of <3.5 mEq/L.
11. **Hyponatremia**: referred to serum sodium levels of < 135 mEq/L.

12. **Ketonuria:** a condition in which abnormally high amounts of ketones and ketone bodies are present in the urine.
13. **Length of hospital stay:** the time interval between date of discharge and date of admission spent by the patient at the hospital**.**
14. **Resolution of DKA:** blood glucose <200 mg/dL and negative dipstick urine ketone for at least two successive measurements two hour apart after treatment interventions.
15. **Resolution of HHS:** blood glucose <300 mg/dL and improvement in mental status after interventions.
16. **Resolution of HEs:** referred to resolution of DKA or HHS as defined above.
17. **Resolution of ketonuria**: a negative urine ketone confirmed with dipstick urine ketone test for at least two successive measurements two hours apart.
18. **Treatment outcome**: it refers to an outcome following treatment intervention(s) like any metabolic complication, improvement and discharge, death, length of hospital stay or any long term sequelae.

4.13. Dissemination of the findings

The findings of this study will be presented to Jimma university pharmacy department and Jimma University clinical staff and at professional meetings. It will also be disseminated to Oromiya Region Health Bureau, Federal Ministry of Health of Ethiopia, Diabetes Associations (EDA and IDF), and other concerned organizations. Finally, effort will be made to be published in a peer reviewed reputable Journal.

Chapter Five: Results

Sociodemographic and clinical characteristics of Patients with Hyperglycemic Emergencies

A total of 421 diabetic patients were admitted and treated for DKA and HHS at Jimma University Specialized Hospital (JUSH) over a three year period. Of these patients, only 163 of them had complete data and were included in the study. Hundred-two (62.6%) of them were males. The mean age of the participants was 36.57±15.91 (range 15 to 84 years). More than half of them (56.4%) were from urban. Family history of diabetes was reported in only 2 of the patients.

The majority, 104 (63.8%), of the participants had type 1 diabetes. All type 1 and 47 (79.7%) of type 2 diabetic patients developed DKA while HHS was noted in type 2 diabetics (P<0.001). Overall, there were 151 (92.6%) cases of DKA and 12 (7.4%) cases of HHS. All HHS cases were seen in patients older than 34 years (Table 1).

Seventy four (45.4%) of the patients were newly diagnosed with diabetes at admission. Eight (66.7%) out of 12 who developed HHS were new DM patients**.** Eighty five (95.5%) patients out of 89 known diabetics developed DKA. The majority, 94 (57.7%), of the patients had diabetes for less than a year while only 6 (3.7%) patients had diabetes for more than 10 years. Ninety five (58.3%) of the study subjects were on antidiabetic medications for <1 year. No HHS patient had either diabetes or was on antidiabetic medications for more than five years.

A total of 87 (53.4%) patients were on antidiabetic medications prior to admission and 58 (66.7%) of them were on insulin. All patients who were on insulin developed DKA (P<0.005). Eighty three (95.4%) of the patients who were on antidiabetic medication(s) developed DKA.

Table 1 Frequency of characteristics of diabetic patients by type of HE admitted to JUSH, from January 2011 to December 2013.

Variable	Variable category	DKA	HHS	Total	P- value
		Frequency (%)	Frequency (%)	Frequency (%)	
Age	15-24	40 (26.5)	0	40 (24.5)	<0.001*
	25-34	38 (25.2)	0	38 (23.3)	
	35-44	33 (21.9)	1 (8.3)	34 (20.9)	
	45-54	18 (11.9)	4 (33.3)	22 (13.5)	
	55-64	16 (10.6)	5 (41.7)	21 (12.9)	
	>64	6 (4.0)	2 (16.7)	8 (4.9)	
Type of DM	Type 1 DM	104 (68.9)	0 (0.0)	104 (63.8)	<0.001*
	Type 2 DM	47 (31.1)	12 (100.0)	59 (36.2)	
History of DM	New DM	66 (43.7)	8 (66.7)	74 (45.4)	0.216
	Known DM	85 (56.3)	4 (33.3)	89 (54.6)	
Duration of DM (years)	<1	85 (56.3)	9 (75.0)	94 (57.7)	
	1-5	34 (22.5)	3 (25.0)	37 (22.7)	0.428
	6-10	26 (17.2)	0	26 (16.0)	
	>10	6 (4.0)	0	6 (3.7)	
Duration of treatment (years)	<1	86 (57.0)	9 (75.0)	95 (58.3)	
	1-5	34 (22.5)	3 (25.0)	37 (22.7)	0.477
	6-10	25 (16.6)	0	25 (15.3)	
	>10	6 (4.0)	0	6 (3.7)	
Patients with prior antidiabetic treatment		83 (55.0)	4 (33.3)	87 (53.4)	0.252
Antidiabetic medications**:**	OGLAs	22 (26.5)	4 (100 .0)	26 (29.9)	0.102
	Insulin	58 (69.9)	0	58 (66.7)	0.005*
	Insulin+OGLAs	3 (3.6 %)	0	3 (3.4)	1.00
Patients with history of HEs admission		11 (7.3)	0	11 (6.7)	1.00
Patients with concomitant medications		13 (8.6)	0	13 (8.0)	0.601
Patients with co-morbidity		34 (22.5)	2 (16.7%)	36 (22.1)	1.00

*Statistically significant (p<0.05), **OGLAs**: Oral Glucose Lowering Agents, **DKA**: Diabetic Ketoacidosis, **HHS**: Hyperosmolar Hyperglycemic State, **DM**: Diabetes Mellitus, **HEs:** Hyperglycemic Emergencies, **JUSH**: Jimma University Specialized Hospital.

NB: Fisher's exact test was done for cells with >20% expected count <5**.**

Thirteen (8.0%) out of 163 patients had been taking concomitant medications prior to admission. There were 36 (22.1%) patients with co-morbidities of which 15 (41.7%) had hypertension (Table 2).

Table 2 Frequency of co-morbidities in diabetic patients with HEs admitted to JUSH, from January 2011 to December 2013.

Co-morbidity	Frequency (%)
Hypertension	15 (41.7)
Cardiovascular Diseases	7 (19.5)
Stroke	6 (16.7)
Viral hepatitis	4 (11.1)
chronic kidney disease	1 (2.8)
Malignancies	2 (5.6)
Others	5 (13.9)

NB: Total percentage is >100% as there were multiple response questions.

More than half (50.9%) of the patients had admission SBP (90-119 mmHg) and DBP (60-79 mmHg) respectively (Table 3). Seventy two (44.2 %) of the patients had SBP ≥120 mmHg and 75 (46.0%) had DBP ≥80 mmHg. Hypokalemia (serum K^+ <3.5 mEq/L) and hyponatremia (Serum Na^+<135 mEq/L) at admission were noted in 37 (22.7%) and 48 (29.4%) of the patients respectively. There were 34 (20.9%) patients with elevated admission serum creatinine (>1.2 mg/dL). The Mean admission blood glucose was 464.93 ± 99.81 mg/dl. Mean durations of diabetes and antidiabetic treatment were 2.42 ± 4.02 and 2.36 ± 3.96 years respectively.

Most of the patients 131 (80.4%) had no altered sensorium at admission (GCS=15) and the remaining 32 (19.6%) had altered sensorium (GCS <15). Admission urine ketone for DKA patients ranged from +2 to +4 with preponderance of +2 level in 81 (49.7%) of the patients.

Table 3 Admission clinical characteristics of diabetic patients with HEs, from January 2011 to December 2013.

Variable category		Frequency (%)
Systolic Blood Pressure(SBP) in mmHg	<90	8 (4.9)
	90-119	83 (50.9)
	120-139	59 (36.2)
	140-159	7 (4.3)
	≥160	6 (3.7)
	Mean ± SD	112.30 ± 24.85
Diastolic Blood Pressure (DBP) in mmHg	<60	5 (3.1)
	60-69	23 (14.1)
	70-79	60 (36.8)
	80-89	55 (33.7)
	90-99	12 (7.4)
	≥100	8 (4.9)
	Mean ± SD	73.56 ± 14.72
Serum Potassium (mEq/L)	<3.5	37 (22.7)
	3.5-5.2	125 (76.7)
	>5.2	1
	Mean ± SD	3.78 ± 0.48
Serum Sodium (mEq/L)	<135	48 (29.4)
	135-145	109 (66.9)
	>145	6 (3.7)
	Mean ± SD	137.54 ± 4.77
Serum chloride (mEq/L)	<95	4 (2.5)
	95-107	88 (54.0)
	>107	71 (43.6)
	Mean ± SD	107.59 ± 7.49
Serum creatinine (mg/dL)	<0.5	2 (1.2)
	0.5-1.2	127 (77.9)
	>1.2	34 (20.9)
	Mean ± SD	1.21 ± 0.99
Blood Urea Nitrogen (BUN) (mg/dL)	<7	1 (0.6)
	7-20	95 (58.3)
	>20	67 (41.1)
	Mean ± SD	30.82 ± 40.36
Blood Glucose (mg/dL)	Mean ± SD	464.93 ± 99.81
Glasgow Coma Scale (GCS)	< 15	32 (19.6)
	15	131 (80.4)
Urine Ketone (DKA)	+2	81 (49.7)
	+3	71 (43.6)
	+4	11 (6.7)

Admission characteristics of DKA and HHS patients were compared in Table 4. Patients with HHS were significantly older than those with DKA (56.25 ± 8.68 vs. 35.00 ± 15.31 years, P<0.001). Admission SBP and DBP (mmHg) of DKA patients were significantly higher than patients with HHS. Mean SBP was 113.6 ± 23.64 and 95.83 ± 33.97 for DKA and HHS patients respectively (P=0.017). Mean DBP of DKA patients was 74.44 ± 13.68 mmHg and 62.50 ± 22.21 mmHg for HHS patients (P=0.006). However, there was no significant mean difference in admission mean serum potassium, serum sodium, serum chloride, serum creatinine, BUN and GCS between DKA and HHS patients.

Table 4 Admission characteristics of diabetic patients by type of HE at JUSH, from January 2011 to December 2013.

Parameter	DKA Mean ± SD	HHS Mean ± SD	P -value
Age (years)	35.00 ± 15.31	56.25 ± 8.68	<0.001*
Blood glucose (mg/dl)	454.20 ± 95.83	>600.00	<0.001*
SBP (mmHg)	113.61 ± 23.64	95.83 ± 33.97	0.017*
DBP (mmHg)	74.44 ± 13.68	62.50 ± 22.21	0.006*
Serum Potassium (mEq/L)	3.78 ± 0.47	3.70 ± 0.57	0.591
Serum Sodium (mEq/L)	137.71 ± 4.52	135.46 ± 7.17	0.116
Serum Chloride (mEq/L)	109.67 ± 7.42	107.79 ± 6.49	0.395
Serum Creatinine (mg/dL)	1.18 ± 0.99	1.63 ± 0.97	0.135
GCS	14.52 ± 1.61	14.00 ± 1.21	0.273

***** Statistically significant**, SBP** = Systolic Blood Pressure, **DBP** = Diastolic Blood Pressure,

BUN = Blood Urea Nitrogen, **GCS** = Glasgow Coma Scale

Precipitants of Hyperglycemic Emergencies

Precipitating factors of HEs were determined for 161 (98.8%) of the patients. The most common precipitants of HEs were infections 95 (59%), non-compliance to antidiabetic medications 52 (32.3%) and newly diagnosed diabetes 38 (23.6%). The major cause of non-compliance was medication discontinuation which was reported in 45 (86.5%) of the patients. Urinary tract infection 61 (64.2%) was the most common infection that precipitated HEs (Table 5).

Table 5 Precipitants of HEs of diabetic patients admitted to JUSH, from January 2011 to December 2013.

Precipitating factor	**Frequency (%) n=161**
Infection	95 (59.0)
Non-compliance	52 (32.3)
Newly diagnosed DM	38 (23.6)
Trauma (injury)	1 (0.6)
Precipitants by type of non-compliance and infection	
Non-compliance to medication(s):	
Medication(s) discontinuation	45 (86.5)
Missed dose of medication	7 (13.5)
Type of Infection:	
UTI	61 (64.2)
Pneumonia	13 (13.7)
Sepsis	10 (10.5)
Pulmonary TB	4 (4.2)
Oral infections	3 (3.2)
Insulin injection site infection	3 (3.2)
DFU	3 (3.2)
Osteomyelitis	2 (2.1)
Gastrointestinal infection	2 (2.1)
Bacterial meningitis	2 (2.1)
Others	13 (13.7)

UTI: Urinary tract infection, **TB**: Tuberculosis, **DFU**: Diabetic foot ulcer

NB: Total percentage is > 100% as there were multiple response questions.

Treatment Interventions and Outcomes of patients with HEs

Mean amount of insulin used (units) till resolution of DKA was 136.85 ± 152.41 whereas 71.83 ± 33.29 units of insulin were used till HHS resolution (Table 6). The durations of treatment till resolution of DKA and HHS were 64.38 ± 76.34 and 29.00 ± 20.58 hours respectively. The mean length of hospital stay for DKA patients was 9.60 ± 11.68 and that of HHS was 6.75 ± 8.08 days.

Table 6 Treatment interventions and length of hospital stays of diabetic patients with HEs at JUSH, from January 2011 to December 2013.

Parameter	DKA Mean ± SD	HHS Mean ± SD
Insulin used till resolution of HEs (units)	136.85 ± 152.41	71.83 ± 33.29
Duration of treatment till resolution of HEs (hours)	64.38 ± 76.34	29.00 ± 20.58
Average LOS	9.60 ± 11.68	6.75 ± 8.08

The majority, 88 (54%), of patients experienced one or more episodes of hyperglycemia after resolution of HEs. It was more common among DKA patients than HHS ones; 82 (93.18%) vs. 6 (6.82%), however, the difference is not statistically significant (p=1.00). Episodes of hypoglycemia were noted in 34 (20.9%) of the patients; 33 (97.1%) of which occurred among DKA ones. Ketonuria after resolution of DKA was documented in 31 (20.5%) of the patients (Table7).

The overall in hospital mortality due to HEs among the study subjects was 16 (9.8%). Mortality rate among DKA patients was 9.9% while a mortality rate of 8.3% was noted in HHS patients. Most, 146 (90%), of the patients had improved and were discharged home.

Table 7 Frequency of metabolic complications and Prognosis of diabetic patients with HEs admitted to JUSH, from January 2011 to December 2013.

Parameter	DKA Frequency (%)	HHS Frequency (%)	Total Frequency (%)	P -value
Episodes of hyperglycemia	82 (93.2)	6 (6.8)	88 (54.0)	1.00
Episodes of hypoglycemia	33 (97.1)	1 (2.9)	34 (20.9)	0.463
Episodes of ketonuria (DKA)	31 (100.0)	-	31(20.5)	0.125
Died	15 (9.9)	1 (8.3)	16 (9.8)	1.00
Improved and discharged	135 (92.5)	11 (7.5)	146 (89.6)	1.00
Left against medical advice	1 (100.0)	0	1 (0.6)	0.074

The mean length of hospital stay (days) was 9.4 ± 11.46. The large majority, 87 (53.4%), of patients had length of hospital stay 1-7 days (Table 8). Ten (6.1%) patients stayed at the hospital for more than 28 days. Most of the deaths, 14 (87%), occurred within the first seven days of admission. There is an association between length of hospital stays and mortality (p=0.011).

Table 8 Frequency of length of hospital stays and mortality of diabetic patients with HEs admitted to JUSH, from January 2011 to December 2013.

LOS Category	Died		Total	P-value
	Yes Frequency (%)	No Frequency (%)	Frequency (%)	
1-7	14 (16.1)	73 (83.9)	87 (53.4)	
8-14	0	35 (100.0)	35 (21.5)	
15-21	0	20 (100.0)	20 (12.3)	0.011*
22-28	2 (18.2)	9 (81.8)	11 (6.7)	
>28	0	10 (100.0)	10 (6.1)	
Total	16 (9.8)	147 (90.2)	163 (100.0)	
Average LOS (days)		Mean ± SD	9.4 ± 11.46	

LOS: Length of hospital stay

NB: Fisher's Exact Test was used as >20% of cells have expected count < 5.

Hyperglycemic Emergencies related mortality and its predictors

Bivariate association between patients' characteristics and treatment outcome (mortality) was analyzed using binary logistic regression (Tables 9 and 10). Mortality rate in males was higher than in females (11.8% vs 6.6%), however, it is not statistically significant (COR=1.90, 95%CI: 0.58-6.18, P=0.286,). The highest mortality rate was observed in age groups ≥65 years, 3(37.5%) whereas the lowest mortality rate occurred in 15-24 age groups, 1(2.5%). Mortality difference in patients ≥65 years and 15-24 age groups was statistically significant (COR=23.40, 95%CI: 2.03-270.4, P=0.012); Table 9.

Mortality rate was higher in urban residents than rural ones (12.0% vs. 7.0%), but this difference is not statistically significant (COR=1.79, 95%CI: 0.59-5.42, P=0.301). There is no a statistically significant difference in mortality rates between DKA and HHS patients; 9.9% vs. 8.3% (COR=1.21, 95%CI: 0.15-10.06, P=0.858). Mortality among known DM patients, 13 (14.6%) was higher than among new ones; 3 (4.1%), **(**COR=4.05, 95%CI: 1.12-14.80, P=0.035).

Table 9 Admission characteristics and mortality of diabetic patients with HEs at JUSH, from January 2011 to December 2013.

Variable category		Died		Total (%)	P-value	COR (95% CI)
		Yes	No			
		n (%)	n (%)			
Sex	F	4 (6.6)	57 (93.4)	61 (37.4)	1	
	M	12 (11.8)	90 (88.2)	102 (62.6)	0.286	1.90 (0.584-6.178)
Age category	15-24	1 (2.5)	39 (97.5)	40 (24.5)	1	
	25-34	2 (5.8)	36 (94.7)	38 (23.3)	0.535	2.17 (0.19-24.93)
	35-44	3 (8.8)	31 (91.2)	34 (20.9)	0.260	3.77 (0.37-38.09)
	45-54	3 (13.6)	19 (86.4)	22 (13.5)	0.126	6.16 (0.60-63.21)
	55-64	4 (19.0)	17 (81.0)	21 (12.9)	0.055	9.18 (0.95-88.30)
	≥65	3 (37.5)	5 (62.5)	8 (4.9)	0.012	23.40 (2.03-270.41)*
Residence	Rural	5 (7.0)	66 (93.0)	71 (43.6)	1	
	Urban	11 (12.0)	81 (88.0)	92 (56.4)	0.301	1.79 (0.59-5.42)
Type of DM	Type 1 DM	8 (7.7)	96 (92.3)	104 (63.8)	1	
	Type 2 DM	8 (13.6)	51 (86.4)	59 (36.2)	0.232	1.88 (0.67-5.31)
Type of HE	DKA	15 (9.9)	136(90.1)	151 (92.6)	1	
	HHS	1 (8.3)	11 (91.7)	12 (7.4)	0.858	1.21 (0.15-10.06)
History of DM	New DM	3 (4.1)	71 (95.9)	74 (45.4)	1	
	Known DM	13 (14.6)	76 (85.4)	89 (54.6)	0.035	4.05 (1.12-14.80)*
Duration of DM (years)	<1	4 (4.3)	90 (95.7)	94 (57.7)	1	1
	1-5	4 (10.8)	33 (89.2)	37 (22.7)	0.173	2.73 (0.65-11.54)
	6-10	8 (30.8)	24 (69.2)	26 (16.0)	<0.001	10.00 (2.72-36.79)*
	>10	0	6 (100.0)	6 (3.7)	0.999	0 (0)
Duration of treatment (years)	<1	4 (4.2)	91 (95.8)	95 (58.3)	1	1
	1-5	4 (10.8)	33 (89.2)	37 (22.7)	0.168	2.76 (0.65-11.66)
	6-10	8 (32.0)	17 (68.0)	25 (15.3)	<0.001	10.71(2.90-39.57)*
	>11	0	6 (100.0)	6 (3.7)	0.999	0 (0)
Concomitant medications	No	10 (6.7)	140 (93.3)	150 (92.0)	1	1
	Yes	6 (46.2)	7 (53.8)	13 (8.0)	<0.001	12.00 (3.39-42.52)*
Co-morbidities	No	4 (3.1)	123 (96.9)	127 (77.9)	1	1
	Yes	12 (33.3)	24 (66.7)	36 (22.1)	<0.001	15.38 (4.57-51.72)*
UTI	No	11 (10.8)	91 (89.2)	102 (62.6)	1	
	Yes	5 (8.2)	56 (91.8)	61 (37.4)	0.592	0.74 (0.244-2.237)
Sepsis	No	10 (6.5)	143 (93.5)	153 (93.9)	1	1
	Yes	6 (60.0)	4 (40.0)	10 (6.1)	<0.001	21.45 (5.19-88.59)*
Pneumonia	No	13 (8.7)	137 (91.3)	150 (92.0)	1	1
	Yes	3 (23.1)	10 (76.9)	13 (10.0)	0.110	3.16 (0.77-12.95)

COR: Crude odds ratio, **CI**: Confidence Interval, ***** statistically significant

The highest mortality, 8 (30.8%), was recorded in patients with 6-10 years duration of diabetes (COR=10, 95%CI: 2.72-36.79, P<0.001). No death was recorded in patients with durations of diabetes and antidiabetic treatment above 10 years.

Six (46.2%) out of 13 patients taking concomitant medications were died (COR=12, 95%CI: 3.39-42.52, P<0.001). Twelve (33.3%) patients died out of 36 who had co-morbidity (COR=15.38, 95%CI: 4.57-51.72, P<0.001). The risk of death for patients with sepsis was greater than patients with no sepsis (COR=21.45, 95%CI: 5.19-88.59, p<0.001).

Other variables that had a significant association with HEs mortality (Table 10) were admission SBP >159 mmHg (COR=15.60, 95%CI: 2.48-98.04, P=0.003), DBP >99 mmHg (COR= 11.40, 95%CI: 1.81-72, P=0.01), and SeCr >1.2 mg/dL (COR=4.58, 95%CI=1.57-13.32, P=0.005).

Table 10 Admission Blood pressure, Serum electrolytes and mortality of diabetic patients with HEs at JUSH, from January 2011 to December 2013.

Variable category		Died		P -value	COR (95% CI)
		Yes (n)	No (n)		
SBP (mmHg) category	<90	1	7	0.491	2.23 (0.23-21.83)
	90-119	5	78	1	1
	120-139	5	54	0.576	1.44 (0.40-5.23)
	140-159	2	5	0.055	6.24 (0.96-40.59)
	≥160	3	3	0.003	15.60 (2.48-98.04)*
DBP (mmHg) category	<60	1	4	0.218	4.75 (0.40-56.71)
	60-69	3	20	0.222	2.85 (0.53-15.28)
	70-79	3	57	1	1
	80-89	4	51	0.613	1.49 (0.32-6.98)
	90-99	2	10	0.171	3.80 (0.56-25.69)
	≥100	3	5	0.01	11.40 (1.81-72.00)*
Serum Potassium (mEq/L)	<3.5	6	31	0.149	2.23(0.75-6.60)
	3.5-5.2	10	115	1	1
	>5.2	0	1	1.00	0 (0)
Serum Creatinine (mg/dL)	<0.5	0	2	0.999	0 (0)
	0.5-1.2	8	119	1	1
	>1.2	8	26	0.005	4.58(1.57-13.32)*

Variables with P<0.25 on a bivariate logistic regression analysis were adjusted on a multivariate logistic regression using a step wise backward logistic regression model (Table 11). On a multivariate model, independent predictors of mortality are elevated admission serum creatinine (>1.2 mg/dL), sepsis and co-morbidity. Previous diabetes history is not a significant predictor of mortality.

Table 11 Independent predictors of HEs related mortality of diabetic patients admitted to JUSH, from January 2011 to December 2013.

Variable category		Died		COR (95% CI)	P-value	AOR (95%CI)
		Yes (n)	No (n)			
History of DM	New DM	3	71	1		1
	Known DM	13	76	4.048 (1.12-14.80)	0.057	4.88(0.95-24.97)
Serum Creatinine (mg/dL)	<0.5	0	2	0.00	0.999	0 (0)
	0.5-1.2	8	119	1		1
	>1.2	8	26	4.58 (1.57-13.32)	0.018	5.86(1.36-25.28)*
Co-morbidity	No	4	123	1		1
	Yes	12	24	15.38 (4.57-51.72)	<0.001	15.26 (3.67-63.41)*
Sepsis	No	10	143	1		1
	Yes	6	4	21.45 (5.19-88.59)	0. 014	9.83 (1.59-60.79)*

AOR: Adjusted odds ratio, ***** statistically significant (P<0.05)

Known diabetic patients are 4.88 times more likely to die than newly diagnosed DM patients at hospital admission, but it was not statistically significant (AOR = 4.88, 95%CI: 0.95-24.97, P=0.057). Patients with elevated admission serum creatinine (>1.2mg/dL) are 5.86 times more likely to die than patients with admission serum creatinine 0.5-1.2 mg/dL (AOR = 5.86, 95%CI: 1.36-25.28, P=0.018). Patients with sepsis as precipitant are 9.83 times more likely to die than patients with no sepsis (AOR=9.83, 95 %CI: 1.59-60.79, P=0.014). In addition, the risk of death is 15.26 times greater for patients with co-morbidity than patients without co-morbidity (AOR = 15.26, 95% CI=3.67-63.41, P<0.001).

Chapter Six: Discussion

Our study showed that DKA was the most common diagnosis among diabetic patients with HEs and infection was the leading precipitating factor of HEs admission. In hospital mortality from HEs was high. Elevated admission serum creatinine, sepsis and co-morbidity were found to be independent predictors of HEs mortality.

We found that DKA and HHS occurred in 92.6% and 7.36% diabetic patients with HEs respectively. In this study the proportion of DKA patients was higher than the findings from other studies, while that of HHS was lower than the same findings (44,45,47). In a study by Ogbera et al (44), 85% and 15% cases of DKA and HHS were noted respectively. Andrew and Ezeani et al (45,47) also reported 41.7% DKA, 58.3% HHS and 31% DKA, 50% HHS cases respectively.

The reasons for the higher proportion of DKA in our finding may be due to the combined effect of: (1) DKA was common in type 1 diabetes where the majority of patients in our study are type 1 diabetics, (2) there are reports (55) that DKA is common in known diabetics and the majority of our patients were known diabetics and on antidiabetic treatment who were non-compliant to medication(s) (52 out of 87 patients that were on treatment were non-compliant), (3) most of the patients were in an actively growing and working age group (15-44 years) whose insulin demand may fluctuate based on their daily activities that need dose adjustment based on demand and (4) high infection rate recorded as the most common precipitant which may increase insulin demand leading to ketoacidosis. Lower incidence of HHS in our finding may be because the minority of patients was type 2 diabetics and the proportion of new diabetic patients was lower than known diabetics as HHS was found to be common among new diabetics.

Admissions for HHS, in contrast to DKA, were more common in patients with a new diagnosis of diabetes (66.7%). This is in line with the finding from South Africa (56) but against the study from Taiwan (40) where HHS was more common in known DM patients than newly diagnosed ones (72.3% vs. 27.7%).

The higher incidence of HHS in new DM patients in our finding and the similarity to the finding from South Africa may be related to relatively older age of patients with HHS (91.67% of HHS

patients were ≥45 years in our study whereas all patients were >40 years old in the South African study) where hyperosmolarity is usually related to an age-related increase in the renal threshold for glucose and reduced sensitivity of the thirst centre. It is also possible that as HHS admissions were mainly of newly diagnosed diabetic subjects who were not aware of their diabetes status, they may have presented relatively late due to delayed recognition of hyperglycemic symptoms or not taken adequate fluids to replenish ongoing renal losses (which an informed known diabetic patient could do so). It also suggests that many adult patients remain undiagnosed of diabetes and present for medical attention after developing diabetic complications and worsening of the conditions.

The higher percentage of HHS in known diabetics in Taiwan may be that they may have public awareness campaigns and diabetes screening that their patients come to medical attention early prior to HHS complications. In our set up there is a need for more public awareness campaigns and screening of diabetes especially for those > 34 years old as HHS is documented above this age group and those with known risk factors for diabetes.

The most common precipitants of HEs in our study were infections 59%, non-compliance to antidiabetic medications 32.3% and newly diagnosed DM 23.6%. These values are higher than the findings from Pakistan and South Africa (38,42). However, a higher rate of infection than our finding was reported from Thailand (37); 73.5% vs.59%.

Poor infection prevention strategies by the patients either due to poor patient awareness or the underlying poverty might have contributed to the higher rate of infection as precipitants. It is also possible that about 45% of patients is new DM patients whose awareness of infection prevention and self care may be low (as known DM patients will be informed on such issues). There is a report that, in Sub Saharan Africa, healthcare systems are scarce due to widespread poverty of individuals and nations alike. So individuals and populations need empowerment through education, nutrition and poverty eradication to improve self-care in health and living with diabetes (48).

The rate of non-compliance in our finding was lower than the findings from America, Thailand, Nigeria and Kenya that range from 34% - 69% (36,37,44,46,57). The lower rate of non-compliance to antidiabetic medications in our finding may be attributed to the high number of

patients with no prior treatment (46.6%) which might have contributed to the decrease in total percentage of non-compliance rate. Otherwise, this non-compliance rate is not acceptable and hence patient education, improvement in accessibility of nearby health facilities that provide medical care for diabetics and economic empowerment of DM patients may be warranted. It has been reported that stopping insulin for economic reasons, unavailability and unaffordability of insulin, missed clinics, perceived ill-health and alternative therapies like herbs, prayers and rituals are common problems that contributed to non-compliance to antidiabetic medications in the Tropical and Sub-Saharan African diabetic patients (48,58).

We found that the mean amount of insulin used till resolution of DKA and HHS was 136.85 ± 152.41 and 71.83 ± 33.29 units respectively. The mean amount of insulin used till resolution of DKA in our study was far higher than the mean amounts of insulin used in the studies from America (49–52) where it was reported to be 76 ± 46, 98 ± 26, 82 ± 28 and 49 ± 29 units respectively. The mean duration of treatment till resolution of DKA in our study was more than five times (64.38 ± 76.34 hours) the time needed in other studies (49–52) that reported 10.5 ± 6.3, 11 ± 4, 11 ± 3 and 10.6 ± 7.4 hours respectively.

The higher amount of insulin use and longer duration of treatment until DKA resolution as compared to other studies can be explained by firstly, the difference in management protocol of DKA between ours and other studies. Other studies used continuous intravenous infusion of regular insulin at high care centers (intensive care units) to manage DKA where there is close monitoring of patients while in our study they were treated at general medical wards with sliding scale insulin). Secondly the pharmacokinetic (absorption, onset and duration of action) difference between intramuscular (IM) and / or subcutaneous (SC) and continues intravenous infusion of regular insulin. Thirdly in our study DKA is said to be resolved based on blood glucose, urine dipstick ketone clearance and clinical parameters while in other studies it is based on blood glucose, PH and serum bicarbonate which is more objective than ours. In addition, the commitment of multidisciplinary team to monitor patients closely and administer hourly IM (SC) insulin injection, severity of DKA at presentation, and the presence of co-morbidities might have contributed for this difference. The use of SC insulin injections on an hourly schedule is reported to be difficult to follow in many medical centers because of the intensity of treatment and shortage of nursing staff in general wards (50,51).

Fisher et al. (59) reported that, in DKA patients treated either with IM or SC injections or with continuous IV infusion of regular insulin, 30–40% of patients in the IM and SC groups did not lower their plasma glucose by 10% in the first hour after insulin injection and that the concentration of ketone bodies was lowered at a significantly faster rate in the IV group than with IM or SC insulin. The delay in onset of action of regular insulin was supported by the report of Menzel and Jutzi (60), who treated patients with frequent small SC injections, but only 4 of 24 patients showed a fall in blood glucose concentration in the first 3 hour of therapy. It was also reported that the mean hourly rate of fall of plasma glucose level was significantly higher in patients treated with intravenous insulin therapy group than patients treated with intramuscular insulin therapy (61). These differences in response can be explained by delays in reaching a maximal circulating insulin concentration to produce the desired therapeutic response.

The mean length of hospital stay was 9.4 ± 11.46 days range from 1-59 days. This finding was far lower than the finding from the study by Ezeani et al (47) who reported a mean duration of 24.2 ± 17.1 ranging 0.5–88 days respectively. However, other studies (19,43) reported a shorter mean length of hospital stay (8.3 ± 6.9 ranging 1–30 days and 4 days respectively) when compared to our finding. The reason for the longer duration of hospital stay in our finding is unclear and probably further research may be needed to figure out the possible reasons. The reason for a shorter duration of hospital stay in our finding may be related to initial patient presentation. For example, DFU was common in the study we compared whereas only 3 patients had DFU in our study. It was reported that (43,47) DFU is usually associated with a much longer duration of hospital stay.

In our finding episodes of hyperglycemia (54.0%) was lower than the report from Thailand (37) where 69.9% of patients developed hyperglycemic episodes during HEs treatment. On the other hand, hypoglycemic episodes (20.9%) in our study were higher than the same study in Thailand (15.7%). Though we are uncertain to explain the noted difference in hyperglycemic episodes between our patients and the Thailand's, it might possibly be related to the difference in patient characteristics at presentation as infection and admission blood glucose were higher than ours. This may be substantiated by the reports from Queale et al (53) where severity of illness, severe diabetic complications, high admission glucose level and admission for infectious disease were found to be independent predictors of hyperglycemic episodes. The higher hypoglycemic

episodes documented in our finding may be related to infrequent patient blood glucose and urine dipstick ketone monitoring to adjust insulin doses based on patient need that may lead to inadvertent use of insulin resulting in hypoglycemia.

We noted that episodes of hypoglycemia among DKA patients were 21.9%. This figure is higher than other studies that reported 5% and 6.7% (50,51) respectively and lower than the reports from Guillermo et al (49) and Jones et al (52) where 41% and 35% of patients respectively experienced hypoglycemic events. While the higher hypoglycemic events in our study might be due to the differences in DKA management protocol and set up (other studies used continuous infusion of regular insulin in intensive care units) and infrequent laboratory monitoring in our set up, the reasons for lower hypoglycemic events may need further investigation to point out the possible difference.

The overall mortality of HEs in this study was 9.8%. This is higher than other studies (37,41,43,45,47) that reported mortality rates ranging from 3.57% - 8.4% and lower than the findings from Nigeria (44) and Kenya (57) where mortality rates of 20% and 29.8% were reported respectively.

The higher mortality rate in our finding may be explained by the difference in inpatient management of HEs, presenting precipitants, age, and co-morbidities, absence of adequate laboratory investigations at presentation, inadequate laboratory monitoring during treatment (Blood glucose, PH, serum ketones and electrolytes, and bicarbonate level measurements) to monitor patient response in our set up might have contributed for this difference. The lower mortality rate in our finding as compared to the Nigeria and Kenya studies possibly lays on the difference in patient characteristics. For example, in Kenyan study subjects more than 90% had altered level of consciousness, almost a quarter were in coma, 36% had systolic hypotension, almost 75% had moderate to severe dehydration and in Nigerian subjects, admission hypokalemia, hyponatremia, older age (mean age 53.9 years), co-morbidity and DFU were more common than ours.

Mortality rates from DKA and HHS in our study were 9.9% and 8.3% respectively. This is in contrast to the findings from Thailand (5.8% in DKA vs.15.8% in HHS), Jamaica (6.7% in DKA vs. 20.3% in HHS) and South Africa (6.8% in DKA vs.16.6% in HHS) (37,39,43). However, a

report from Nigeria (45) showed mortality rate from DKA was twice of that of HHS (2.4% vs. 1.2%). While other findings (20–23) have also shown a higher mortality from HHS than DKA, our finding did not reveal a statistically significant mortality difference between DKA and HHS patients (p=1.00). Though a very low incidence of HHS in our facility (7.4%) as compared to others and differences in the initial presentations of patients might have contributed to this almost similar mortality rates from DKA and HHS, further research may be needed to objectively explain the reasons for this similarity.

The majority of deaths (81.2%), occurred in known DM patients (P = 0.047) and all deaths were documented in patients with <11 years of diabetes duration prior to presentation. This is comparable with the findings by Ogbera et al (44) and Ezeani et al (47) who reported that (78.2%) and all the mortalities respectively were in subjects who had diabetes duration of less than 10 years prior to presentation. This may be due to ignorance of diabetes complications and the need for early presentation to the hospital when complications arise.

Age above 65 years old, previously known DM, DM duration 6-10 years, antidiabetic treatment for 6-10 years, SBP >159 mmHg, DBP >99 mmHg, SeCr >1.2 mg/dL, concomitant medications, co-morbidity, and sepsis are found to have a significant association with HEs related mortality on a bivariate logistic regression model. It was also reported (39,44) that co-existing medical disease, being elderly, sepsis and short duration of DM were predictors of HEs related mortality on a bivariate logistic regression model.

Of note in this study; 6, 12 and 8 of the subjects who died had sepsis, co-morbidity and elevated serum creatinine (>1.2mg/dL) respectively. We found that elevated admission serum creatinine (>1.2 mg/dL), co-morbidity, and sepsis are independent predictors of HEs related mortality on a multivariate logistic regression model. This entails for physicians due attention of diabetic patients with HEs that present with elevated serum creatinine, sepsis and co-morbidity in order that mortality can be decreased.

Chapter Seven: Conclusion and Recommendations

7.1. Conclusion

The majority of diabetic patients hospitalized due to HEs had Diabetic ketoacidosis. It was noted that electrolyte derangements were common at initial presentation. Infections, non-compliance to antidiabetic medications and new onset diabetes were the most common precipitants of HEs. The amount of insulin required and the time needed till resolutions of DKA were found to be high. Recurrent hyperglycemia, hypoglycemia and ketonuria were common problems seen during the management of HEs. Lengths of hospital stays and mortality rate from HEs were high. Three fourth of the mortality was documented in patients with co-morbidity. This study also revealed that all mortalities occurred in patients who have had diabetes for less than 11 years. Elevated admission serum creatinine (>1.2mg/dL), co-morbidity and sepsis were found to be independent predictors of HEs related mortality.

7.2. Recommendations

Based on our findings, we would like to recommend the following:-

- Health care providers and diabetic associations should promote self-monitoring of blood glucose and educate patients on diabetes self-care practices.
- Infection prevention strategies should be designed and implemented by diabetic patients, diabetes associations, the general public, health care providers and the government to reduce infection related admissions of HEs.
- The hospital should develop evidence based HEs treatment protocol, Organize HEs managing multidisciplinary team and avail biochemical tests at affordable costs.
- Physicians should detect and manage precipitants of HEs and co-morbidities as early as possible at initial patient presentation at the hospital.
- Physicians should also give due attention and treat accordingly for patients who present with elevated serum creatinine and sepsis.
- At last, we recommend large scale multicenter prospective studies on diabetes at large and HEs in particular to assess the limitations in diabetes care in Ethiopians and to devise strategies for cost-effective and evidence-based care of patients with this problem.

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Annexes

Annex I: Data Abstraction Tool

Patient Medical Record Number (MRN): _____

Date of admission (in Ethiopian Calendar) _____Diagnosis_____

Part I. Socio-demographic characteristics of DM patients with HEs at JUSH.

(NB: Put a tick in front of each variable)

101) Sex: 1) Male ____ 2) Female _____

102) Age (years): _____

103) Residence: _____1) Urban: _____ Rural): _____

104) Is there family history of DM?

1) Yes): _____ 2) No: _____

Part II: Clinical characteristics of DM patients with HEs at JUSH.

201) Type of diagnosed DM:

1) Type-1 DM: _____ 2) Type-2 DM: _____3) other (specify): _____

202) Duration of DM since confirmed by a physician (in years): _____

203) Duration of treatment with antidiabetic medications (in years): _____

204) Admission Measured Clinical parameters and laboratory data of patients with HEs. (N.B: Copy the clinical parameters in to the following table)

Se.No.	Measured clinical parameters and laboratory data at admission		Date		
1	Blood glucose (mg/dL)	RBS			
		FBS			
2	Blood Pressure in mmHg				
3	Urine ketone (- or +1,+2,+3…if positive)				
4	Serum K^+ (mEq/L)				
5	Serum Na^+ (mEq/L				
6	Serum Cl^- (mEq/L)				
7	SeCr (mg/dl)				
8	BUN (mg/dl)				
9	Glasgow coma scale (GCS) value out of 15				

RBS: Random Blood Sugar

FBS: Fasting Blood Sugar

205) was there previous admission to the Hospital due to HEs in the last 12 months?

1) Yes: _____2) No: _____

206) Type and dose of anti-diabetic, and concomitant medication(s) the patient was taking prior to admission.

Medication	Dose of the medication the patient was taking	Frequency of the medication the patient was taking	Comment
Amount of insulin (NPH or NPH +R) in units			
Insulin+Glibenclamide			
Insulin+metformin			
Glibenclamide (mg)			
Metformine (mg)			
metformin+Glibenclamide			
Concomitant medication (s) : _____ 2._____ 3._____ 4._____ 5._____			

Part III: Precipitating factors for HEs related admissions and co-morbidities of diabetic patients with HEs admitted to JUSH, Southwest Ethiopia.

Part III.I: Precipitating factors for HEs related hospital admission of diabetic patients with HEs admitted to JUSH:

301) Is (are) the precipitant(s) for HEs related hospital admission known?

1) Yes: ____ (If yes please tick the type of precipitant below) 2) No: _____

302) Non -compliance of the patient to antidiabetic medication (s) :

1) Yes: _____2) No:_____

3011) If yes in question number 302 above, the type of noncompliance:

1) Missed dose of the medication: _____2) under dose of the medication: _____

3) Inappropriately stored (damaged product) injected (if insulin) and /or taken:_____4) other (specify):_____

303) Infection 1) Yes:_____2) No:_____

3021)If yes in question 303, Type of infection 1) pneumonia: __2) urinary tract infection (UTI):__3) sepsis:___4) Diabetic Foot Ulcer (DFU):__5) Other (specify): ____

304) Trauma (Injury)

1) Yes: _____, specify it: _____2) No: _____

305) Newly diagnosed DM;

1) Yes: _____ 2) No: _____

Part III. II: Co-morbidities of diabetic patients with HEs admitted to JUSH, Southwest Ethiopia.

3021)Any co-morbid medical condition (co-morbidity): 1) yes :_____2) No: _____

3022)If yes in question 3021, what is the type of co-morbid medical condition?

1) Hypertension: ___2) Cardiovascular diseases: _____3) Stroke: _____

4) Viral Hepatitis: ____5) chronic kidney disease: ____ other (specify): _____

Part IV: medication profile and laboratory data of DM patients admitted with HEs at JUSH, Southwest Ethiopia.

401) Insulin therapy and response of the patient with HEs at admission and during hospital stay

Date: Time:						
INSULIN						
Regular (units) and route						
NPH (units) and route						
Blood glucose (mg/dl)						
Urine ketones						

Part V: Treatment interventions and outcomes of patients with HEs at JUSH.

501) Treatment interventions (N.B: Put the values in each box)

Se. No.	Treatment intervention(s)	Values
1	Amount of insulin used till resolution of HE	
2	Amount of insulin used till resolution of ketonuria	
3	Duration of treatment till resolution of ketonuria	
4	Duration of treatment till resolution of HE	

502) Episodes of metabolic complications during treatment, if any

Se No.	Metabolic complication	No of episodes during hospital stay
1	Episodes of hyperglycemia after resolution of HE	
2	Episodes of hypoglycemia	
3	Episodes of ketonuria after resolution of HE	

503) Final patient prognosis after treatment and duration of hospital stay

(NB: Please put a tick in front of each variable and write time of event)

Se.No	**Patient prognosis**	**Time event happened from admission (hours or days)**
1	Died_____	
2	Discharged _____	
3	Left against medical advice	
4	Referred for a better care_____	
5	Discharged for hospice care_____	
6	Length of hospital stay (admission to discharge)	