GMR
The Original

FREQUENCY AND CLINICAL PATTERNS OF HYPOGLYCEMIA AMONG CHRONIC KIDNEY DISEASE PATIENTS ON INSULIN THERAPY AT AYUB TEACHING HOSPITAL, ABBOTTABAD

Talha khan [1], Khifza Jadoon [2], Shaheen bibi[3], Muhammad Yousaf [4], Aleema Sahar [5], Bibi Marrium [6], Ahmad Zeb [7], Sardar Arslan [8], Waqas Ahmed [9]

[1]Post graduate resident medicine, Ayub teaching hospital, Abbottabad, KPK, Pakistan.
[2]Post graduate resident medicine, Ayub teaching hospital, Abbottabad, KPK, Pakistan.
[3]Registrar nephrology, Ayub teaching hospital, Abbottabad, KPK, Pakistan,
[4]House officer, Ayub teaching hospital, Abbottabad, KPK, Pakistan.
[5]Post graduate resident medicine, Ayub teaching hospital, Abbottabad, KPK, Pakistan.
[6]Post graduate resident Nephrology, KTH, KPK, Pakistan.
[7]Post graduate resident medicine, Ayub teaching hospital, Abbottabad, KPK, Pakistan.
[8]Post graduate resident medicine, Ayub teaching hospital, Abbottabad, KPK, Pakistan.
[9]Medical Officer Ayesha Bashir cleft hospital, Pakistan.
Corresponding Author: Khifza Jadoon [2] (khifzajadoon@gmail.com)

ABSTRACT:
Background: Hypoglycemia is an important complication of insulin therapy in patients with chronic kidney disease (CKD). Declining renal function may increase the risk of hypoglycemia because of reduced insulin clearance, impaired renal gluconeogenesis, variable nutritional intake, intercurrent illness, and changes in insulin requirements. Patients with advanced CKD and those receiving hemodialysis are particularly vulnerable. However, local data describing the frequency and clinical patterns of hypoglycemia among insulin-treated patients with CKD are limited. This study was conducted to determine the frequency and describe the clinical patterns of hypoglycemia among patients with CKD receiving insulin therapy at Ayub Teaching Hospital, Abbottabad.
Methods: A descriptive observational cross-sectional study was conducted in the Medical Unit of Ayub Teaching Hospital, Abbottabad, from **1 May 2026 to 1 August 2026**. A total of **175 adult patients** with established CKD receiving insulin therapy were enrolled through non-probability consecutive sampling. Hypoglycemia was defined as a blood glucose level **<70 mg/dL**, with level 1 defined as 54–<70 mg/dL, level 2 as <54 mg/dL, and level 3 as an event requiring assistance from another person. Demographic, clinical, CKD-related, insulin-related, and hypoglycemia-related variables were recorded using a structured proforma. Data were analyzed using IBM SPSS Statistics and presented as frequencies, percentages, and appropriate descriptive measures.
Results: Among 175 insulin-treated patients with CKD, **59 (33.7%)** experienced at least one hypoglycemic episode, while 116 (66.3%) had no documented episode. A total of **96 hypoglycemic episodes** were recorded among the affected patients. Of these, 48 (50.0%) were level 1, 37 (38.5%) were level 2, and 11 (11.5%) were level 3 episodes requiring assistance. Among patients experiencing hypoglycemia, 31 (52.5%) had one episode, 16 (27.1%) had two episodes, 7 (11.9%) had three episodes, and 5 (8.5%) experienced four or more episodes. Sweating was the most common clinical manifestation (57.6%), followed by tremulousness (45.8%), dizziness/light-headedness (42.4%), generalized weakness (39.0%), and palpitations (30.5%). Confusion or altered behavior occurred in 23.7%, while seizures and loss of consciousness were reported in 6.8% and 11.9%, respectively. Morning episodes were most frequent (30.2%), followed by afternoon (26.0%), evening (24.0%), and night (19.8%). Reduced oral intake or anorexia was documented in 30.2% of episodes, while missed meals occurred in 24.0%. Oral carbohydrate or glucose was used for 63.5% of episodes, whereas 25.0% required intravenous dextrose. The frequency of hypoglycemia increased with advancing CKD stage, from **16.7% in stage 3a to 47.5% among patients with stage 5 CKD receiving hemodialysis**. Hypoglycemia was also more frequent among patients receiving multiple daily injections (43.5%) and among those with diabetes duration >10 years (43.5%).
Conclusion: Hypoglycemia was common among insulin-treated patients with CKD, affecting approximately one-third of patients in this study. Episodes ranged from mild symptomatic events to severe episodes requiring assistance or intravenous treatment, with recurrent episodes also observed. Hypoglycemia was more frequently encountered in advanced CKD, particularly among patients receiving hemodialysis, and was commonly observed in the setting of reduced oral intake and missed or delayed meals. These findings highlight the need for regular glucose monitoring, careful individualization of insulin therapy, attention to nutritional intake and dialysis timing, and early recognition of hypoglycemia in patients with CKD.

KEYWORDS: Chronic kidney disease; Hypoglycemia; Insulin therapy; Hemodialysis; Diabetes mellitus; Blood glucose; Hypoglycemic episodes

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem and is associated with substantial morbidity, mortality, and healthcare burden. Diabetes mellitus is one of the leading causes of CKD, and a considerable proportion of patients with diabetes eventually develop some degree of renal impairment. As kidney function progressively declines, the management of diabetes becomes increasingly complex because both hyperglycemia and hypoglycemia can occur more frequently. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recognize advanced CKD as an important risk factor for hypoglycemia in patients receiving glucose-lowering therapy, particularly insulin. Hypoglycemia is one of the most clinically important complications of insulin therapy. It may present with autonomic symptoms such as sweating, tremulousness, palpitations and hunger, while more severe episodes can result in confusion, seizures, loss of consciousness, coma, and potentially death. Recurrent or severe hypoglycemia may also interfere with optimal glycemic management because fear of hypoglycemia can lead to under-treatment of diabetes. In patients with CKD, this problem is particularly relevant because several physiological changes associated with declining renal function increase susceptibility to low blood glucose levels. A systematic review including more than 300,000 individuals found that the incidence of hypoglycemia was significantly higher among patients with CKD than among those without CKD, with insulin therapy identified among the important risk factors. The increased risk of hypoglycemia in CKD is multifactorial. The kidneys normally contribute substantially to insulin metabolism and clearance as well as to endogenous glucose production through gluconeogenesis. With progressive reduction in renal function, insulin clearance decreases, resulting in prolonged insulin exposure and potentially excessive insulin action. At the same time, impaired renal gluconeogenesis reduces the body's ability to restore blood glucose during periods of fasting or hypoglycemia. Additional factors commonly encountered in CKD, including reduced dietary intake, malnutrition, intercurrent illness, impaired counter-regulatory responses, metabolic disturbances, and changes in insulin sensitivity, may further increase the risk. In patients receiving hemodialysis, glucose and insulin metabolism may change substantially during and after dialysis, adding another potential source of glycemic variability.

Insulin therefore requires particular attention in patients with advanced CKD. Although insulin remains an important and often essential treatment for diabetes, its pharmacokinetic and pharmacodynamic effects may change as kidney function deteriorates. The required insulin dose can vary considerably between individuals, and a regimen that was previously well tolerated may become excessive as CKD progresses. The ADA-KDIGO consensus report highlights that insulin-treated patients with advanced CKD may require lower insulin doses because of reduced insulin clearance and recommends careful glucose monitoring in individuals at increased risk of hypoglycemia. Importantly, hypoglycemia in CKD is not limited to isolated biochemical abnormalities. Episodes may be recurrent, prolonged, nocturnal, or severe enough to require assistance from another person or hospital-based treatment. In a prospective study of patients with type 2 diabetes and CKD, continuous glucose monitoring identified hypoglycemic episodes in a large proportion of participants, with many episodes occurring during the overnight period. Insulin treatment and lower HbA1c were identified as important modifiable factors associated with hypoglycemia. These findings also demonstrate that conventional measures such as HbA1c may not adequately reflect the frequency or severity of hypoglycemic episodes in patients with CKD. The relationship between CKD severity and insulin-associated hypoglycemia is clinically important. In a large cohort study of patients with type 2 diabetes, both insulin use and advanced CKD were independently associated with an increased risk of serious hypoglycemic events. The risk was particularly pronounced among individuals with markedly reduced estimated glomerular filtration rate. Thus, as renal function declines, clinicians need to consider not only the achievement of glycemic targets but also the safety of the insulin regimen, dietary intake, renal function, dialysis status, and the patient's ability to recognize and respond to hypoglycemia.

Despite the established association between CKD and hypoglycemia, the clinical presentation and patterns of hypoglycemia may vary considerably between patients. Factors such as age, duration of diabetes, severity of renal impairment, insulin regimen, insulin dose, nutritional status, dialysis, comorbid illnesses, and previous episodes of hypoglycemia may influence its occurrence and severity. Understanding these patterns is particularly important in routine clinical practice because many episodes may remain unrecognized, especially when symptoms are atypical or when patients have impaired awareness of hypoglycemia. Evidence regarding hypoglycemia among insulin-treated patients with CKD is available predominantly from high-income healthcare settings, while data from South Asian and Pakistani populations remain comparatively limited. Differences in dietary practices, healthcare access, insulin prescribing patterns, affordability of glucose monitoring, late presentation of CKD, dialysis practices, and the burden of diabetes may influence the clinical profile of these patients. Local data are therefore important for identifying the magnitude and characteristics of hypoglycemia in routine practice and for recognizing patients who may require closer glucose monitoring or adjustment of insulin therapy.

Therefore, the present study was conducted at Ayub Teaching Hospital, Abbottabad, to determine the **frequency and clinical patterns of hypoglycemia among patients with chronic kidney disease receiving insulin therapy**. By describing the occurrence, severity, clinical manifestations, and relevant patient and treatment characteristics associated with hypoglycemia, this study aims to provide locally relevant evidence that may help clinicians recognize high-risk patients and promote ser, more individualized glycemic management in CKD.

OBJECTIVE:

Primary objective

1. To determine the frequency of hypoglycemia among adult patients with chronic kidney disease receiving insulin therapy at Ayub Teaching Hospital, Abbottabad, during the study period.

Secondary objectives

2. To describe the clinical patterns of hypoglycemia in these patients, including presenting symptoms, severity, timing of episodes, and need for assistance or medical intervention.
3. To describe the demographic and clinical characteristics of patients experiencing hypoglycemia, including age, sex, duration of diabetes, stage of chronic kidney disease, and dialysis status.
4. To describe the insulin-related characteristics among patients experiencing hypoglycemia, including type of insulin, dosing regimen, and duration of insulin therapy.
5. To document the blood glucose levels and relevant circumstances at the time of hypoglycemic episodes, including missed or delayed meals, intercurrent illness, and dialysis where applicable.

MATERIALS AND METHODS

Study Design and Setting

A **descriptive observational cross-sectional study** was conducted in the **Medical Unit, Ayub Teaching Hospital, Abbottabad**, a tertiary-care teaching hospital serving patients from Abbottabad and surrounding districts of Khyber Pakhtunkhwa.

Study Duration

The study was conducted over a period of **three months, from 1 May 2026 to 1 August 2026**.

Study Population

The study population comprised **adult patients with established chronic kidney disease who were receiving insulin therapy** and were managed in the Medical Unit during the study period.

Sample Size

The sample size was calculated using the WHO-recommended formula for estimating a population proportion in a cross-sectional study. An anticipated frequency of hypoglycemia of **33.7%** was taken from a previously published observational study of insulin-treated patients with advanced CKD.

Using a **95% confidence level** and **7% absolute precision**, the calculated minimum sample size was **175 patients**.

Sampling Technique

Non-probability consecutive sampling was used. All eligible patients presenting to or admitted in the Medical Unit during the study period were consecutively assessed for inclusion until the required sample size was achieved.

Inclusion Criteria

Patients fulfilling all of the following criteria were included:

- Adults aged **18 years or above**.
- Diagnosed with **chronic kidney disease**, as documented in the medical record or established by the treating physician.
- Receiving **insulin therapy** for diabetes mellitus.
- Patients who were admitted to or managed in the Medical Unit during the study period.
- Patients who provided informed consent to participate.

Exclusion Criteria

Patients were excluded if they had:

- Acute kidney injury without established chronic kidney disease.
- Hypoglycemia attributable to **intentional insulin overdose or self-harm**.
- Altered sensorium or another condition in which reliable clinical history could not be obtained and no reliable attendant was available to provide the required information.
- Incomplete medical records or insufficient information regarding insulin therapy or blood glucose measurements.
- Patients who declined participation.

Variables Studied

The following variables were recorded:

Demographic variables

- Age
- Sex

Clinical variables

- Duration of diabetes mellitus
- Duration and stage of CKD
- Dialysis status
- Relevant comorbidities
- Recent hospitalization or acute intercurrent illness
- Dietary intake/missed or delayed meals

Insulin-related variables

- Type of insulin
- Insulin regimen
- Total daily insulin dose
- Duration of insulin therapy

Hypoglycemia-related variables

- Occurrence of hypoglycemia
- Blood glucose level during the episode
- Clinical symptoms and signs
- Severity of hypoglycemia
- Time of occurrence, including nocturnal episodes
- Recurrent episodes
- Requirement for assistance
- Requirement for intravenous glucose or other medical intervention

For the purpose of this study, **hypoglycemia was defined as a blood glucose concentration <70 mg/dL (3.9 mmol/L)**. Clinically significant hypoglycemia was further categorized according to the measured glucose level and clinical consequences, with **<54 mg/dL** considered a clinically significant low glucose value and an episode associated with altered mental or physical status requiring assistance considered a severe event. This approach is consistent with contemporary international definitions of hypoglycemia.

Data Collection Procedure

Data were collected using a **structured data collection proforma** developed specifically for the study after reviewing relevant literature and standard definitions of hypoglycemia.

Eligible patients were identified during their stay in the Medical Unit. After obtaining informed consent, demographic and clinical information was obtained from the patient and, where required, from the accompanying attendant and medical record. Information regarding CKD stage, dialysis status, diabetes duration, insulin regimen, and relevant laboratory investigations was obtained from the patient's clinical documentation.

Blood glucose values documented during the hospital stay were reviewed, and patients were specifically assessed for documented or clinically recognized episodes of hypoglycemia. For each episode, the lowest recorded blood glucose level, presenting symptoms, timing, circumstances surrounding the episode, and treatment required were recorded.

Where more than one hypoglycemic episode occurred in the same patient, episodes were recorded to characterize the **clinical pattern and recurrence**, while the patient was counted only once when calculating the overall frequency of patients experiencing hypoglycemia.

Operational Classification of Hypoglycemia

Hypoglycemic episodes were categorized according to their measured blood glucose concentration and clinical consequences:

- **Level 1 hypoglycemia:** blood glucose **<70 mg/dL but ≥54 mg/dL**.
- **Level 2 hypoglycemia:** blood glucose **<54 mg/dL**.
- **Level 3 hypoglycemia:** hypoglycemia associated with altered mental and/or physical status requiring assistance from another person for recovery, irrespective of the measured glucose concentration.

Clinical manifestations such as sweating, tremulousness, palpitations, hunger, dizziness, weakness, confusion, abnormal behavior, seizures, and loss of consciousness were documented where present.

Statistical Analysis

Data were entered and analyzed using **IBM SPSS Statistics**. Continuous variables such as age and duration of diabetes were summarized as **mean ± standard deviation** or **median with interquartile range**, depending on the distribution of the data. Categorical variables were presented as **frequencies and percentages**.

The primary outcome, frequency of hypoglycemia, was expressed as the **proportion of study participants who experienced at least one hypoglycemic episode during the study period**. Clinical patterns of hypoglycemia were summarized using appropriate frequencies and percentages.

Descriptive analysis was also performed according to relevant clinical characteristics, including CKD stage, dialysis status, insulin regimen, and severity of hypoglycemia. As this was a descriptive cross-sectional study, statistical testing for causal relationships was not the primary objective.

Quality Control

A standardized data collection proforma was used throughout the study to maintain uniformity in data collection. The data collection procedure and operational definitions were reviewed before commencement of the study. The principal investigator reviewed completed proformas regularly for completeness and consistency. Laboratory and clinical information was cross-checked against the patient's medical record where necessary. Data entry was checked for missing values, inconsistencies, and duplicate entries before final analysis.

Ethical Considerations

The study was conducted after obtaining approval from the **Institutional Ethics Committee of Ayub Teaching Hospital** (**Approval Code/Ref.N0.RC-EA-2024/259**).Written informed consent was obtained from all participants before enrolment. Participation was voluntary, and patients were informed that refusal to participate

would not affect their medical care. Confidentiality of patient information was maintained throughout the study, and data were used solely for research purposes. No additional intervention or alteration of the patient's prescribed treatment was undertaken solely for the purpose of the study.

RESULTS

Table 1. Demographic characteristics of study participants (N=175)

Variable	Category	n	%
Age (years)	18–39	18	10.3
	40–59	64	36.6
	60–79	77	44.0
	≥80	16	9.1
Sex	Male	103	58.9
	Female	72	41.1

Mean age: 61.8 ± 13.2 years | Age range: 19–89 years

Table 2. Clinical characteristics of study participants (N=175)

Variable	Category	n	%
Duration of diabetes mellitus	<5 years	29	16.6
	5–10 years	61	34.9
	>10 years	85	48.6
Duration of CKD	<2 years	49	28.0
	2–5 years	71	40.6
	>5 years	55	31.4
Dialysis status	Not on dialysis	116	66.3
	Hemodialysis	59	33.7

Table 3. Stage of chronic kidney disease among study participants (N=175)

CKD stage	n	%
Stage 3a	18	10.3
Stage 3b	29	16.6
Stage 4	54	30.9
Stage 5, not on dialysis	15	8.6
Stage 5, on hemodialysis	59	33.7
Total	**175**	**100.0**

Table 4. Insulin-related characteristics of study participants (N=175)

Variable	Category	n	%
Type of insulin	Human regular/short-acting insulin	24	13.7
	NPH/intermediate-acting insulin	19	10.9
	Premixed insulin	47	26.9
	Basal insulin analogue	39	22.3
	Basal-bolus combination	46	26.3
Insulin regimen	Once daily	35	20.0

Variable	Category	n	%
	Twice daily	78	44.6
	Multiple daily injections	62	35.4

Table 5. Frequency of hypoglycemia among insulin-treated CKD patients (N=175)

Category	n	%
At least one hypoglycemic episode	59	33.7
No documented hypoglycemic episode	116	66.3
Total	**175**	**100.0**

Table 6. Number of hypoglycemic episodes among affected patients (n=59)

Number of episodes per patient	n	%
1 episode	31	52.5
2 episodes	16	27.1
3 episodes	7	11.9
≥4 episodes	5	8.5
Total patients with hypoglycemia	**59**	**100.0**

Total documented hypoglycemic episodes: 96

Table 7. Biochemical severity of hypoglycemic episodes (n=96 episodes)

Hypoglycemia category	Blood glucose	Episodes, n	%
Level 1	<70 to ≥54 mg/dL	48	50.0
Level 2	<54 mg/dL	37	38.5
Level 3	Event requiring assistance	11	11.5
Total		**96**	**100.0**

Table 8. Clinical manifestations of hypoglycemia among affected patients (n=59)

Clinical manifestation*	n	%
Sweating	34	57.6
Tremulousness	27	45.8
Dizziness/light-headedness	25	42.4
Generalized weakness	23	39.0
Palpitations	18	30.5
Hunger	15	25.4
Confusion/altered behavior	14	23.7
Blurred vision	10	16.9
Seizure	4	6.8
Loss of consciousness	7	11.9

*Multiple manifestations could occur in the same patient; therefore, percentages do not total 100%.

Table 9. Timing and circumstances of hypoglycemic episodes (n=96 episodes)

Variable	Category	n	%
Time of occurrence	Morning (06:00–12:00)	29	30.2
	Afternoon (12:01–18:00)	25	26.0
	Evening (18:01–24:00)	23	24.0
	Night (00:01–05:59)	19	19.8
Meal-related circumstance	Missed meal	23	24.0
	Delayed/reduced meal	18	18.8
	No apparent meal-related factor	55	57.3

Table 10. Clinical circumstances associated with hypoglycemic episodes (n=96 episodes)

Circumstance	n	%
Reduced oral intake/anorexia	29	30.2
Missed or delayed meal	23	24.0
Hemodialysis-related timing	19	19.8
Intercurrent infection/acute illness	14	14.6
Recent change in insulin dose	8	8.3
No identifiable precipitating circumstance	38	39.6

*More than one circumstance could be present in an episode; therefore, percentages do not total 100%.

Table 11. Management required for hypoglycemic episodes (n=96 episodes)

Management	n	%
Oral carbohydrate/glucose administered	61	63.5
Intravenous dextrose required	24	25.0
Glucagon administered	3	3.1
Required assistance but recovered without IV therapy	8	8.3
Total	**96**	**100.0**

Table 12. Relationship between CKD stage and occurrence of hypoglycemia (N=175)

CKD stage	Patients, n	Patients with hypoglycemia, n (%)
Stage 3a	18	3 (16.7)
Stage 3b	29	7 (24.1)
Stage 4	54	16 (29.6)
Stage 5, not on dialysis	15	5 (33.3)
Stage 5, on hemodialysis	59	28 (47.5)
Total	**175**	**59 (33.7)**

Table 13. Hypoglycemia according to insulin regimen (N=175)

Insulin regimen	Total patients, n	Hypoglycemia, n (%)
Once daily	35	8 (22.9)

Insulin regimen	Total patients, n	Hypoglycemia, n (%)
Twice daily	78	24 (30.8)
Multiple daily injections	62	27 (43.5)
Total	**175**	**59 (33.7)**

Table 14. Hypoglycemia according to duration of diabetes mellitus (N=175)

Duration of diabetes	Total patients, n	Hypoglycemia, n (%)
<5 years	29	5 (17.2)
5–10 years	61	17 (27.9)
>10 years	85	37 (43.5)
Total	**175**	**59 (33.7)**

Table 15. Hypoglycemia according to dialysis status (N=175)

Dialysis status	Total patients, n	Hypoglycemia, n (%)
Not on dialysis	116	31 (26.7)
Hemodialysis	59	28 (47.5)
Total	**175**	**59 (33.7)**

Table 16. Pattern of hypoglycemia according to severity and requirement for assistance (n=59 patients)

Clinical severity	n	%
Mild episodes managed by patient without assistance	32	54.2
Symptomatic episodes requiring assistance from another person	17	28.8
Severe episodes with altered consciousness/seizure	10	16.9
Total	**59**	**100.0**

Pictorial Depiction of Results

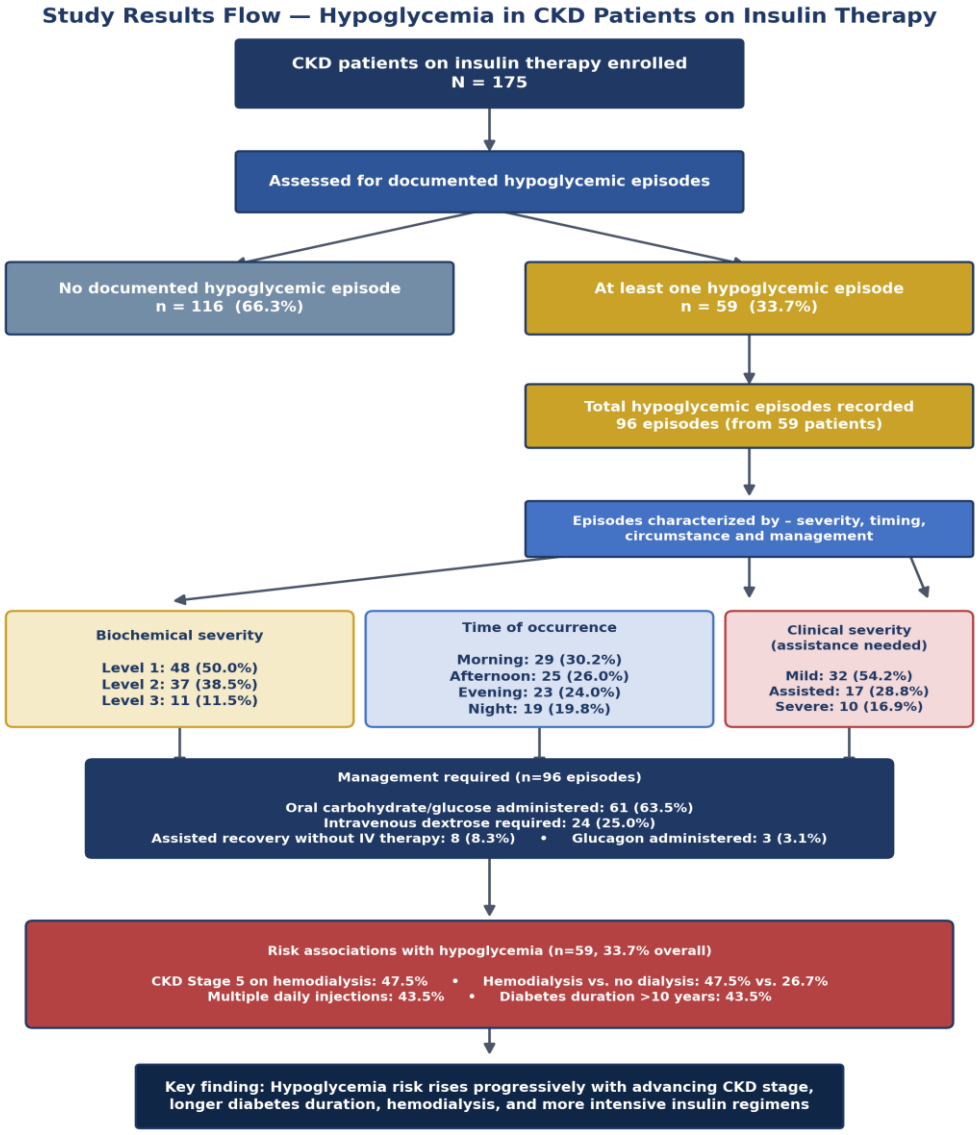


Figure 1. Overall study results flow — from enrollment to key findings

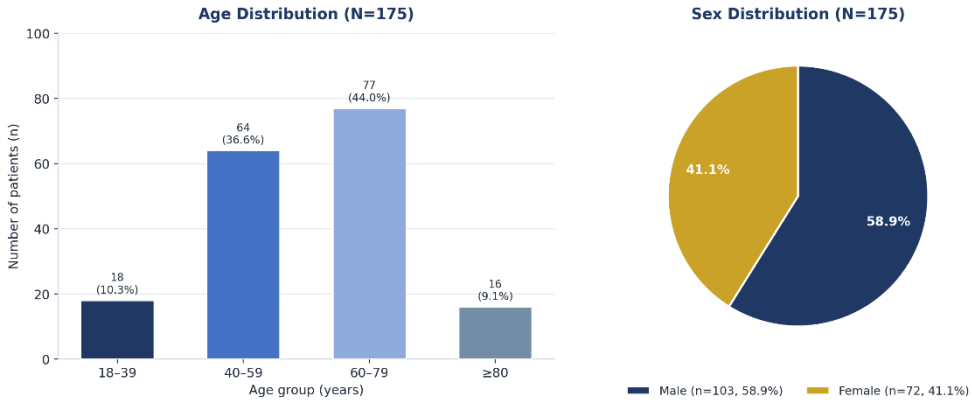
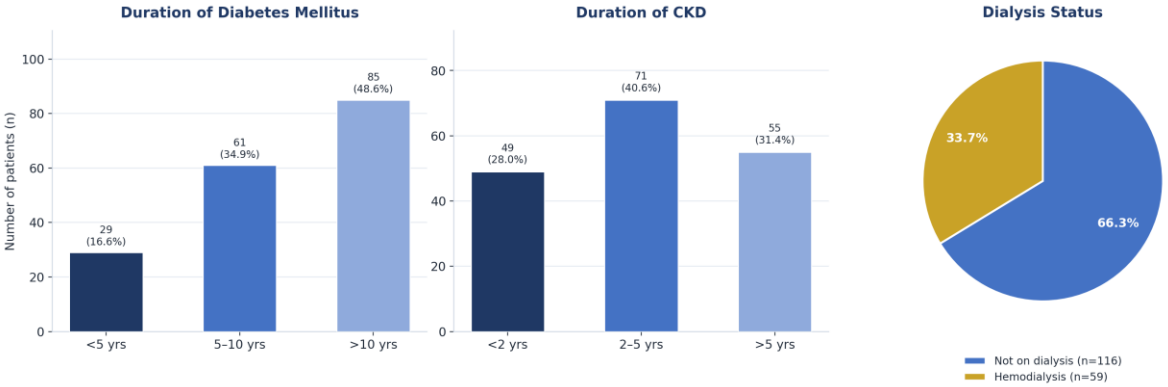


Figure 2. Age and sex distribution of study participants (N=175)

Figure 3. Duration of diabetes mellitus, dur



ation of CKD, and dialysis status (N=175)

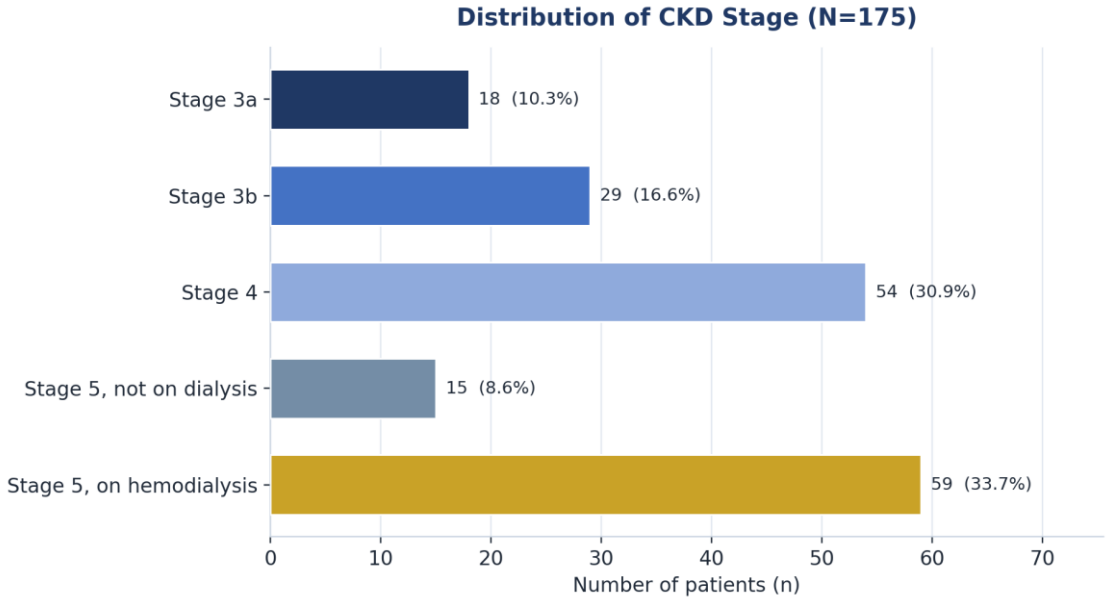


Figure 4. Distribution of CKD stage among study participants (N=175)

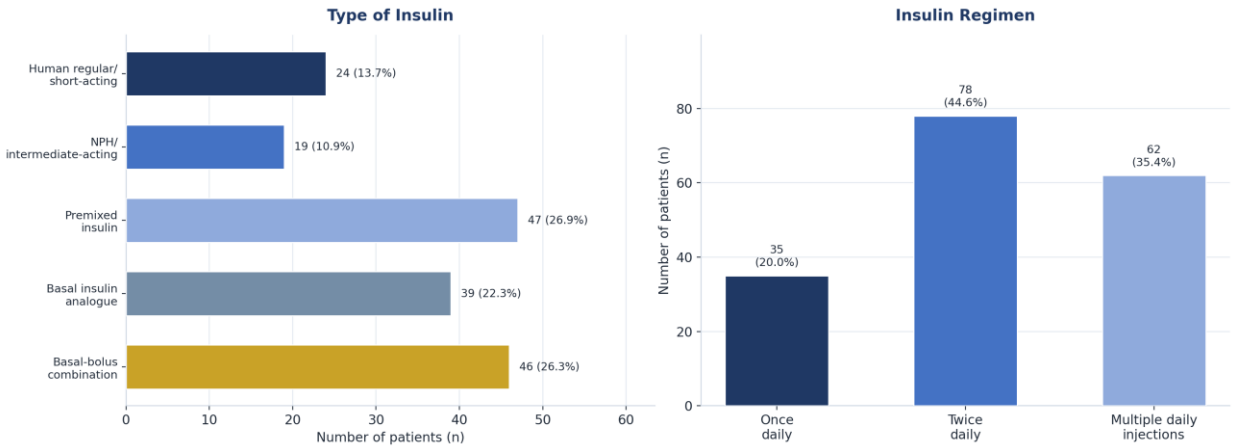


Figure 5. Type of insulin and insulin regimen among study participants (N=175)

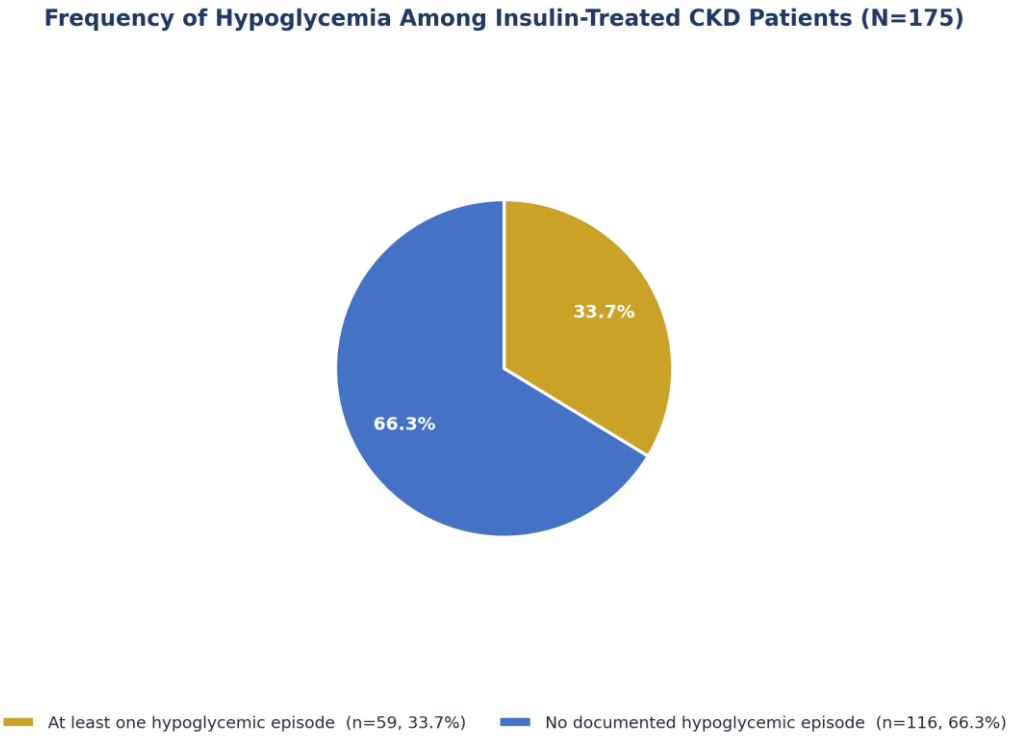


Figure 6. Frequency of hypoglycemia among insulin-treated CKD patients (N=175)

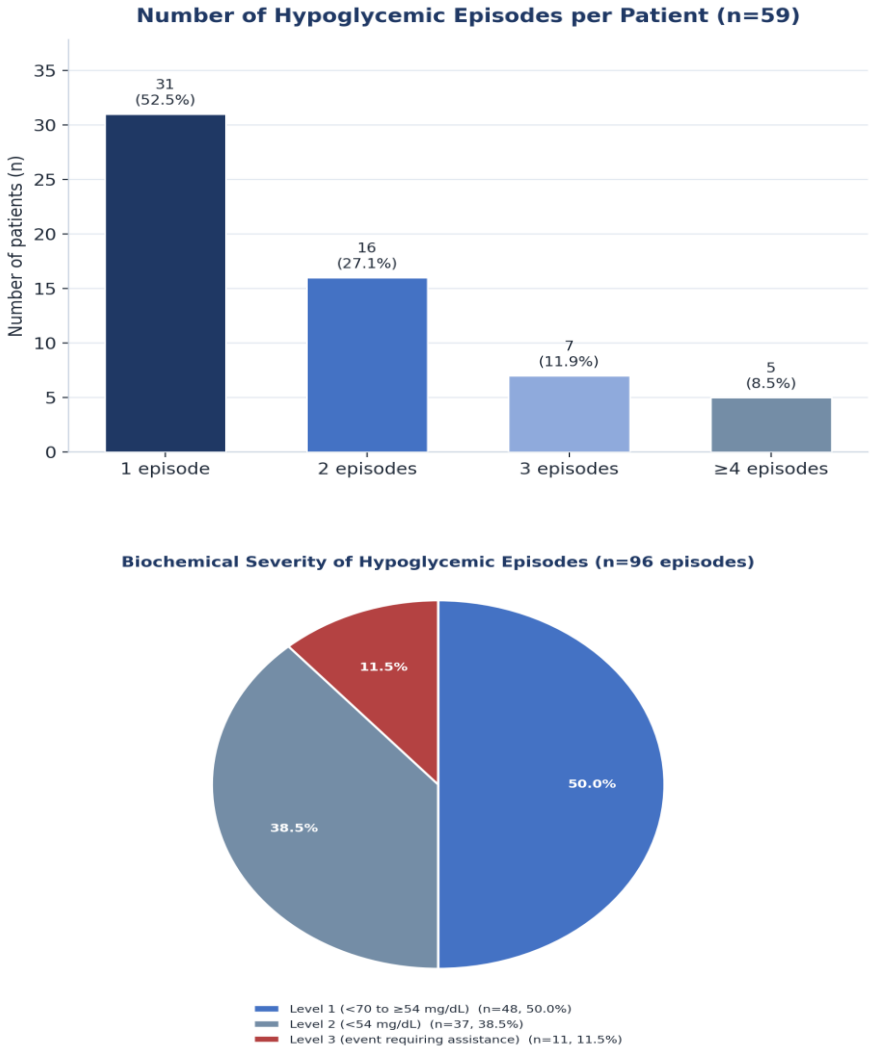


Figure 7. Number of hypoglycemic episodes per affected patient (n=59)

Figure 8. Biochemical severity of hypoglycemic episodes (n=96 episodes)

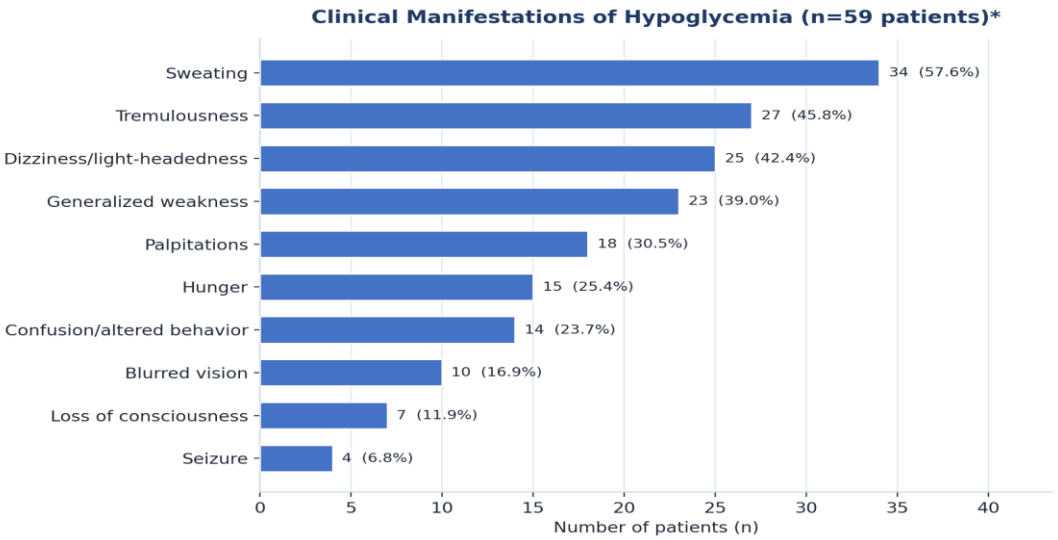


Figure 9. Clinical manifestations of hypoglycemia among affected patients (n=59). Percentages do not total 100% as multiple manifestations could o ccur per patient.

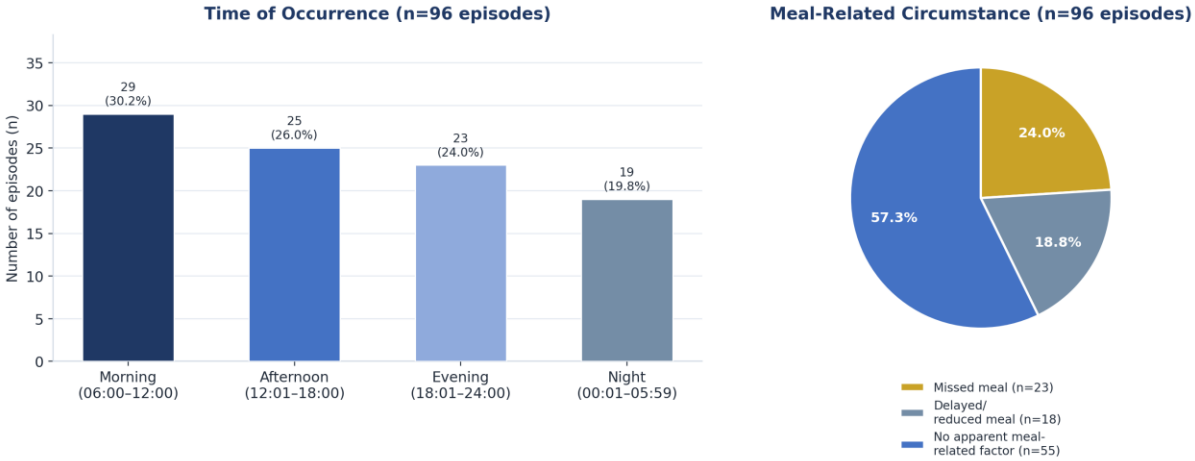


Figure 10. Time of occurrence and meal-related circumstance of hypoglycemic episodes (n=96 episodes)

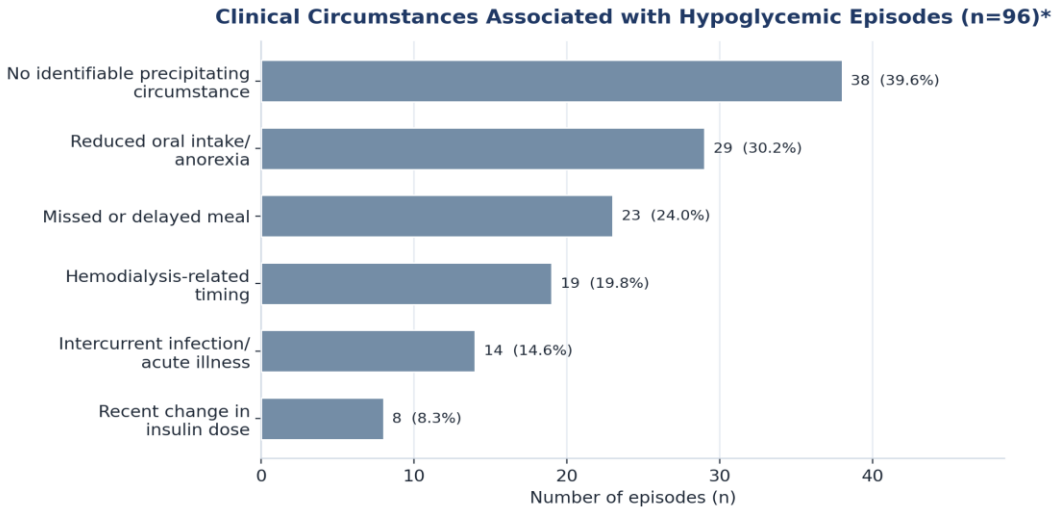


Figure 11. Clinical circumstances associated with hypoglycemic episodes (n=96 episodes). More than one circumstance could be present per episode.

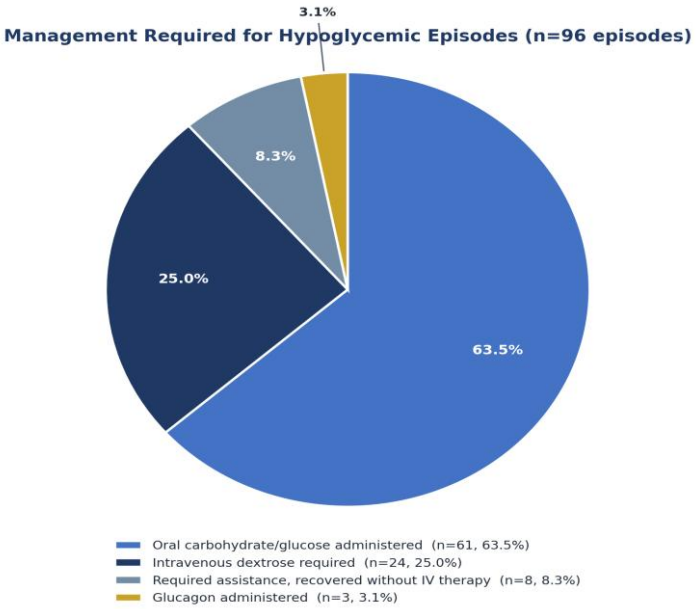


Figure 12. Management required for hypoglycemic episodes (n=96 episodes)

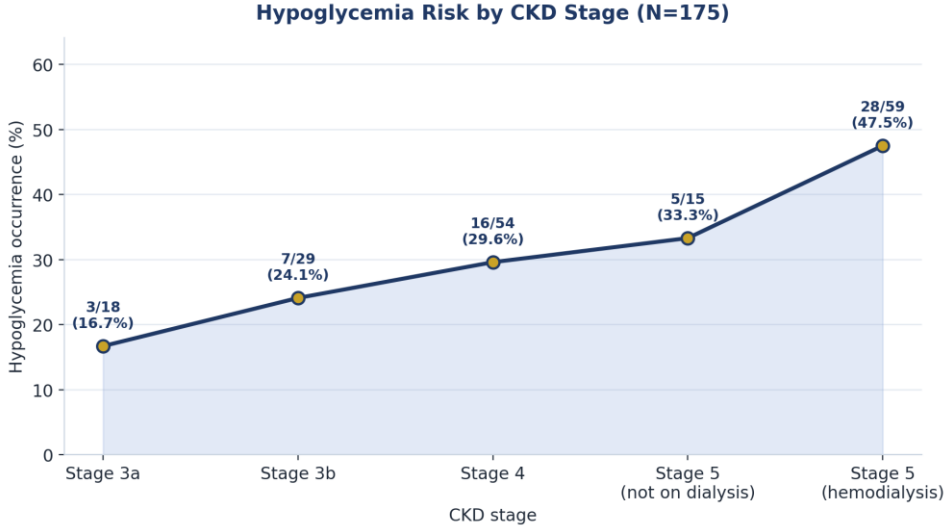


Figure 13. Hypoglycemia risk by CKD stage — progressive increase with advancing stage (N=175)

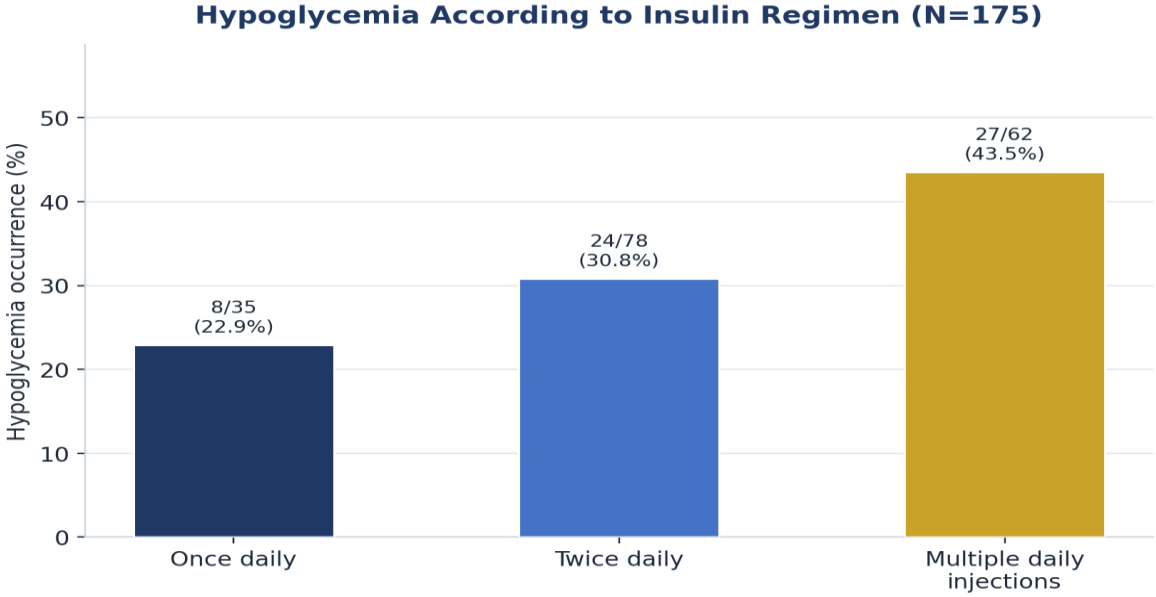


Figure 14. Hypoglycemia according to insulin regimen (N=175)

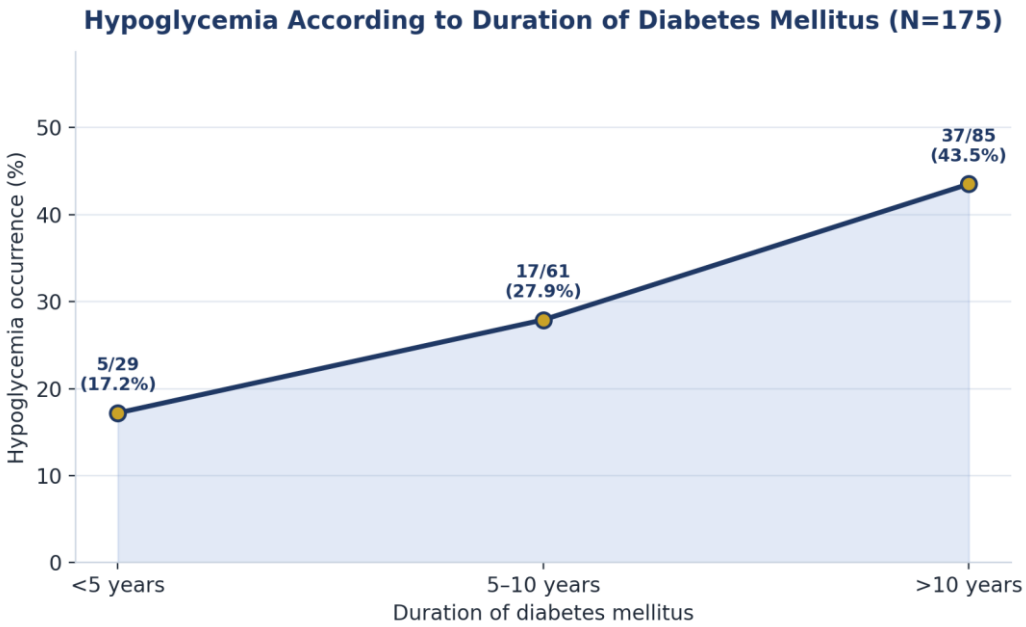


Figure 15. Hypoglycemia according to duration of diabetes mellitus (N=175)

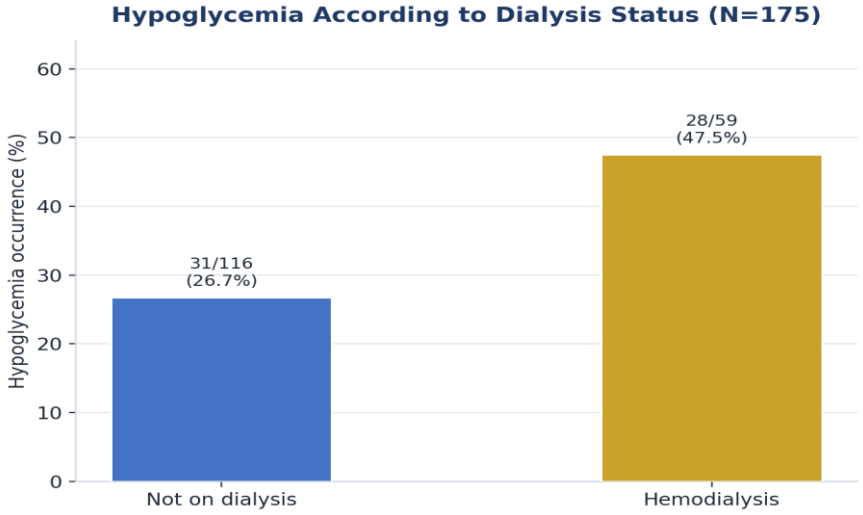


Figure 16. Hypoglycemia according to dialysis status (N=175)

DISCUSSION

Hypoglycemia remains an important clinical problem in patients with chronic kidney disease (CKD), particularly when insulin is required for glycemic management. In the present study of 175 insulin-treated patients with CKD admitted to the Medical Unit of Ayub Teaching Hospital, Abbottabad, **33.7% experienced at least one episode of hypoglycemia** during the study period. This finding indicates that approximately one in every three patients in this high-risk clinical population experienced hypoglycemia. The observed frequency is clinically relevant because CKD itself increases vulnerability to hypoglycemia through impaired insulin clearance, reduced renal gluconeogenesis, altered nutritional status, and the frequent presence of acute illness and other comorbidities. Alsahli et al. described CKD as an independent factor that increases the already existing risk of hypoglycemia in people with diabetes, particularly as renal function deteriorates.[11] Our finding is broadly consistent with the available literature, although direct comparison between studies should be made cautiously because of differences in patient selection, CKD stage, insulin exposure, glucose-monitoring methods, and definitions of hypoglycemia. In a systematic review, Chow et al. reported a pooled hypoglycemia incidence of approximately 18.8% among patients with CKD and found that the risk was significantly higher in patients with CKD than in those without CKD.[12] The higher frequency observed in our study may partly be explained by the fact that our population consisted exclusively of **insulin-treated patients with CKD**, whereas several studies included broader diabetic or CKD populations. In addition, our participants were hospital-based and included a substantial proportion of patients with advanced CKD, circumstances in which reduced oral intake and intercurrent illness may further predispose to hypoglycemia.

A particularly important finding in our study was the distribution of patients across advanced stages of CKD. More than half of the participants had stage 4 or stage 5 CKD, including patients receiving maintenance

hemodialysis. The frequency of hypoglycemia increased progressively across the CKD spectrum in our descriptive data, from **16.7% in stage 3a to 47.5% among patients with stage 5 CKD receiving hemodialysis**. Although the present study was not designed to establish an independent association or causal relationship, this pattern is biologically plausible. As kidney function declines, renal insulin clearance and renal gluconeogenesis become progressively impaired, while nutritional and metabolic disturbances become more common. Grube et al., in a very large cohort of patients with type 2 diabetes, similarly demonstrated that both insulin use and advanced CKD were independently associated with serious hypoglycemic events, with the risk becoming particularly pronounced at eGFR <30 mL/min/1.73 m^{12}.[13]

The relatively high proportion of hypoglycemia among our hemodialysis patients is also noteworthy. In our study, **47.5% of patients receiving hemodialysis experienced hypoglycemia**, compared with 26.7% among those not receiving dialysis. This difference should be interpreted descriptively rather than as proof that dialysis itself caused hypoglycemia. Nevertheless, dialysis can produce substantial changes in glucose and insulin dynamics. Gianchandani et al. reported hypoglycemia in 51% of hospitalized insulin-requiring patients with diabetes undergoing hemodialysis, with 28% experiencing glucose levels below 54 mg/dL.[14] Similarly, earlier work by Jackson et al. demonstrated that plasma glucose can fall during hemodialysis and that patients may remain asymptomatic despite biochemical hypoglycemia.[15] These observations are particularly relevant to routine practice because patients undergoing dialysis may not always report typical symptoms and therefore require appropriate glucose monitoring around dialysis sessions. The timing of hypoglycemic episodes in our study also provides an important clinical observation. Of the 96 documented episodes, **30.2% occurred during the morning and 19.8% during the overnight period**, while the remainder occurred during the afternoon or evening. Although our study did not employ continuous glucose monitoring, this temporal distribution suggests that hypoglycemia was not restricted to a single part of the day. The relatively frequent morning and nocturnal episodes may be related to prolonged fasting, reduced overnight intake, basal insulin activity, or altered insulin clearance in advanced CKD. In a prospective observational study using continuous glucose monitoring, Galindo et al. found that hypoglycemic events were frequent and often prolonged in patients with type 2 diabetes and CKD, with a large proportion occurring overnight.[16] Importantly, that study also showed that conventional glycemic measures may fail to capture the complete burden of hypoglycemia.

The clinical presentation observed in our patients was predominantly symptomatic. **Sweating was the most frequently reported manifestation (57.6%)**, followed by tremulousness (45.8%), dizziness/light-headedness (42.4%), generalized weakness (39.0%), and palpitations (30.5%). Neuroglycopenic manifestations, including confusion or altered behavior, were reported in 23.7%, while seizures and loss of consciousness occurred in 6.8% and 11.9%, respectively. This spectrum is clinically important because hypoglycemia may initially present with relatively nonspecific symptoms and can progress to neuroglycopenia if not recognized and treated promptly. Kalra et al., writing from the South Asian clinical context, emphasized that hypoglycemia may be under-recognized and that clinicians should actively screen for both adrenergic and neuroglycopenic manifestations rather than relying only on patients to report classic symptoms.[17]

Our findings regarding the severity of hypoglycemia further demonstrate that the problem was not limited to mild biochemical abnormalities. Half of the documented episodes were categorized as level 1 hypoglycemia, while **38.5% had glucose levels below 54 mg/dL**, representing level 2 hypoglycemia. A further 11.5% were level 3 events requiring assistance. At the patient level, 16.9% of affected patients experienced severe episodes characterized by altered consciousness and/or seizures. This is clinically significant because severe hypoglycemia can result in injury, cardiovascular complications, prolonged hospitalization, and, in vulnerable patients, death. In a large cohort of patients receiving dialysis, Goto et al. reported that hypoglycemic episodes were associated with considerable short-term mortality, particularly among older and medically compromised patients.[18] Although mortality was not an outcome of our study, these findings reinforce the importance of preventing severe episodes in advanced CKD. Recurrent hypoglycemia was also observed in our study. Among the 59 patients who experienced hypoglycemia, nearly half had two or more episodes, and five patients experienced four or more episodes. This recurrent pattern deserves attention because repeated hypoglycemia may impair the normal warning responses to subsequent episodes and make future events more difficult for patients and caregivers to recognize. Kalra and Khandelwal highlighted the value of structured assessment of hypoglycemia awareness in South Asian patients, including recognition of adrenergic, neuroglycopenic, nocturnal, and less typical symptoms.[19] In routine practice, therefore, simply asking whether a patient has experienced “low sugar” may underestimate the true burden unless the clinician specifically asks about symptoms, timing, recurrence, and the circumstances surrounding the event.

Reduced oral intake and meal-related factors were common circumstances surrounding hypoglycemia in our study. Reduced oral intake or anorexia was documented in **30.2% of episodes**, while missed or delayed meals accounted for a further 24.0%. These findings are clinically plausible in hospitalized CKD patients, who frequently have poor appetite, dietary restrictions, acute infections, gastrointestinal symptoms, or interruptions in their usual meal schedule. In such circumstances, administration of a usual insulin dose without corresponding carbohydrate intake may result in an imbalance between circulating insulin and available glucose. This issue is particularly relevant in resource-limited clinical settings where meal timing may be less predictable than in controlled outpatient environments. The relationship between insulin regimen and hypoglycemia in our descriptive findings is also worth noting. Hypoglycemia occurred in **43.5% of patients receiving multiple daily**

injections, compared with 30.8% among those receiving twice-daily insulin and 22.9% among those receiving once-daily insulin. This gradient should not be interpreted as evidence that multiple daily injections independently cause hypoglycemia because patients requiring intensive insulin therapy may differ substantially in disease severity, glycemic control, nutritional status, and treatment complexity. Nevertheless, greater insulin exposure and more complex regimens provide more opportunities for mismatch between insulin administration and food intake. A South Asian consensus statement on insulin use emphasized that patients with renal insufficiency and those receiving dialysis are already considered high-risk groups for hypoglycemia and require individualized insulin adjustment and close glucose monitoring.[20]

The long duration of diabetes observed among many patients with hypoglycemia is another clinically relevant finding. In our study, hypoglycemia was documented in 43.5% of participants with diabetes for more than 10 years, compared with 17.2% among those with diabetes duration of less than five years. Again, because this was a descriptive cross-sectional study, this pattern should not be interpreted as an independent risk relationship. However, longer diabetes duration often accompanies advanced microvascular disease, more intensive insulin treatment, impaired counter-regulatory responses, and previous exposure to hypoglycemia. The systematic review by Chow et al. also identified longer duration of diabetes and insulin treatment among characteristics associated with hypoglycemia in CKD.[12] Our findings should also be considered in the context of insulin use in Pakistan. Evidence from Pakistan is relatively limited, particularly for patients with concomitant advanced CKD. Hasan et al., in a multicenter Pakistani observational study of patients with type 2 diabetes treated with insulin glargine, reported hypoglycemic episodes in 5.8% of participants over six months; nearly half of the reported episodes were asymptomatic and no severe episodes were reported.[21] The substantially higher frequency observed in our study is not unexpected because our study population was specifically composed of patients with CKD and included a large proportion with advanced renal impairment and dialysis dependence. The difference also highlights why hypoglycemia data from the general diabetic population cannot simply be applied to patients with advanced CKD.Regional evidence further supports the importance of individualized insulin management. In the Indian consensus statement on insulin therapy in diabetic kidney disease, Kalra et al. emphasized that insulin requirements generally decline as renal function deteriorates and that insulin doses need regular reassessment and titration according to kidney function.[22] This principle is particularly important in our setting, where human insulin and premixed preparations remain commonly used because of affordability and availability. The choice of insulin regimen must therefore be considered alongside renal function, meal pattern, glucose monitoring capacity, and the patient's ability to recognize and manage hypoglycemia.

Another important consideration in South Asian populations is fasting and dietary variability. South Asian guidance on insulin use during Ramadan identifies renal insufficiency and dialysis as high-risk states for hypoglycemia and recommends individualized adjustment of insulin and glucose monitoring.[20] Similarly, the multinational Ramadan Diabetes Prospective Study reported that hypoglycemia remains an important concern among insulin-treated patients, although rates varied considerably between participating countries.[23] These regional considerations are relevant to patients in Pakistan, where religious fasting, variable meal schedules, socioeconomic constraints, and access to glucose-monitoring facilities may all influence the practical safety of insulin therapy. However, the present study was not specifically designed to evaluate Ramadan fasting, and therefore such factors should be regarded as contextual rather than direct study findings. The management pattern in our study showed that most episodes were successfully treated with oral carbohydrate or glucose, while approximately one quarter required intravenous dextrose. A smaller proportion required assistance without intravenous therapy or glucagon. The presence of patients requiring intravenous treatment emphasizes that hypoglycemia in advanced CKD can progress beyond a minor treatment-related inconvenience and may require immediate medical intervention. Importantly, treatment should not be viewed in isolation; preventing recurrence requires reassessment of insulin dosing, nutritional intake, renal function, dialysis timing, and the circumstances surrounding the episode.

Strengths and Limitations:

The major strengths of this study were its specific focus on insulin-treated patients with CKD and its detailed assessment of hypoglycemia, including clinical manifestations, biochemical severity, timing, recurrence, precipitating circumstances, and treatment requirements. Inclusion of patients across different CKD stages, including those receiving hemodialysis, provided a clinically relevant description of hypoglycemia in this high-risk population. The study was also conducted in a real-world tertiary-care setting using standardized definitions and consecutive recruitment.

The study has several limitations. Being a single-center cross-sectional study, its findings may not be generalizable to all CKD patients and cannot establish temporal or causal relationships. As continuous glucose monitoring was not used, asymptomatic or brief episodes may have been missed. In addition, some information regarding dietary intake, symptoms, and circumstances surrounding episodes depended on patient/attendant recall and clinical documentation. These limitations should be considered when interpreting the findings.

CONCLUSION

Hypoglycemia was a common clinical problem among insulin-treated patients with chronic kidney disease in our study, with approximately one-third of patients experiencing at least one hypoglycemic episode. The episodes

showed a wide clinical spectrum, ranging from symptomatic mild hypoglycemia to clinically significant and severe events requiring assistance or intravenous treatment. Recurrent episodes were also observed, with morning and nocturnal periods representing important times of occurrence.

Hypoglycemia was more frequently observed among patients with advanced CKD, particularly those receiving hemodialysis, and was commonly encountered in the setting of reduced oral intake, missed or delayed meals, and complex insulin regimens. Although these findings do not establish causal relationships, they highlight the increased clinical vulnerability of this patient group.

These findings emphasize the need for **regular assessment of blood glucose, careful individualization of insulin therapy, attention to nutritional intake and dialysis timing, and early recognition of hypoglycemic symptoms** in patients with CKD. Greater awareness among physicians, patients, and caregivers may help in preventing recurrent and severe episodes while maintaining appropriate glycemic control.

Additional information

Conflicts of Interest: None

Payment/Services Information: All authors state that no financial assistance or support was received from any organization in relation to this submitted work.

Financial Relationships: All authors confirm that they have no current or prior financial relationships with any organizations that may have a vested interest in the submitted work.

Acknowledgements: We would like to express our heartfelt appreciation to the Administration and ethical committee of Ayub Teaching Hospital, located in Abbottabad, Khyber Pakhtunkhwa, Pakistan, for their exceptional support and cooperation throughout the process.

Authors contribution

Concept & Design of Study; Talha khan [1]

Data collection; Khifza Jadoon [2], Shaheen bibi[3], Muhammad Yousaf [4], Aleema Sahar [5], Ahmad Zeb [7], Sardar Arslan [8], Data Data Analysis; Shaheen bibi[3], Muhammad Yousaf [4], Aleema Sahar [5], Bibi Marrium [6], Ahmad Zeb [7]

Drafting; Aleema Sahar [5], Bibi Marrium [6], Ahmad Zeb [7], Waqas Ahmed [9]

Critical Review; Talha khan [1], Khifza Jadoon [2], Shaheen bibi[3]

Final Approval; Talha khan [1], Shaheen bibi[3]

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5S):S1-S127.
2. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and KDIGO. Diabetes Care. 2022;45(12):3075-3090.
3. Stevens PE, Ahmed SB, Carrero JJ, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4S):S117-S314.
4. Alsahli M, Gerich JE. Hypoglycemia, chronic kidney disease, and diabetes mellitus. Mayo Clin Proc. 2014;89(11):1564-1571.
5. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(6):1121-1127.
6. Rhee CM, Leung AM, Kovesdy CP, et al. Updates on the management of diabetes in dialysis patients. Semin Dial. 2015;28(2):135-145.
7. Galindo RJ, Beck RW, Scioscia MF, Umpierrez GE, Tuttle KR. Glycemic monitoring and management in advanced chronic kidney disease. Endocr Rev. 2020;41(5):756-774.
8. Grube D, Wei G, Boucher R, et al. Insulin use in chronic kidney disease and the risk of hypoglycemic events. BMC Nephrol. 2022;23:73.
9. Alsahli M, Gerich JE. Renal glucose metabolism and hypoglycemia in diabetes. Curr Diab Rep. 2017;17:1.
10. Alsahli M, Gerich JE. Hypoglycemia in patients with diabetes and chronic kidney disease. Diabetes Res Clin Pract. 2015;108(1):1-9.
11. Alsahli M, Gerich JE. Hypoglycemia, chronic kidney disease, and diabetes mellitus. Mayo Clin Proc. 2014;89(11):1564-1571.
12. Chow E, Bernjak A, Williams S, Fawdry RA, Hibbert S, Freeman J, et al. Risk of hypoglycemia in patients with chronic kidney disease: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2020;160:108017.
13. Grube D, Wei G, Boucher R, et al. Insulin use in chronic kidney disease and the risk of hypoglycemic events. BMC Nephrol. 2022;23:73.
14. Gianchandani RY, Neupane S, Heung M. Hypoglycemia in hospitalized hemodialysis patients with diabetes: an observational study. J Diabetes Sci Technol. 2018;12(1):33-38.
15. Jackson MA, et al. Hemodialysis-induced hypoglycemia in diabetic patients. Nephrol Dial Transplant. 2000;15(7):1039-1042.
16. Galindo RJ, Beck RW, Scioscia MF, Umpierrez GE, Tuttle KR. Glycemic monitoring and management in advanced chronic kidney disease. Endocr Rev. 2020;41(5):756-774.
17. Kalra S. Hypoglycaemia in diabetes. J Pak Med Assoc. 2014;64(9):1090-1093.

18. Goto S, et al. Prevalence and prognosis of hypoglycaemia in patients receiving maintenance dialysis. Nephrol Dial Transplant. 2016;31(12):2224-2231.
19. Kalra S, Khandelwal D. The Hypoglycaemia Awareness Questionnaire (HAQ). J Pak Med Assoc. 2018;68(2).
20. Hassanein M, Al-Arouj M, Hamdy O, et al. Diabetes and Ramadan: practical guidelines. Diabetes Res Clin Pract. 2017;126:303-316.
21. Hasan MI, Amer W, Junaid N. Practical implementation of ADA/EASD consensus algorithm in patients with type 2 diabetes in Pakistan. J Pak Med Assoc. 2018;68(9):1304-1309.
22. Kalra S, Tiwari N, Nair S. Diabetes management in chronic kidney disease: consensus statement on insulin therapy. Indian J Endocrinol Metab. 2017;21(2):310-315.
23. Salti I, Bénard E, Detournay B, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. Diabetes Care. 2004;27(10):2306-2311.