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Clinical Profiles of Patients Presenting with Hypoglycemia in Emergency Department of Bir Hospital

Sumit Prajapati[1,*], Nhuchhe Man Dangol[2]

Abstract

Hypoglycemia stands as a primary reason for visits to the Emergency Department (ED), ranking high among the most frequent and easily avoidable hormonal emergencies. The aim of this research is to investigate the occurrence of hypoglycemia and identify its underlying causes. As the number of diabetes cases rises, along with different methods of tightly managing blood sugar levels, the likelihood of hypoglycemia also increases. Given that extended periods of hypoglycemia can result in serious health issues and even death, it is crucial to accurately diagnose the cause of each hypoglycemic episode and implement preventive strategies. This study focuses on the medical histories of individuals who come to the Emergency Department of Bir Hospital, a part of the National Academy of Medical Science (NAMS), Bir Hospital in Mahaboudha, Kathmandu, Nepal, who are experiencing hypoglycemia. This study aims to provide a comprehensive analysis of hypoglycemia cases presented at Bir Hospital by collecting data on patient demographics, medical history, and potential risk factors associated with hypoglycemic episodes. We will categorize the patients based on their underlying conditions, such as type 1 and type 2 diabetes, as well as other comorbidities that may contribute to the occurrence of hypoglycemia. Additionally, we will explore the impact of medication adherence, dietary habits, and lifestyle choices on blood glucose levels. Through a detailed examination of these factors, the research intends to identify trends and common causes of hypoglycemia in this population. Ultimately, our findings aim to inform clinical practices and enhance preventive measures to reduce the incidence of hypoglycemic emergencies in the community.

Keywords- Hypoglycemia, emergency department (ED), blood sugar management, health issues, preventive strategies, medication adherence

INTRODUCTION

Hypoglycemia is a critical medical condition that can severely impact a patient's mental state, leading to confusion, lethargy, and even organ dysfunction. Numerous studies have identified various causes of hypoglycemia, including advanced age, missed meals, infections, chronic liver and kidney diseases, and repeated episodes of low blood sugar. Among these, drug-induced hypoglycemia poses a significant challenge for patients attempting to manage their blood glucose levels effectively. Iatrogenic hypoglycemia, which occurs due to medical treatment, contributes to recurring physical and psychological harm, and in some cases, death – particularly in individuals with insulin-dependent diabetes (IDDM) and, to a lesser extent, those with non-insulin-dependent diabetes (NIDDM) [1–5]. The most common triggers for hypoglycemia are medications used to manage diabetes, although other substances like alcohol and certain conditions, including sepsis, organ failure, hormonal deficiencies, and insulinoma, can also lead to

***Author for Correspondence**
Sumit Prajapati
E-mail: sumitpraja5@gmail.com

[1]Emergency Physician and Researcher, Department of Family Medicine and Emergency Medicine, Civil Service Hospital, Minbhawan, Kathmandu, Nepal.
[2]Professor, Department of General Practice and Emergency Medicine, National Academy of Medical Science (NAMS), Bir Hospital, Mahaboudha, Kathmandu, Nepal.

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dangerously low blood sugar levels. Hypoglycemia is typically diagnosed using Whipple's triad:

1. Symptoms consistent with low blood sugar.
2. A low plasma glucose level measured through precise methods (not using a glucose monitor).
3. Symptom relief once glucose levels are restored.

While the normal fasting plasma glucose level is around 70 mg/dL (3.9 mmol/L), lower glucose levels are often seen several hours after a meal. Hypoglycemia is confirmed when blood glucose levels drop below 55 mg/dL (3.0 mmol/L) and symptoms subside after treatment. Severe hypoglycemia, particularly if it persists over time, can cause significant health complications and may even be fatal. It should be considered in any patient presenting with confusion, altered consciousness, or seizures [6-10]. Hypoglycemia is also a common reason for emergency department (ED) visits and remains the most frequent yet preventable endocrine emergency. Given the rising prevalence of diabetes and the increasingly intensive methods for managing blood sugar levels, the risk of hypoglycemia is expected to increase proportionally. Thus, it is crucial to address each episode by identifying its underlying causes and implementing preventative measures. The incidence of severe hypoglycemia (SH) varies, with reported rates ranging from 0.038 to 3.2 episodes per patient per year in those with Type 1 diabetes, and 0.0004 to 0.96 episodes per patient per year in Type 2 diabetes. Mild hypoglycemia presents uncomfortable autonomic and neuroglycopenic symptoms, whereas SH is defined by episodes requiring assistance from another person for recovery. SH can lead to a coma or seizures and, in extreme cases, be life-threatening. Although several factors can cause hypoglycemia, including drugs, endocrine disorders, malnutrition, malignancies, and renal failure, the most common cause is the use of antidiabetic medications. The contributing factors may also vary depending on local medical resources and the sociocultural and economic status of the population [11–14].

Hypoglycemia continues to be associated with high rates of morbidity and mortality. Accurate diagnosis and prompt treatment can significantly improve patient outcomes. However, most studies on hypoglycemia have primarily focused on diabetic patients and are often conducted outside regions with more diverse populations. These studies fail to capture the full range of genetic, dietary, drug sensitivity, socioeconomic, and disease epidemiology variations seen in places like South Asia [15–17]. This study was conducted to determine the incidence of hypoglycemia in patients admitted to the ED, as well as to analyze the clinical and demographic factors, causes, and mortality rates associated with hypoglycemia. Hypoglycemia is a frequent complication of both insulin therapy and oral hypoglycemic agents due to increased insulin concentrations. Symptoms of hypoglycemia depend on blood glucose levels and the patient's ability to recognize the physiological changes triggered by hormonal counter regulation. Severe hypoglycemia can result in life-threatening conditions, such as coma or seizures, and in many cases, requires another person's help for recovery [18–22].

REVIEW OF LITERATURE

Hypoglycemia, commonly known as low blood sugar, occurs when blood glucose levels drop below 70 mg/dL. It is sometimes called an insulin reaction or insulin shock. Recognizing the symptoms of hypoglycemia is crucial, as they serve as warning signs of low blood sugar. However, everyone may experience different symptoms, so it is important to be familiar with your own body's response [23–25]. The only way to confirm hypoglycemia is by checking your blood sugar level. If this is not possible during a symptomatic episode, it is essential to treat the low blood sugar immediately. Severe hypoglycemia can lead to serious consequences such as accidents, injuries, coma, or even death. Symptoms of hypoglycemia often appear suddenly and require quick action [26].

HYPOGLYCEMIA CAUSES, SYMPTOMS AND RISK FACTORS

Classification of hypoglycemia based on clinical manifestation and ability to self-treat has been shown in Figure 1. Iatrogenic hypoglycemia, caused by diabetes medications, is one of the leading reasons for low blood sugar in diabetic patients. While the frequency of hypoglycemic episodes is lower in those treated with oral antidiabetic drugs (OADs) or incretin-based therapies compared to insulin-treated patients, studies indicate a higher incidence of hypoglycemia when OADs or incretin therapies

are used, particularly when glucagon-like peptide-1 receptor agonists are combined with sulfonylureas. This suggests that most hypoglycemic events in diabetes are medication related. Less common causes of hypoglycemia include pancreatic or non-islet cell tumors, autoimmune disorders, organ failure, endocrine diseases, metabolic disorders, dietary toxins, alcohol, stress, infections, and other conditions like sepsis, starvation, and extreme physical exertion [27–30].

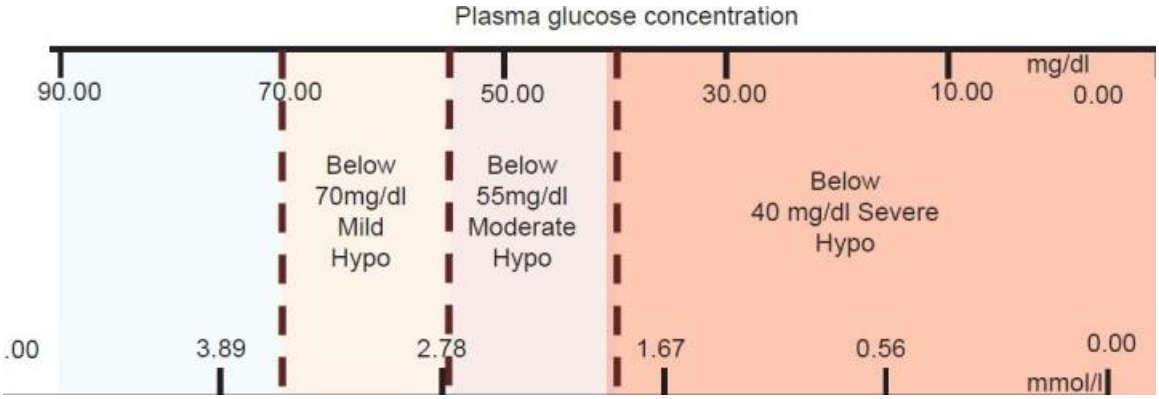

Figure 1. Classification of hypoglycemia.

Symptoms of hypoglycemia are classified as neuroglycopenic or neurogenic (autonomic), with the latter further divided into adrenergic and cholinergic symptoms. outlines the typical symptoms and signs of hypoglycemia in people with diabetes. The primary risk factor for hypoglycemia is the intensity of treatment aimed at controlling blood sugar. Numerous randomized controlled trials (RCTs), such as DCCT, UKPDS, 4-T, ADVANCE, ACCORD, and VADT studies, have shown a higher incidence of severe hypoglycemia with aggressive glucose control. In addition to glucose-lowering medications, factors like previous hypoglycemic episodes, alcohol use, increased glucose utilization (such as during exercise), reduced glucose production (as in liver disease), female sex, sleep, long-standing diabetes, older age, and progressive insulin deficiency are linked to an elevated risk of hypoglycemia in patients with Type 2 diabetes, especially those on insulin therapy for more than 10 years [31–32].

Several risk factors contribute to hypoglycemia in the general population, and the issue is particularly concerning elderly diabetic patients. highlights common risk factors in this population. Over time, the intensity of hypoglycemic symptoms may decrease or even disappear entirely, leading to hypoglycemia unawareness in many patients with diabetes. This condition significantly raises the risk of severe hypoglycemia, increasing it sixfold in patients with Type 1 diabetes and ninefold in those with Type 2 diabetes. lists the general risk factors for hypoglycemia in people with diabetes. This study will highlight the causes of hypoglycemia (Table 1) and the associated signs and symptoms (Table 2). Additionally, the risk factors for hypoglycemia in adults (Table 3) will be identified and the various risk factors (Table 4) will be examined. The physiological impact of hypoglycemia on different systems, along with their counter-regulatory responses, will be illustrated (Figure 2).

Table 1. Causes of hypoglycemia.

Early Adrenergic Symptoms	**Neuroglycopenic Signs**
Pallor	Confusion
Diaphoresis	Slurred speech
Shakiness	Irrational or uncontrolled behavior
Hunger	Disorientation
Anxiety	Loss of consciousness
Irritability	Seizures
Headache	Pupillary sluggishness
Dizziness	Decreased response to noxious stimuli

PHYSIOLOGICAL IMPACT ON BODY BY HYPOGLYCEMIA

Autonomic activation after hypoglycemia can trigger symptoms ranging from sweating and palpitations to cognitive issues and seizures. Severe or prolonged hypoglycemia may lead to coma or death and could even cause sudden cardiac death due to ischemic or electrical changes in the heart. In young children, repeated cognitive impairment may have lasting negative effects on intellectual development.

Table 2. Sign and symptoms of hypoglycemia.

Cause	Examples
Incorrect insulin administration	Insulin taken in excess or at the wrong time relative to food intake and/or physical activity; incorrect type of insulin taken.
Insufficient exogenous carbohydrate	Delayed or missed meals or overnight fast.
Decreased endogenous glucose production	Excess alcohol consumption.
Increased utilization of carbohydrate/depletion of hepatic glycogen stores	Exercise or weight loss.
Increased insulin sensitivity	During the night, exercise, weight loss.
Delayed gastric emptying	Conditions such as gastroparesis.
Decreased insulin clearance	Condition, such as progressive renal failure.

Table 3. Risk factors for hypoglycemia in adults.

Category	Causes
Lifestyle related	Dietary error, excessive physical activity, alcohol intake.
Drug related	Wrong dosage, wrong time of administration, wrong technique of administration.
Medical disease related	Renal dysfunction, hepatic dysfunction, gastrointestinal dysfunction/malabsorption.
Endocrine related	Hypo-pituitarism, hypo-thyroidism, hypo-adrenalism.
Nervous system related	Cognitive impairment, autonomic neuropathy, gastrointestinal neuropathy.

Table 4. Risk factors for hypoglycemia.

Common Risk Factors of Hypoglycemia	Less Common Risk Factors of Hypoglycemia
Strict glycemic control.	Endocrine deficiencies (cortisol, growth hormone, or both), non-β-cell tumor.
Mismatch of insulin timing, amount, or type of carbohydrate intake.	Sudden reduction of corticosteroid dose.
History of severe hypoglycemia.	Pathological condition such as emesis/vomiting.
Sleep/general anesthesia or sedation that places the patient in an altered consciousness.	Reduced rate of intravenous dextrose administration.
Duration of diabetes and age.	Unexpected interruption of enteral feeding or parenteral nutrition.
Reduction of oral intake/new non-per oral status.	Drug dispensing error.
Impaired awareness of hypoglycemia.	
Angiotensin-converting enzyme genotype/C-peptide negativity.	
Critical illness (hepatic, cardiac, renal failure; sepsis, severe trauma).	
Unexpected travel after injection of rapid- or fast-acting insulin.	

HYPOGLYCEMIA AND THE BRAIN

Glucose is the brain's primary fuel, and any sudden disruption in its supply can result in brain dysfunction, potentially leading to coma or death. Studies have shown a link between repeated severe hypoglycemia and long-term cognitive impairment, with children who experienced severe episodes scoring lower on cognitive tests compared to those without such history. Earlier research also found

that severe hypoglycemia can worsen neurocognitive issues in diabetic patients. In older adults, severe episodes are linked to a higher risk of dementia, brain dysfunction, and cerebellar ataxia. Autopsies and animal studies have revealed damage to the cerebral cortex, hippocampus, and caudate nucleus following severe hypoglycemia, with more recent findings suggesting that seizure-like activity exacerbates damage in these brain regions [33].

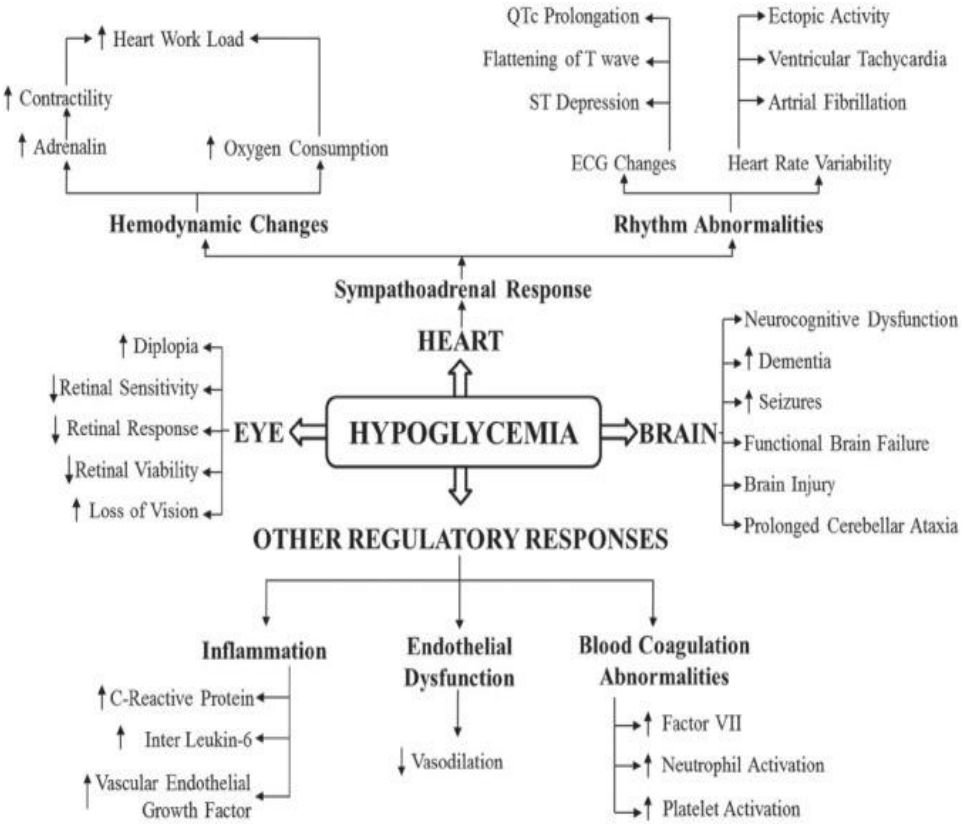

Figure 2 Physiological impact of hypoglycemia on different systems and their counter-regulatory responses. ECG: Electrocardiogram; ↑ denotes increased response; ↓ denotes decreased response.

HYPOGLYCEMIA AND THE HEART

Patients with Type 2 diabetes (T2DM) face a higher risk of cardiovascular disease. Trials, such as the ACCORD study, have shown that intensive blood sugar control can increase mortality in patients who experience hypoglycemia. Achieving HbA1c levels below 6.5% has been linked to a threefold rise in hypoglycemic episodes. Hypoglycemia significantly impacts cardiovascular function, triggering the release of epinephrine, which causes changes like increased heart rate, higher peripheral blood pressure, and greater cardiac output. This elevated cardiac workload can be especially dangerous for older adults with coronary artery disease, as it may reduce coronary perfusion and promote myocardial ischemia.

In people with diabetes, long-term arterial stiffness lessens the ability of arteries to respond to hypoglycemia, which can further strain the heart by affecting central blood pressure. Hypoglycemia also creates a pro-arrhythmic state due to elevated catecholamine levels, increasing the risk of dangerous arrhythmias, prolonged QT intervals, and even sudden cardiac death. Nocturnal hypoglycemia has been linked to sudden death during sleep in patients with Type 1 diabetes, likely due to severe arrhythmias. Additionally, hypoglycemia may lead to abnormal heart repolarization from low potassium levels caused by hyperinsulinemia and catecholamine release. These effects, combined with disturbances in heart rate variability, can contribute to adverse cardiac events. Although it is challenging to directly link hypoglycemia to fatal cardiovascular events due to a lack of simultaneous blood glucose and heart monitoring, reports have associated hypoglycemia with heart attacks and various ECG changes, such

as arrhythmias and ST depression. More extensive clinical trials are needed to better understand the connection between hypoglycemia and cardiovascular events [34–36].

HYPOGLYCEMIA AND COUNTER REGULATORY RESPONSES

Hypoglycemia triggers several counter-regulatory responses, including reduced insulin secretion from pancreatic beta cells, increased glucagon release from alpha cells, and heightened sympathy-adrenal activity, leading to a spike in adrenaline, norepinephrine, and ACTH/glucocorticoids. It also raises levels of inflammatory markers such as C-reactive protein, IL-6, IL-8, tumor necrosis factor-α, and endothelin-1, which can cause endothelial damage and coagulation abnormalities, increasing the risk of cardiovascular events. Additionally, inflammatory cytokines like IL-1 can worsen hypoglycemia, creating a harmful feedback loop. Hypoglycemia also affects platelet function and activates the fibrinolytic system [37].

HYPOGLYCEMIA AND THE EYE

Hypoglycemia can lead to visual disturbances in people with diabetes, including double vision, blurred vision, and reduced contrast sensitivity. Studies in animals and in vitro have shown that low glucose levels can reduce retinal sensitivity, cause retinal cell death, impair vision, and increase retinal degeneration. Recent research has also demonstrated that hypoglycemia in humans can significantly decrease central retinal function and contrast sensitivity [38].

HYPOGLYCEMIA

Impact on Quality of Life (QOL)

Hypoglycemia negatively impacts psychological well-being and quality of life, often causing feelings of powerlessness, anxiety, and depression for both patients and their families. Acute episodes can lead to mood swings, irritability, and stubbornness. Nocturnal hypoglycemia is particularly concerning as it may occur without symptoms due to a weakened counter-regulatory hormone response during sleep. Sleep also reduces the body's defenses against hypoglycemia, increasing the risk of undetected episodes, some of which can lead to dangerous arrhythmia. Continuous glucose monitoring has shown that many hypoglycemic episodes, especially at night, go unnoticed. While nocturnal hypoglycemia is often symptomless, some patients may experience disturbed sleep, morning headaches, fatigue, or mood changes. Convulsions or bedwetting are also seen in children during these episodes [39–42].

EMPLOYMENT AND HYPOGLYCEMIA

Hypoglycemia at workplace can be awkward, embarrassing and frightening. Moreover, it is unacceptable in certain types of employment. In a prospective survey for a year of 243 diabetic patients treated with insulin, it was found that 30% episodes of mild, and 11% episodes of severe hypoglycemia occurred at work 60. The data clearly indicates that hypoglycemia can be dangerous to individuals working at heights or underwater, on railway tracks, on oil rigs, in coal mines, handling hot metals or heavy machines. A positive correlation has been observed between reduced productivity and increased health care costs associated with hypoglycemia among patients with T1DM or T2DM [43].

HYPOGLYCEMIA

A Barrier in Diabetes Management

Hypoglycemia is known to be an important limiting factor in glycemic management with diabetes. It is a significant barrier in the case of adherence to medication and achieving normoglycemia with intensive therapy.

Patient and Physician Perceptions Towards Hypoglycemia

Patients often perceive hypoglycemia differently than clinical definitions suggest. For instance, someone experiencing hypoglycemia for the first time may label the episode as "severe" due to the fear of losing control and needing external help. This perception can lead to lower treatment satisfaction and adherence, negatively impacting clinical outcomes. Additionally, healthcare providers may hesitate to

initiate insulin therapy because of the associated hypoglycemia risk. Understanding these barriers can highlight gaps in diabetes management. Studies have shown that focusing solely on medical targets is insufficient, as many patients still struggle with their health and quality of life. There is a clear need for a more holistic approach that incorporates psychosocial and behavioral factors alongside glycemic control. Furthermore, research indicates that about one-third of insulin-treated patients report missing doses due to various modifiable factors, such as practical challenges and lifestyle constraints. Recent findings also emphasize the significant burden placed on families of individuals with diabetes, underscoring the need for better support for caregivers [44–46].

Hypoglycemia Unawareness

Repeated episodes of hypoglycemia can dull both the symptomatic and hormonal responses to future occurrences, resulting in hypoglycemia unawareness – a condition often seen in individuals undergoing insulin treatment. This syndrome occurs when a person can no longer recognize the onset of hypoglycemia at the plasma glucose levels that typically trigger warning symptoms. Awareness of hypoglycemia can be classified into three categories:

1. *Normal awareness:* The individual consistently recognizes the onset of hypoglycemia.
2. *Partial awareness:* The person experiences a reduction in either intensity or number of symptoms, recognizing some but not all episodes.
3. *No awareness:* The individual no longer perceives any episodes of hypoglycemia.

Hypoglycemia unawareness, which increases the risk of severe hypoglycemia by three to six times, affects 25% to 30% of adults with Type 1 diabetes, with prevalence rising alongside the duration of insulin therapy. In contrast, fewer than 10% of adults with Type 2 diabetes on insulin display this unawareness; however, for those affected, the risk of severe hypoglycemia rises six to sevenfold, making intensified insulin therapy generally inadvisable. Moreover, nocturnal hypoglycemia can exacerbate cognitive impairment during subsequent episodes, contributing to the development of hypoglycemia unawareness in those with Type 1 diabetes [47–48].

AGENTS WITH A HIGHER RISK OF CAUSING HYPOGLYCEMIA

Insulin

Despite the high risk of hypoglycemia, many international diabetes guidelines advocate intensive insulin treatment to lower the risk of long-term complications. However, the increased incidence of hypoglycemia, particularly in patients on insulin for extended periods, highlights that as the disease progresses and insulin use rises, the risk of hypoglycemia grows, with consequences that can range from mild discomfort to coma or death. For instance, a study showed that the incidence of severe hypoglycemia in individuals with Type 1 diabetes treated with insulin for over 15 years was three times higher than those treated for less than five years. In patients with Type 2 diabetes, the prevalence of severe hypoglycemia jumped from 7% in those on insulin for less than two years to 25% in those treated for more than five years. Consequently, many patients delay starting insulin therapy due to a significant fear of hypoglycemia.

Sulphonylureas

Sulfonylureas are commonly used as second-line treatments for Type 2 diabetes, promoting insulin release regardless of glucose levels, which makes hypoglycemia a common side effect. A meta-analysis of 21 studies found that glyburide was associated with an 83% higher risk of hypoglycemia compared to other sulfonylureas and a 52% higher risk compared to other insulin secretagogues. In a multi-center trial assessing modified release gliclazide and glimepiride over six months, glimepiride was linked to a higher hypoglycemia rate (8.9%) than gliclazide (3.7%). A study evaluating chlorpropamide, tolbutamide, glyburide, glipizide, and gliclazide also found that patients on glyburide had a greater risk of hypoglycemia compared to those on other sulfonylureas. Additionally, another study indicated that glyburide users experienced hypoglycemia twice as often as those taking glipizide [49].

Meglitinides

They trigger insulin secretion with a faster onset and shorter duration of action anticipating a lower risk of hypoglycemia. However, studies have shown that the risk of hypoglycemia with repaglinide was like second-generation sulfonylureas 88. A recent meta-analysis examining clinical trials with nateglinide added to metformin showed a greater risk of hypoglycemia with nateglinide than with sulfonylureas (RR = 7.4 vs. 4.57, respectively).

MANAGEMENT OF HYPOGLYCEMIA

The primary objective is to identify patients at high risk for hypoglycemia and adjust their treatment plans according to their individual needs. Strategies for managing hypoglycemia fall into three main categories:

1. Prevention of hypoglycemia.
2. Utilization of new therapeutic agents or treatment regimens with minimal or no risk of hypoglycemia.
3. Treatment of hypoglycemia**.**

PREVENTION OF HYPOGLYCEMIA

To lower the risk of hypoglycemia, patients must understand and commit to their treatment plan, including medications and lifestyle changes. Educating both patients and their families, along with regular self-monitoring of blood glucose, is crucial in preventing hypoglycemic episodes.

Patient Education

Achieving effective glycemic control without causing significant hypoglycemia is essential for optimal diabetes care. Education should be tailored to the patient's understanding and focus on recognizing early hypoglycemic symptoms, their causes, preventive measures, and treatment options. Programs should emphasize the importance of regular self-monitoring of blood glucose, accurate record-keeping, and consistent follow-up with healthcare providers. Evidence suggests that blood glucose awareness training and cognitive behavioral therapy can enhance diabetes management. Interventions addressing health beliefs and attitudes towards hypoglycemia may be more effective than traditional education centered solely on symptom recognition in reducing hypoglycemia unawareness.

Blood Glucose Monitoring

Regular blood glucose monitoring is crucial for tracking trends and detecting asymptomatic hypoglycemia, making it an essential part of diabetes self-management for insulin-treated patients. Monitoring can be done through periodic self-assessments of capillary blood glucose or continuous glucose monitoring (CGM). To identify hypoglycemia unawareness or risky patterns, periodic 7-point profile testing is recommended. Self-monitoring helps patients detect hypoglycemia, allowing for necessary insulin dose adjustments. While often emphasized for patients with Type 1 diabetes, those with Type 2 diabetes on insulin can also benefit from regular monitoring. The ADA recommends that patients using multiple daily insulin injections or continuous infusion test their glucose levels at least 6-8 times a day. CGM offers real-time notifications of blood glucose levels and provides alerts for extreme changes, particularly useful for detecting nocturnal hypoglycemia in Type 1 diabetes. Combined with intensive insulin therapy, CGM can help lower HbA1c levels in adults with Type 1 diabetes.

Use of Novel Therapeutic Agents/Treatment Regimens with Low/No Occurrence of Hypoglycemia

Pharmacological treatments for diabetes should aim to achieve optimal glycemic control while minimizing the risk of hypoglycemia. These glucose-lowering agents can be classified based on their hypoglycemia risk: high-risk agents include insulin, sulfonylureas, and meglitinides, which elevate insulin levels independently of glucose levels. In contrast, low-risk agents, such as biguanides (like

metformin), DPP-4 inhibitors, GLP-1 receptor agonists, alpha-glucosidase inhibitors, bile acid sequestrants (like colesevelam), thiazolidinediones, and amylin analogs (like pramlintide), function in a glucose-dependent manner. It is essential to choose the right treatment regimen for patients with diabetes, considering the associated risk of hypoglycemia to maintain effective glycemic control [50].

Insulin Therapy

An ideal insulin regimen for diabetes patients should consist of long-acting basal insulin to replicate the pancreas's 24-hour insulin secretion and bolus or short-acting insulin to simulate the normal physiological response to meals. Advances in molecular biology have enabled the creation of insulin analogs that closely mimic endogenous insulin, offering improved glycemic control and a lower risk of hypoglycemia compared to traditional human insulin therapies like neutral protamine Hagedorn (NPH) insulin. Modern insulin analogs include long-acting options (such as detemir and glargine), short-acting varieties (like aspart, glulisine, and lispro), and premixed formulations (such as biphasic insulin aspart and insulin lispro).

Basal Insulin

Currently, basal insulins include NPH (isophane insulin), insulin glargine, and insulin detemir. NPH is a crystalline suspension that releases insulin slowly, offering intermediate action but often leads to early morning hypoglycemia due to its variable absorption. To overcome these issues, long-acting basal insulin analogs like glargine and detemir have been developed, providing a more stable insulin release that mimics the body's natural secretion over 24 hours. After once-daily administration, both glargine and detemir maintain a flat insulin profile, significantly reducing the risk of hypoglycemia while achieving comparable or better glycemic control than NPH.

Rapid-Acting Insulin

Basal/bolus therapy attempts to mimic the physiological insulin release and provides a delicate balance between tight glycemic control and avoidance of hypoglycemia by combining insulins with different kinetic properties (intermediate- or long-acting-basal, with short-or rapid-acting-bolus). Bolus insulin needs are fulfilled by preparations like insulin lispro, insulin aspart, and insulin glulisine. These insulins act quickly and have a shorter duration, helping to minimize postprandial blood glucose spikes and reduce the risk of hypoglycemia between meals. Insulin glulisine provides improved glycemic control with comparable symptomatic hypoglycemia versus regular human insulin (RHI) in the outpatient setting and may be considered a better choice than RHI in non-critically ill hospitalized patients

Premixed Insulin

Premixed insulin formulations combine short-acting and intermediate-acting insulin in set proportions, allowing for both basal and bolus coverage in a single injection, which reduces the number of daily injections. However, they should be used cautiously in individuals with less structured eating habits. Studies suggest that premixed insulin analogues may lower the risk of hypoglycemic events compared to premixed human insulins. Meta-analyses have shown that these analogues can reduce nocturnal hypoglycemia in people with type 2 diabetes and that BIAsp 30 significantly lowers the rates of nocturnal and major hypoglycemia compared to human insulin.

Continuous Sub-Cutaneous Insulin Infusion

The ADA and the National Institute for Health and Clinical Excellence recommend CSII for patients who fail to achieve euglycemia with multiple daily injections (MDI) of insulin due to hypoglycemia. A meta-analysis of 22 randomized controlled trials found that continuous subcutaneous insulin infusion (CSII) significantly lowers both HbA1c levels and the incidence of severe hypoglycemia compared to multiple daily injections (MDI). CSII is considered a safer intensive insulin regimen due to this reduced hypoglycemia risk. Recent non-randomized clinical trials also indicate that switching patients from MDI to CSII can enhance glycemic control without increasing the risk of severe hypoglycemia.

Incretin Therapy

Incretin-based therapies represent a recent advancement in diabetes management. Incretins are hormones from the gastrointestinal tract that stimulate insulin release from beta cells in a glucose-dependent manner, known as the "incretin effect." This system can be targeted with GLP-1 analogues and DPP-4 inhibitors. GLP-1 analogues are injectable peptides that act as GLP-1 receptor agonists and are more resistant to degradation by DPP-4, offering a longer duration of action compared to human GLP-1. In contrast, DPP-4 inhibitors are oral medications that enhance the activity of naturally released GLP-1 and GIP by inhibiting the DPP-4 enzyme, with a notably low risk of hypoglycemia due to their glucose-dependent mechanism. Recent meta-analyses have shown that incretin therapies, particularly when combined with metformin, result in lower hypoglycemia rates. The "Liraglutide Effect and Action in Diabetes" (LEAD) trials confirmed that liraglutide does not increase hypoglycemia risk.

Glucagon

Glucagon is a hormone that counteracts insulin, released by the pancreas to support glucose production in the liver. It is often the first-line treatment for severe hypoglycemia in insulin-treated diabetes patients. Recombinant glucagon has a short half-life of about 8 to 18 minutes and reaches peak plasma concentration quickly after subcutaneous or intramuscular injections. This rapid action minimizes treatment delays and the need for hospitalization during severe hypoglycemic episodes. Research shows that glucagon is effective and well-tolerated, quickly restoring blood glucose levels and facilitating faster recovery than waiting for emergency medical services to administer intravenous dextrose.

Typically, parenteral glucagon is used for severe hypoglycemia in type 1 diabetes patients, while intravenous glucose is preferred for those with type 2 diabetes. However, glucagon may also be appropriate for advanced type 2 diabetes patients on intensive insulin therapy but should be avoided in those taking sulfonylureas. Side effects like nausea and vomiting are generally rare, and glucagon toxicity is not reported.

Treatment of Hypoglycemia

To treat a conscious patient experiencing hypoglycemia, administer 15–20 grams of carbohydrates, such as four teaspoons of sugar or glucose. After 15 minutes, check blood glucose levels and repeat treatment if necessary. Advise the patient to have a meal or snack to prevent further hypoglycemia. For unconscious patients unable to consume food, intravenous glucose should be given immediately, or glucagon can be administered intramuscularly by a family member. Treatment plans may need to be adjusted if hypoglycemia occurs frequently at specific times or if the patient shows signs of hypoglycemia unawareness.

Severe hypoglycemia is a significant predictor of macrovascular events, adverse outcomes, and mortality in individuals with type 2 diabetes. The connection between hypoglycemia and these risks remains unclear; it may either be a direct cause or simply an indicator of susceptibility. Large clinical trials indicate a higher risk of mortality and cardiovascular events in type 2 diabetes patients experiencing severe hypoglycemia, though this association has not been confirmed in prospective studies involving type 1 diabetes.

Research has shown that cardiovascular issues can arise during hypoglycemic episodes, leading to increased cardiac workload, potential reductions in myocardial perfusion, and other harmful physiological effects. While mechanistic studies suggest a possible causal link between hypoglycemia and cardiovascular events, substantial evidence from larger studies is still lacking. Existing cardiovascular risk factors may be the primary contributors to these events, with low blood glucose levels acting as triggers in susceptible patients.

In a study of 11,140 type 2 diabetes patients, severe hypoglycemia was linked to a significantly increased risk of major macrovascular and microvascular events, as well as mortality. Over five years, 231 patients (2.1%) experienced at least one severe hypoglycemic episode, with higher rates among those receiving intensive glucose control. The median time from severe hypoglycemia to significant cardiovascular or microvascular events and death varied, but the associations were consistent across different outcomes.

Although mild hypoglycemia can disrupt daily life, severe episodes can result in life-threatening situations, including coma and seizures. Recurrent mild hypoglycemia can also impair the body's counter-regulatory responses, leading to hypoglycemia unawareness and an elevated risk for severe episodes, which diminishes the quality of life for affected patients.

While hypoglycemia is well-documented in type 1 diabetes, less is known about its prevalence in type 2 diabetes. Research has shown that intensive treatment in type 1 diabetes significantly increases severe hypoglycemia rates. In type 2 diabetes, some studies have indicated an increase in mild and moderate hypoglycemia, but not severe episodes, while others found no increase in any hypoglycemia with intensive treatment.

Despite the recognized risks of hypoglycemia in diabetes management, there is limited information on how often hypoglycemia occurs in typical clinical settings. A cross-sectional study focused on urban, predominantly African American patients with type 2 diabetes revealed a high overall prevalence of hypoglycemia (24.5%), but a very low incidence of severe hypoglycemia (0.5%). The highest prevalence of any hypoglycemic episode was found in patients undergoing triple therapy, even when their HbA1c levels were not particularly low. Prevalence tended to rise as HbA1c decreased, especially among insulin users with levels below 7.0%.

OBJECTIVES

General Objective

To assess the outcomes and epidemiology of patients experiencing hypoglycemia during their attendance in the emergency ward.

Specific Objectives

1. To identify the underlying causes of hypoglycemia.
2. To evaluate the incidence of hypoglycemia in diabetic patients using hypoglycemic agents, including oral medications, injectable insulin, or a combination of both.

Methodology

a. *Study design:* This research will employ a prospective observational study design.
b. *Participants:* The study will involve patients who visit the emergency department at BIR Hospital, NAMS.
c. *Sample size calculation:* To determine the sample size, we will use the following formula:

$$n = \frac{Z^2 pq}{d^2}$$

In this equation:

- Z represents the critical value for the normal distribution, which is 1.96 for a 95% confidence level (a = 0.05).
- p is the prevalence of hypoglycemia observed in the emergency ward, noted as 1.97% (as recorded in January 2018).
- q is calculated as 100 – p, resulting in 98.03%.
- d is the permissible error margin, set at 5%.

Plugging these values into the formula yields:

$$n = \frac{1.96^2(1.97)(98.03)}{(5)^2}$$

This calculation results in:

N ≈ 29.67

For the study, we will therefore recruit a minimum of 30 participants.

d. Selection Criteria for Participants
   a. *Inclusion criteria:* Patients with a blood glucose level of 55 mg/dL or lower, regardless of whether they display symptoms of hypoglycemia.
   b. *Exclusion criteria:* Patients whose capillary blood glucose is below 55 mg/dL but whose actual blood glucose exceeds 55 mg/dL, with or without symptoms.

e. *Control group:* Not applicable for this study.
f. *Setting:* The research will be conducted in a hospital or community hospital environment.
g. *Study duration:* The study is projected to span 12 months, from February 2018 to February 2019, with data collecting over three months.
h. *Ethical approval:* Before the study begins, we will seek ethical approval from the Institutional Review Committee (IRC) at NAMS.
i. *Conflict of interest:* There are no conflicts of interest to declare.
j. *Sampling method:* Convenience sampling will be utilized, with emergency medical officers or paramedics responsible for participant selection.
k. *Randomization and blinding:* Not applicable, as this is not a randomized controlled trial.

METHODS

This study will be a prospective, cross-sectional design. Informed consent will be obtained from all patients who meet the inclusion criteria. Patients presenting to the Emergency Department of General Practice and Emergency Medicine will be triaged, and emergency paramedics or medical officers will record their blood pressure, pulse rate, respiratory rate, mental status, and capillary blood sugar levels.

Capillary blood sugar will be measured using a VivaChek Ino device with glucose strips, with samples taken from the right index finger using a sterilized needle; any finger may be used if necessary. The test strips are manufactured in Wilmington, USA, and are valid until October 2020. Patients with a capillary blood sugar level below 55 mg/dL will be included in the study and assessed accordingly.

Definition for Study Population

All patients are presenting in emergency on preliminary investigation diagnosing to have hypoglycemia. Patients whose blood glucose level are less than 55 mg/dl are being treated.

Mortality, defined as death of population under study in Emergency ward, would be the primary endpoint of the study.

OUTCOME MEASURES

Primary Outcome Variables

- Discharge
- Admission to ward
- ICU admission
- Referral
- Leave against medical advice
- Mortality

Other Variables

a. *Identification:* Name, age, gender, caste, religion, address, referral source, patient ID, contact number, occupation, education.
b. *Triage parameters:* Temperature, blood pressure, pulse rate, respiratory rate, and random blood sugar (RBS).
c. *Laboratory details:* Random blood sugar and capillary blood glucose level.

Data Management and Statistical Analysis

a. *Data handling:* All collected data will be assigned a unique identification number to maintain confidentiality and will be entered into Microsoft Excel 2007.
b. *Coding:* Each variable will receive a unique code for identification while ensuring confidentiality.
c. *Monitoring:* Every second data entry will be verified for accuracy.
d. *Statistical methods proposed:* Data analysis will be conducted using Microsoft Excel 2007 and then converted to SPSS version 11.5 (Statistical Package for Social Science). The student's T-test will be used for comparing the means of continuous variables. For associations between categorical variables, Chi-square tests or Fisher's exact tests will be applied. To identify independent predictors of mortality, variables with p-values <0.25 from a bivariate binary logistic regression model will be included in a multivariate logistic regression model. Variables with p-values <0.05 will be considered statistically significant.

ETHICAL CONSIDERATION

Ethical approval will be obtained from NAMS IRB following proposal acceptance. Participants will be informed about the study's purpose, and written consent will be secured. All information gathered will be used solely for research purposes and kept confidential.

Regarding the Human Participants

Human participants are required to research for examinations.

What Is Expected of the Research Participants During the Research?

Participants will undergo examinations and provide blood samples. Glucose test strips will be supplied at no charge through research funding.

Are There Any Risks Involved for the Participants?

Mild pain while pricking with needle to index finger and while drawing blood samples.

Are There Any Benefits Involved for Participants?

Yes, participants will get managed and treated or get referred accordingly.

RESULTS AND ANALYSIS

A total of 53 patients attending to the emergency ward whose glucose random blood sugar were analyzed. The predominant age group was from 30 to 70 years. Male made up 62.3% of the study subject. The distribution of cases of hypoglycemia by age and sex are shown in Figures 3 and 4.

Out of 53 patients with hypoglycemia, 50.9% of patients have a history of diabetes mellitus and 49.1 percent patients has other history related to hypoglycemia (Figure 5).

Out of 53 patients with hypoglycemia, 48.1% patients were on medication and 51.9% patients were not under any medications. Out of 48.1% with medication maximum patient were taking OHA which was 32.7%. Similarly, insulin users were 9.6% and those patients who took both Insulin and OHA were less 5.8%. (Figure 6).

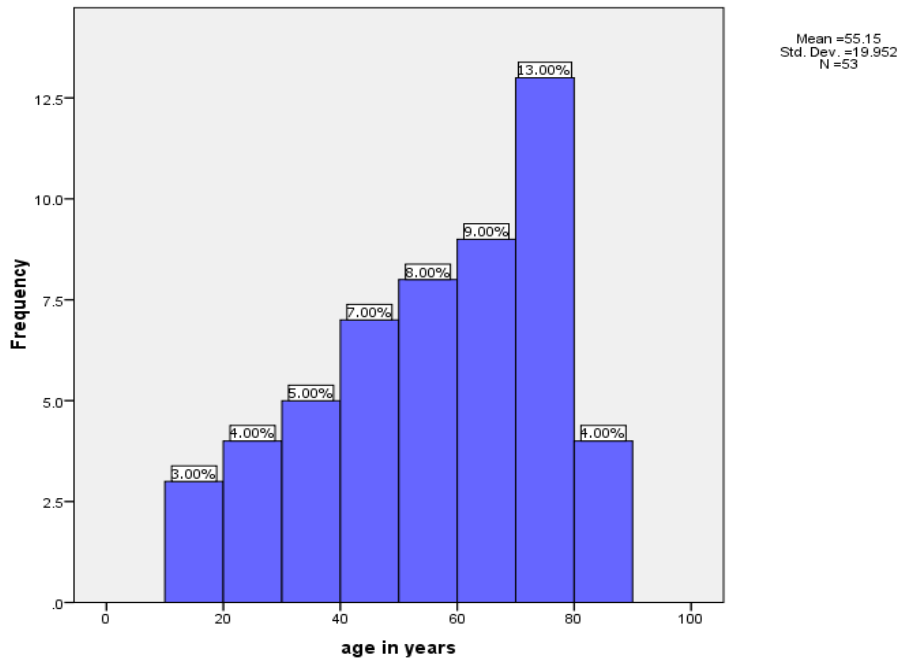

Figure 3. Frequency of hypoglycemia by age.

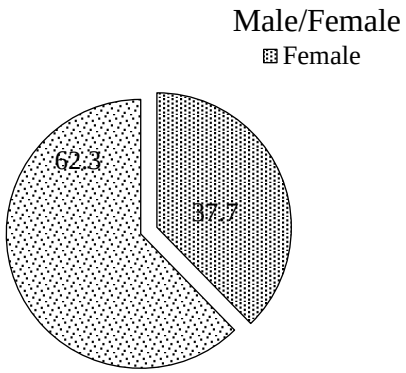

Figure 4. Frequency of hypoglycemia by sex.

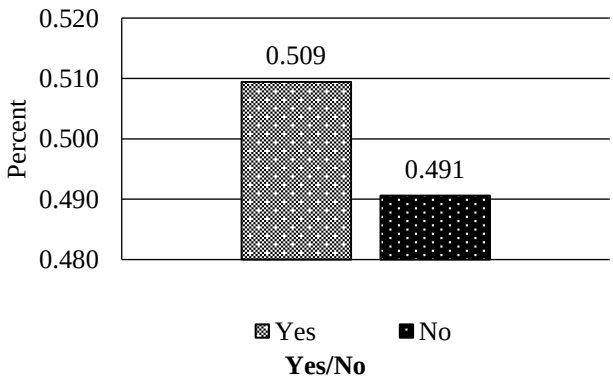

Figure 5. History of diabetes mellitus in hypoglycemic patients.

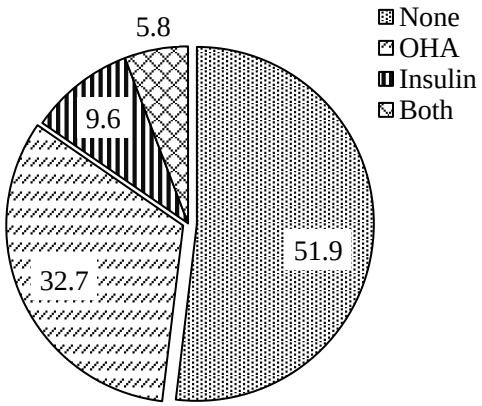

Figure 6. Patients with hypoglycemia on medication.

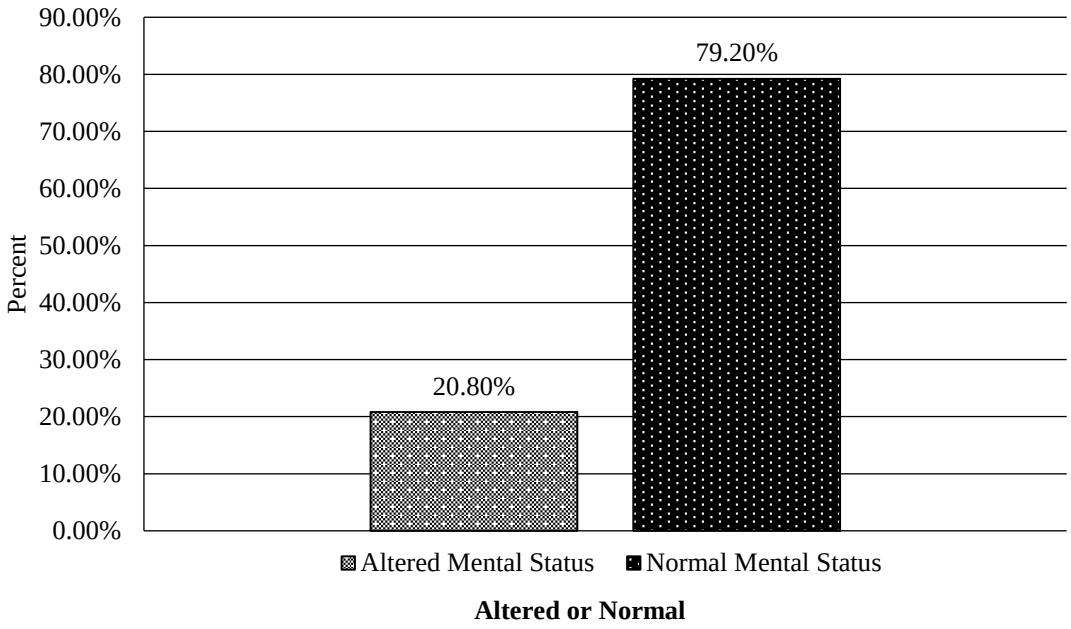

Figure 7. Mental status of hypoglycemic patient.

Out of 53 patients presented with hypoglycemia only 20,8% of patients' mental status were altered and 79.2% of patients had normal mental status (Figure 7).

The mean blood sugar level was 40.94 (SD 14.492, minimum 10) (Figure 8).

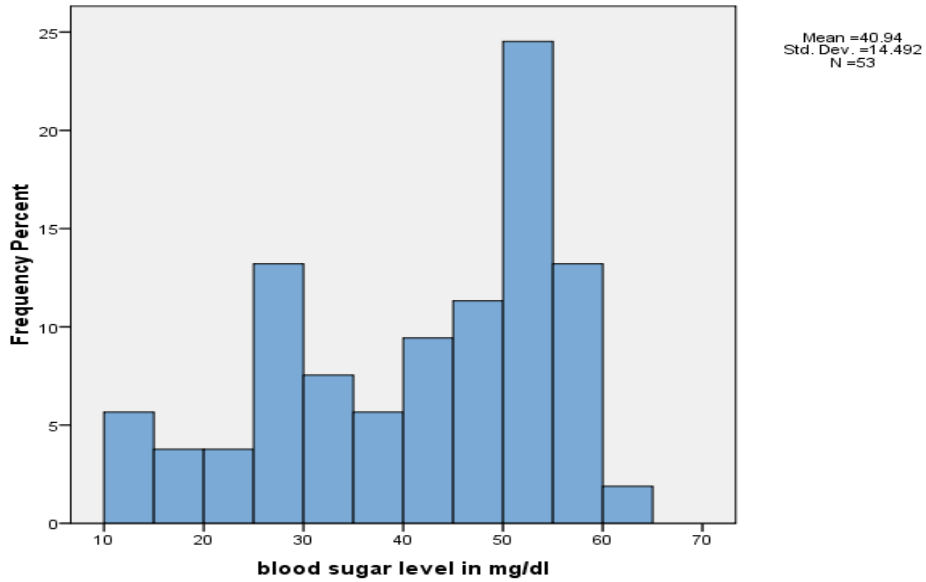

Figure 8. Blood sugar level of hypoglycemic patients.

PRESENTING COMPLAINS

Out of 53 patients presented with hypoglycemia in emergency ward, the most common presenting complaints were shortness of breath (20.75%) followed by altered mental status, weakness, slur speech which were 11.32% of all (Figure 9).

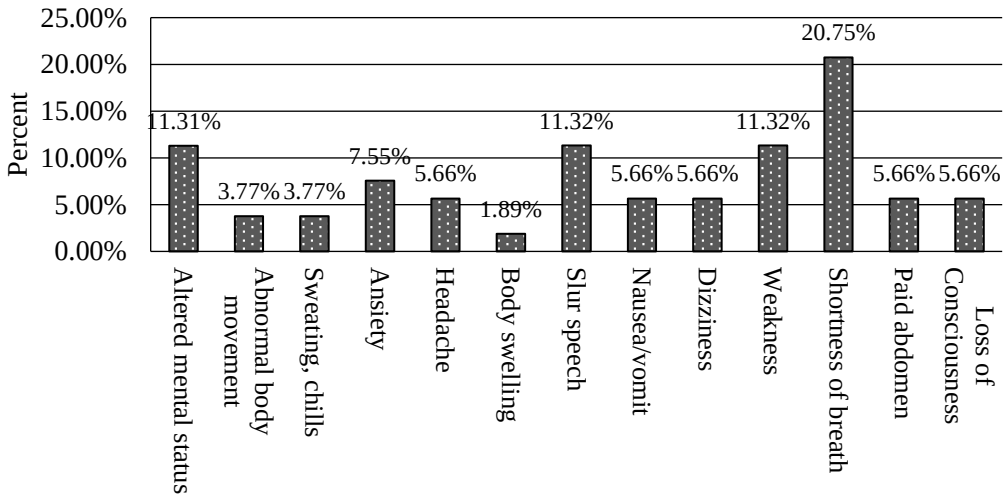

Figure 9. Presenting chief complaints of patients.

Table 5. Diagnosis distribution among patients.

Diagnosis	Number	Percentage
Complicated DM	25	47.2
CKD	8	15.1
CVA	09	17.0
HTN	16	30.2
COPD	10	18.9
CLD	6	11.3

The total percentage is more than 100 as more than one diagnosis is possible. The most common diagnosis is complicated DM which was 47.2% (Table 5).

HISTORY OF ALCOHOL INTAKE

Out of 53 patients who are presented with hypoglycemia, 32.1% of patients have history of alcohol intake (Figure 10).

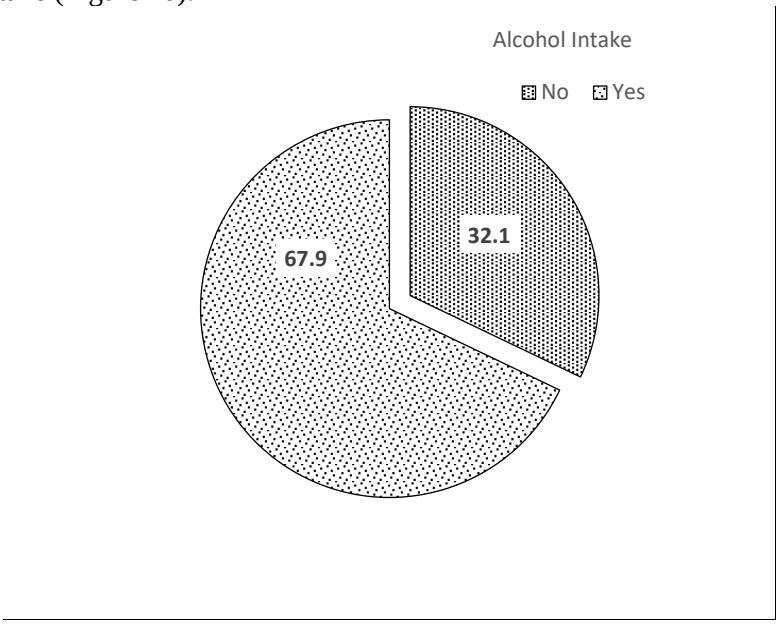

Figure 10. History of alcohol intake by patients. Outcome by history of alcohol intake.

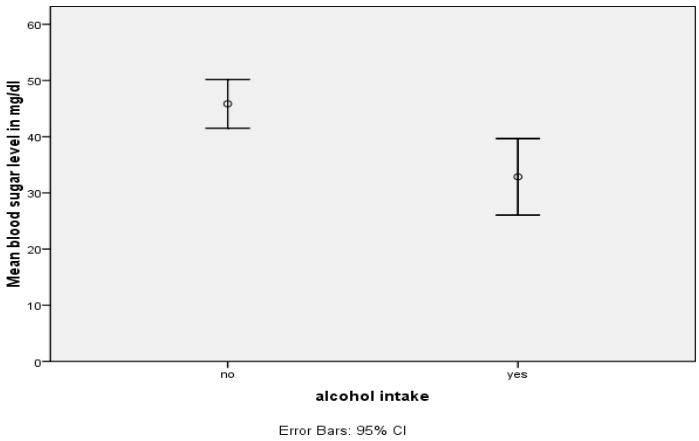

Figure 11. Outcome by history of alcohol intake.

The number of patients who consume alcohol, their blood sugar levels were comparatively low (Figure 11).

Out of 53 patients presented with hypoglycemia in emergency ward,52.8% patients were admitted for further management, 28.3% patients were discharged from ED,17.0% patients were referred to another center, and 1.9% patients have mortality.

Table 6. Outcomes of patients in the study.

Outcome					
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Mortality	1	1.9	1.9	1.9
	Admission	28	52.8	52.8	54.7
	Discharge	15	28.3	28.3	83.0
	Refer	9	17.0	17.0	100.0
	Total	53	100.0	100.0	

In a study assessing outcomes among patients with hypoglycemia, mortality was observed in 1.9% of cases, while 52.8% were admitted for further treatment. A total of 28.3% of patients were discharged, and 17.0% were referred to other facilities, resulting in a total of 53 patients analyzed (Table 6 and Figure 12).

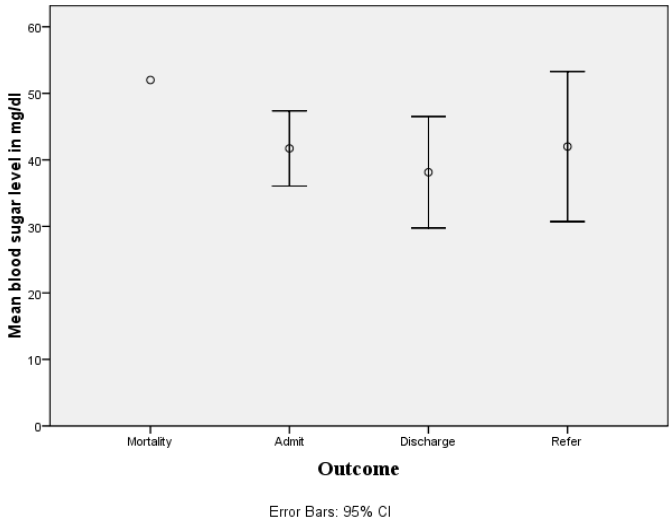

Figure 12. Outcome of hypoglycemic patients.

DISCUSSION

In this study, while the participants were divided into diabetic and non-diabetic groups, their baseline characteristics differed significantly, making direct comparisons difficult. Hypoglycemia primarily affected middle-aged and elderly individuals. A previous study indicated that 79.83% of hypoglycemic cases in emergency departments involved diabetic patients. The number of female patients experiencing hypoglycemia was lower compared to males, likely due to a smaller female representation in the study. Consistent with prior research, the main cause of hypoglycemia among diabetics was found to be intensive blood glucose management with antidiabetic medications. This contrasts with another study that identified missed meals as the primary cause of hypoglycemia.

In non-diabetic cases, hypoglycemia was frequently linked to infections, liver and kidney diseases, and cancer, a finding supported by the current results. Notably, hypoglycemia related to renal impairment was more prevalent among diabetic patients than non-diabetics, likely due to renal disease's effects on gluconeogenesis and insulin degradation.

Among diabetic patients, infections primarily stemmed from the genitourinary system, while in non-diabetic patients, the main infection focus was hepatobiliary, followed by surgical infections. Further research is needed to explore specific associations with different infection sources.

The incidence of hypoglycemia in emergency settings was recorded at 16.51 per 1000 visits, significantly lower than the 37.5 per 1000 reported in another study. The current findings also noted fluctuations in hypoglycemia incidence over several years. The overall mortality rate was 0.91 per 1000 visits, with variations in mortality reported in other studies. The study highlighted those recurrent admissions for hypoglycemia occurred frequently, indicating its serious impact on patients.

CONCLUSION

Hypoglycemia in diabetic patients is primarily linked to medications, while infections are the main cause in non-diabetic individuals. Among the 53 patients studied, those who consumed alcohol tended to have lower blood sugar levels, like patients on insulin and oral hypoglycemic agents. Most patients were admitted for further assessment and treatment. It is crucial that no patient leaves the emergency department without a thorough evaluation of the causes of their hypoglycemia, and each case must be addressed individually. The rising incidence of fatalities over the years is concerning, highlighting the need for further research to identify the underlying causes.

Limitations

- Shorter duration of study.
- Single centered study.
- Limited number of samples.
- Nonrandomized sample size.
- Examiner's bias.

Recommendations

This study should be conducted on a larger scale to have a clear picture of the prevalence of hypoglycemia. Hypoglycemia was associated with significantly poor quality of life and reduced treatment satisfaction. Patients with diabetes who become hypoglycemic are also more susceptible to developing defective counter-regulation, leading to hypoglycemia unawareness which is a life-threatening situation and must be aggressively addressed.

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