BMJ Open Diabetes Research & Care

Burden of impaired awareness of hypoglycemia in people with diabetes undergoing hemodialysis

Hellena Hailu Habte-Asres ,[1,2] Yutong Jiang,[3] Miranda Rosenthal,[1] David Collins Wheeler [4]

To cite: Habte-Asres HH, Jiang Y, Rosenthal M, *et al*. Burden of impaired awareness of hypoglycemia in people with diabetes undergoing hemodialysis. *BMJ Open Diab Res Care* 2024;**12**:e003730. doi:10.1136/bmjdrc-2023-003730

Received 29 August 2023
Accepted 8 December 2023

[1]Royal Free London NHS Foundation Trust, London, UK
[2]Diabetes, King's College London Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, London, UK
[3]Department of Nephrology, UCL, London, UK
[4]Department of Renal Medicine, UCL, London, UK

Correspondence to
Dr David Collins Wheeler; d.wheeler@ucl.ac.uk

ABSTRACT

Introduction Impaired awareness of hypoglycemia (IAH) refers to a diminished capacity to detect hypoglycemia. IAH can result in severe and even life-threatening outcomes for individuals with diabetes, especially those in advanced stages of the disease. This study aimed to assess the prevalence of IAH in people with diabetes on hemodialysis.

Research design and methods We conducted a single-center audit to assess the prevalence of IAH using the Clarke questionnaire. Simultaneously, we measured fear of hypoglycemia with an adapted version of the Hypoglycemia Survey and recorded the incidence of severe hypoglycemia. Data were presented as mean±SD or counts/percentages. Logistic regression was then employed to analyze the association between IAH and various sociodemographic and clinical factors.

Results We included 56 participants with diabetes on hemodialysis, with a mean age of 67.2 years (±12.9), of whom 51.8% were male. The ethnic distribution was 23.2% white, 23.2% black, 19.6% Asian, and 33.9% unspecified. The mean HbA1c was 52 mmol/mol (±18.6). The majority (91.1%) had a diagnosis of type 2 diabetes, and 55.4% of those were treated with insulin. The use of diabetes technology was low, with 2.8% of the participants using a continuous glucose monitor. IAH prevalence was 23.2%, and among the 57 participants, 23.6% had a history of severe hypoglycemia, and 60.6% reported fear of hypoglycemia. There were no significant differences in sociodemographic and clinical characteristics between those with IAH and normal hypoglycemia awareness.

Conclusions We observed that 23.2% of individuals with diabetes undergoing hemodialysis had IAH. IAH was more prevalent in people who reported a fear of hypoglycemia and had a history of severe hypoglycemia episode. The study highlights the unmet needs and disparities in access to diabetes technology within this population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Limited information exists regarding the occurrence of impaired awareness of hypoglycemia (IAH) in people with diabetes on hemodialysis.
⇒ To the best of our knowledge, this study is the first to investigate the prevalence of IAH in people on hemodialysis.

WHAT THIS STUDY ADDS

⇒ The prevalence of IAH was 23.2% in people with diabetes on hemodialysis.
⇒ Impaired hypoglycemia was common in individuals who expressed a fear of hypoglycemia and those who had experienced severe hypoglycemia.
⇒ The study highlights the unmet needs and disparities in access to diabetes technology for people with diabetes on hemodialysis who are treated with insulin.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This finding emphasizes the importance of routinely assessing hypoglycemia awareness status in this population to reduce the risk of hypoglycemia, severe hypoglycemia, and IAH.
⇒ More primary studies on IAH in people with diabetes on hemodialysis are needed.

INTRODUCTION

Hypoglycemia is a well-recognized complication of diabetes treatment, especially in individuals using sulfonylureas (SU) or insulin.[1] The reported hypoglycemia incidence rate varied between 0.072 and 42 890 episodes per 1000 person-years.[2] Individuals with diabetes undergoing kidney replacement therapies (KRT) are more vulnerable to hypoglycemia due to several factors. These include decreased kidney gluconeogenesis, reduced clearance of insulin and glucose-lowing medications and reduced degradation of insulin.[3–5] Additionally, the impact of uremic toxins can lead to appetite suppression, which often results in malnutrition. This, in turn, reduces glycogen store, potentially further exacerbating the occurrence of hypoglycemia in this population.[4] Hypoglycemia is strongly associated with an increased risk of hospitalization[6–10] morbidity and mortality among individuals with diabetes undergoing KRT.[11 12] Moreover, hypoglycemia can affect the quality of life and increased healthcare cost.[9 13]

While most people with diabetes experience hypoglycemia accompanied by autonomic or neurological symptoms, recurrent episodes

can lead to a defective counter-regulatory hormone response, resulting in reduced awareness of hypoglycemia (IAH).[14 15] The pooled prevalence of impaired awareness of hypoglycemia (IAH) in people with type 1 and type 2 diabetes was found to be 23.2% (95% CI 18.4% to 29.3%) as assessed via the Clarke questionnaire.[16] IAH is associated with a threefold to sixfold increase in the risk of severe hypoglycemia and mortality.[7–9 14] The evaluation of hypoglycemia awareness can be conducted through self-reported questionnaires, with the most frequently employed ones being those developed by Gold *et al*[17] or Clarke *et al*.[18]

The prevalence of IAH in individuals with diabetes undergoing hemodialysis has not been previously studied. Our aim is to present the prevalence of IAH in this population. A secondary objective was to assess the association between IAH and sociodemographic and clinical characteristics.

RESEARCH DESIGN AND METHOD

Setting and participants

This was a prospective audit conducted at a single center, encompassing the entire adult population (≥18 years) with diabetes undergoing hemodialysis and receiving KRT at North Central London Dialysis Unit. Participants gave informed consent to participate in the study before taking part.

Subjects and inclusion criteria

We identified adults (aged ≥18) with diabetes who were undergoing hemodialysis between April 2023 and August 2023. The following selection criteria were applied:

- Adults aged ≥18 diagnosed with diabetes and undergoing hemodialysis.
- Individuals with diabetes undergoing hemodialysis and treated with either SU or insulin.
- Individuals who had been undergoing KRT for a minimum of 6 months.

We excluded:

- Individuals with diabetes on hemodialysis who were not treated with SU or insulin.
- Individuals with diabetes undergoing hemodialysis who did not regularly measure their capillary or interstitial glucose levels.

We used a previously developed algorithm for determining diabetes diagnosis,[19] which was based on either the date a person first received a diagnostic record or if diabetes therapy was prescribed, or if they had an HbA1c reading ≥48 mmol/mol.

Data collection

Hypoglycemia awareness was assessed using the Clarke Score,[18] where a score of ≥4 indicates IAH, while a score ≤3 suggests normal hypoglycemia awareness.[18] Additionally, the frequency of severe hypoglycemia in the past 12 months was determined based on participants' responses regarding the number of times they required third-party assistance. An adapted version of the Hypoglycemia Fear Survey-II Worry scale questionnaire was included to assess participants' concerns related to hypoglycemia.[20 21] Sociodemographic and clinical information about the participants was retrieved from electronic medical records. This information included age, sex, ethnicity, weight, height, systolic and diastolic blood pressure, HbA1c levels, Frailty Score, Index of Multiple Deprivation (IMD) score, type of diabetes, and diabetes medication. Participants' ages were calculated using their year of birth, and they were assigned a nominal birthday of April 1, 2023. Ethnicity was categorized into four groups: white, black, Asian, and unknown. The Frailty Score was dichotomized into two categories: a score of <4 indicated the absence of frailty, while a score ≥4 indicated moderate to severe frailty. Body mass index (BMI) was calculated using the formula BMI=kg/m^2 and categorized into three groups: ≤25, 25 to <30, and ≥30, broadly indicating healthy weight, overweight, and obesity, respectively. The patient-level IMD was used as a measure of deprivation, categorized into quintiles (1 being the most deprived and 5 the least deprived). HbA1c values were grouped as follows: <48, 48 to <58, and ≥58 mmol/mol.

Statistical analysis

Descriptive statistics were calculated to summarize participants' sociodemographic and clinical characteristics. Continuous variables with a normal distribution were presented as the mean±SD, while non-normally distributed variables are reported as the median with the IQR. Categorical variables were expressed as percentages. Differences in participant characteristics, stratified by hypoglycemia awareness status, were assessed using the χ^2 test. Logistic regressions were conducted to investigate the association between clinical and sociodemographic variables and IAH. Unadjusted and adjusted analyses were conducted for most of the available data; however, to address concerns related to data sparsity and low cell counts, the following variables were excluded: IMD score, ethnicity, access to diabetes technology, diabetes treatment, and type of diabetes. Data were missing for 1.8% of Frailty Scores, 1.8% of IMD scores, 12.5% of BMI values, and 33.9% of ethnicity information. The proportion of participants with missing data in variables other than ethnicity was very small. Therefore, we performed a complete case analysis. Individuals with missing ethnicity data were included by categorizing them as 'Unknown ethnicity'. The analyses were conducted using the Stata package.

RESULTS

Participant characteristics

A total of 114 individuals with diabetes undergoing hemodialysis attended the North Central London Dialysis Unit between April and August 2023. Of those, 57 individuals treated with SU or insulin were eligible for inclusion in the analysis. The breakdown of exclusions from the source data file is summarized in figure 1.

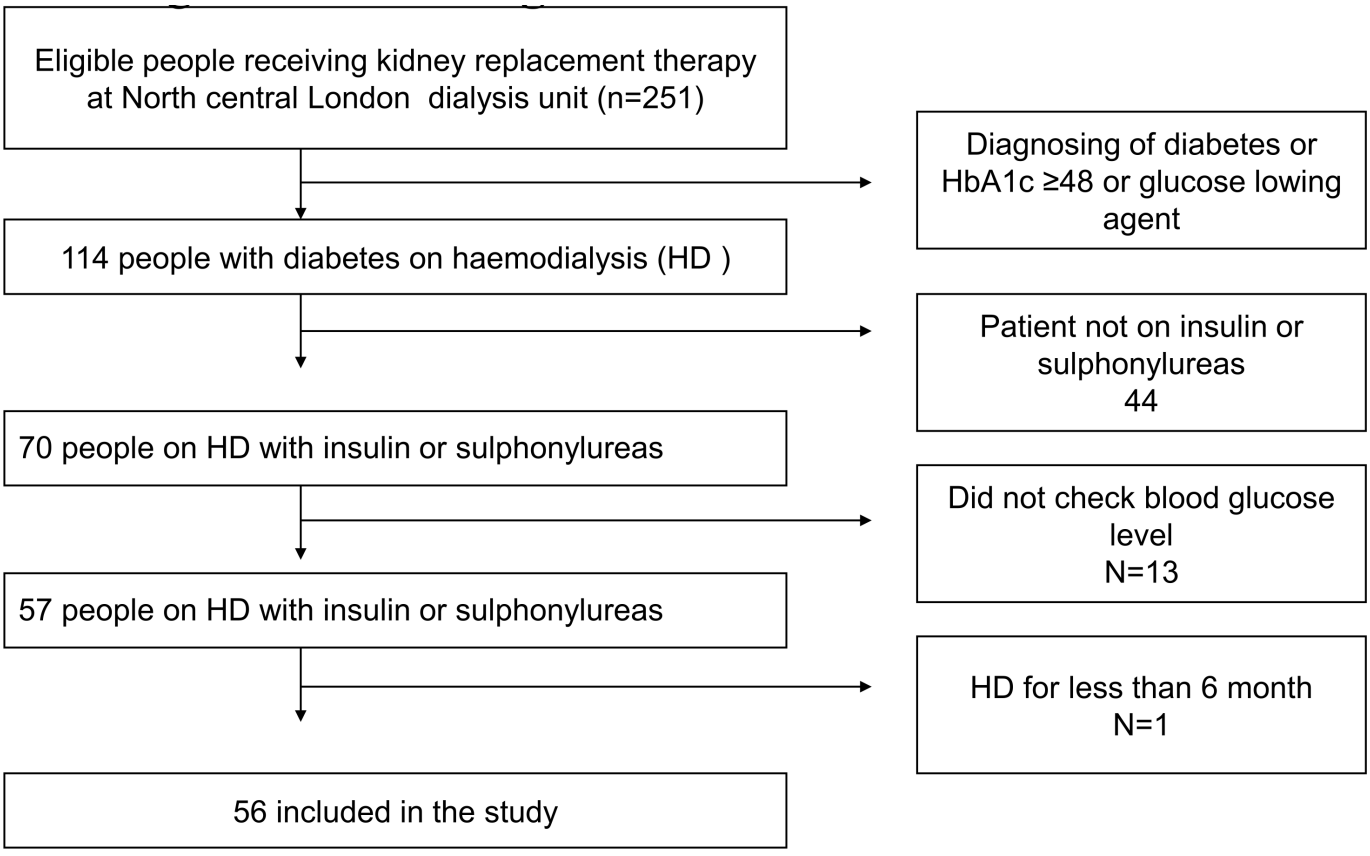

Figure 1 Flow diagram of cohort.

The participants had a mean age of 67.2 (±12.9) years, and 51.8% were male. The ethnic distribution mirrored the demographics of local population, with 23.2% identified as black, 23.2% as white%, 19.6% as Asian and 33% with unknown ethnicity. The mean HbA1c was 52 mmol/mol (±18.6), the mean systolic blood pressure was 148.5 mm Hg (±23.9), and the mean diastolic blood pressure was 73.91 mm Hg (±12.6). Of the total, 8.9% had diagnosis of type 1 diabetes and were treated with multiple daily doses of insulin and none were on insulin pump therapy, while 91.1% had type 2 diabetes with 44.6% using SU and 55.4% relied on insulin. Access to technology for glycemic management was limited, with only 2.8% having flash or continuous glucose monitor (CGM). Please refer to table 1 for detailed participant characteristics.

Prevalence of IAH

The prevalence of IAH in hemodialysis patients with diabetes was 23.2%, as shown in figure 2. This prevalence varied significantly based on diabetes type, with rates of 3.6% for type 1 diabetes and 19.6% for type 2 diabetes. Importantly, there was no statistically significant difference in mean HbA1c levels between individuals with IAH (mean HbA1c of 47.9 mmol/mol±19.2) and those with normal hypoglycemia awareness (53.2 mmol/mol±18.43; p=0.37). Moreover, 69.2% of participants with IAH were treated with insulin or a combination of insulin and other agents, while only 30.8% of those with normal hypoglycemia awareness received SU, either alone or in combination with other agents. Additionally, a weak positive correlation (r=0.027, p=0.84) was observed between the Clarke Score and HbA1c. For a visual representation, please refer to figure 3, displaying the scatterplot illustrating the relationship between Clarke Score and HbA1c.

Prevalence of severe hypoglycemia and fear of hypoglycemia

In the 12 months leading up to the audit, 23.6% of participants reported experiencing at least one episode of severe hypoglycemia. Among those self-reporting severe hypoglycemia, 46.2% had IAH, and 52.9% were classified as having moderate to severe frailty. There was no statistically significant difference in mean HbA1c between participants who reported experiencing severe hypoglycemia (57.8 mmol/mol±29.3) and those without severe hypoglycemia (50.5±14.0; p=0.22). Additionally, a significant proportion (76.9%) of participants with a history of severe hypoglycemia were treated exclusively with insulin or a combination of insulin and other agents. The prevalence of severe hypoglycemia, stratified by IMD scores, was as follows: 66.6%, 52.3%, 30.0%, 75.0%, and 50.0% for IMD scores 1–5, respectively. A moderate positive correlation was observed between Clarke Score and severe hypoglycemia (Spearman's correlation r=0.48, p=0.0002).

Out of the 51 participants who responded, 60.6% reported having fear of hypoglycemia. Among those who reported this fear, a significant proportion (29.0%) had

Table 1 Descriptive distribution of baseline demographic and clinical characteristics

Variable	Category	Missing (%)	n (%) or mean±SD
Age			67.2 (±12.9)
Sex	Female Male		27 (48.2) 29 (51.8)
Ethnicity	White Black Asian Unknown		13 (23.2) 13 (23.2) 11 (19.6) 19 (33.9)
Frailty Score	<4 (No frailty) ≥4 (Moderate to severe frailty)	1.8%	21 (38.2) 34 (61.8)
IMD score	1 (Most deprived) 2 3 4 5 (Least deprived)	1.8%	18 (32.7) 21 (38.2) 10 (18.2) 4 (7.3) 2 (3.6)
Body mass index (BMI)	<24.9 25.0–29.9 ≥30.0	12.5%	13 (26.5) 11 (22.5) 25 (51)
Mean BMI			30.4 (±6.8)
Mean systolic blood pressure (SBP)			148.5 (±23.9)
Mean diastolic blood pressure (DBP)			73.91 (±12.6)
Type of diabetes treatment	SU Insulin		25 (44.6) 31 (55.4)
HbA1c	<48 48 to <58 ≥58		22 (39.3) 18 (32.1) 16 (29.6)
Mean HbA1c			52 (±18.6)
Occurrence of hypoglycemia (≤3.9 mmol)	With symptoms Without symptoms		25 (44.6) 15 (26.8)
Fear of hypoglycemia	Yes No		31 (55.4) 25 (44.6)
Number of severe hypoglycemia episodes in last 12 months			13 (23.6)
Hypoglycemia awareness status	Hypoglycemia aware Hypoglycemia unaware		43 (76.8) 13 (23.2)
Access to diabetes technology or CGM	Yes No		1 (2.8) 55 (98.2)

CGM, continuous glucose monitor; IMD, Index of Multiple Deprivation; SU, sulfonylurea.

IAH and 32.2% had a history of severe hypoglycemia. Additionally, a large number (83.9%) had an HbA1c less than 58 mmol/mol. A weak positive correlation was observed between severe hypoglycemia and HbA1c (Spearman's correlation r=0.06, p=0.66).

Association of IAH and sociodemographic and clinical variables

Unadjusted and adjusted analyses were performed for various sociodemographic and clinical variables to assess their individual odds of being associated with IAH. The results, as presented in table 2, indicate that there was no significant association between IAH and age, sex, mean BMI, mean systolic blood pressure, or mean HbA1c level.

CONCLUSION

The study aimed to determine the prevalence of IAH in adults with diabetes undergoing hemodialysis at the North Central London Dialysis Unit using Clarke's hypoglycemia questionnaire. Limited information exists on the occurrence of IAH in this population, and to our knowledge, this study is the first to investigate its prevalence. We have demonstrated that almost one in four individuals with diabetes on hemodialysis have IAH, putting them at risk of severe hypoglycemia. This observed prevalence is higher than that reported in previous studies involving individuals with diabetes on peritoneal dialysis. In the study by Haboosh *et al*,[22] colleagues reported

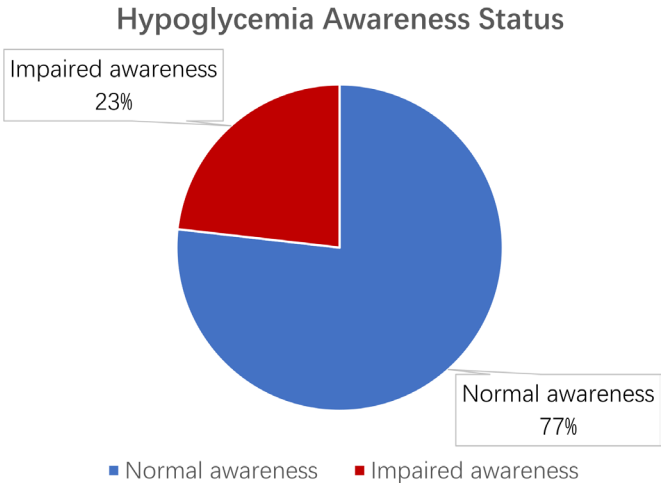

Figure 2 Prevalence of impaired awareness of hypoglycemia.

a 15% prevalence of IAH in individuals with diabetes undergoing peritoneal dialysis. Furthermore, Hayashi *et al*[23] found asymptomatic hypoglycemia in over 20% of their study participants with diabetes undergoing hemodialysis using CGM.

The prevalence of severe hypoglycemia was higher in our study, with 23.6% of participants reporting at least one event in the preceding 12 months. Hsiao *et al*[4] reported in the year before commencement of dialysis that severe hypoglycemia occurred in 11.5% of patients with advanced diabetes kidney disease (DKD). Chu *et al*[24] reported that 19.18% of patients with advanced DKD had at least one episode of hypoglycemia in the year leading up to the start of their dialysis therapy. Data on the prevalence of severe hypoglycemia in hemodialysis population are lacking, making it essential to quantify the burden of severe hypoglycemia.

We observed half (50%, n=6) of the participants who experienced severe hypoglycemia had IAH, a rate higher than previously reported. In the Diabetes Control and Complications Trial study, 36% of serious hypoglycemia incidents were attributed to hypoglycemia unawareness.[25] This finding demonstrated the need to routinely assess hypoglycemia awareness status in this population to reduce the risk of hypoglycemia.

In our analysis, we found no significant difference in mean HbA1c between participants with IAH and those with normal hypoglycemia awareness. This contrasts with findings from studies by Amiel *et al*,[26] which reported lower HbA1c levels in patients with IAH in people with type 1 diabetes.

Our data suggest that eligible individuals, according to existing National Institute for Health and Care Excellence guidance,[27] often lack access to diabetes technology that could aid in managing their glucose levels effectively. These technologies offer real-time insights into glucose patterns, making it vital to promote their adoption and improve access. FreeStyle Libre has been shown significant improvements in glycaemic control, hypoglycemia awareness, and reduced hospital admissions.[28] Nevertheless, there is currently no evidence to support the use of FreeStyle Libre in improving glycemic control or reducing hypoglycemia among individuals with diabetes undergoing hemodialysis.[3] This highlights the clear need for additional research to determine whether the use of FreeStyle Libre could potentially lead to a decrease in the occurrence of hypoglycemia, severe hypoglycemia, and IAH in individuals with diabetes undergoing hemodialysis.

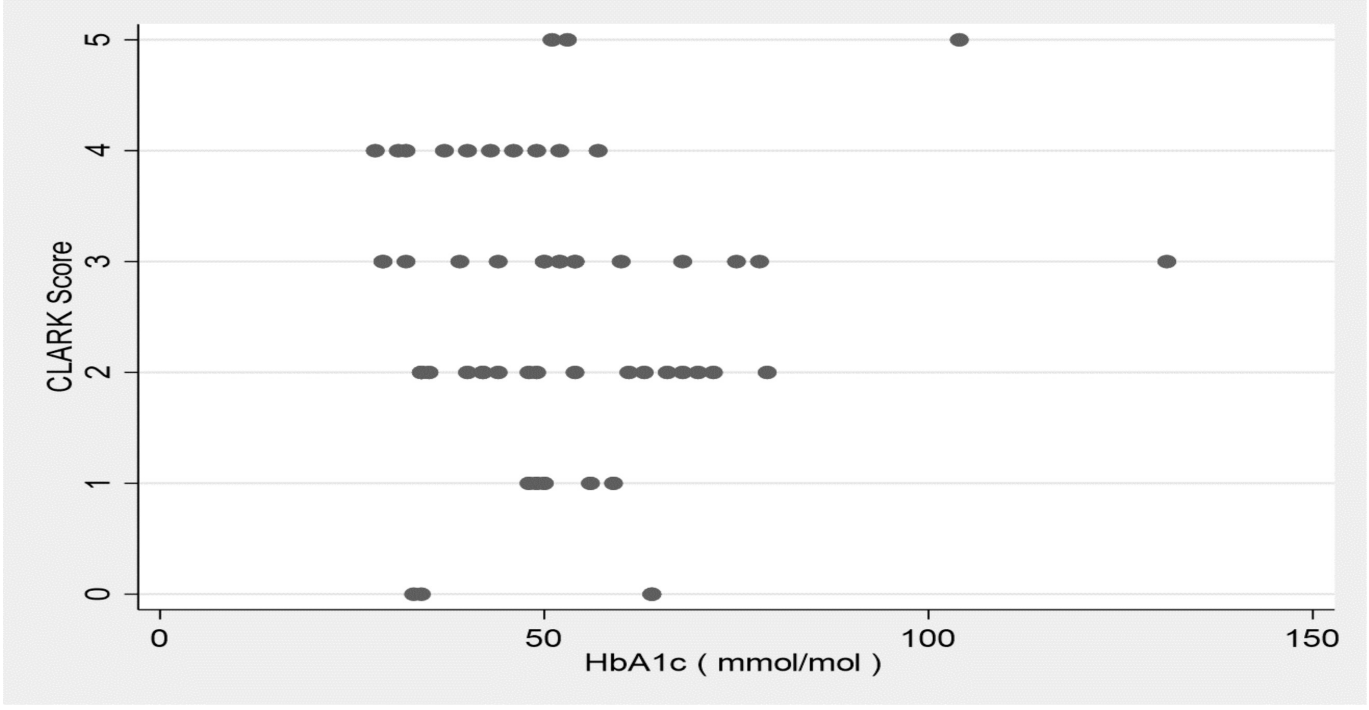

Figure 3 Scatterplot of Clarke Score and HbA1c: Pearson's correlation=0.03.

Table 2 Unadjusted OR for hypoglycemia awareness status

Variable	Category	Unadjusted OR of IAH (95% CI)* Model 1	Adjusted OR of IAH (95% CI)† Model 2
Age		0.97 (0.93–1.02)	0.96 (0.90–1.02)
Sex	Female Male	1.00 1.11 (0.32–3.86)	1.63 (0.36–7.48)
Frailty Score	<4 (No frailty) ≥4 (Moderate to severe frailty)	1.00 0.98 (0.27–3.54)	1.27 (0.28–5.67)
Mean BMI		1.05 (0.96–1.16)	1.02 (0.91–1.14)
Mean systolic blood pressure (SBP)		1.02 (0.99–1.05)	1.04 (1.00–1.08)
Mean HbA1c		0.98 (0.94–1.02)	0.94 (0.88–1.00)

*Model 1: crude association.
†Model 2: adjusted for age, sex, Frailty Score, mean BMI, mean HbA1c and mean systolic blood pressure.
‡OR (95% CI) shown in bold indicates that the 95% CI does not include 1.
BMI, body mass index; IAH, impaired awareness of hypoglycemia.

Our study has several limitations. First, due to the cross-sectional nature of the analysis, we cannot infer causal relationships. Second, the study's single-center design limits its external validity and broader clinical application. However, we anticipate that similar results would be obtained in other dialysis units. Third, the assessment of hypoglycemia awareness status unavoidably relies on subjective measures and is subject to potential recall bias, especially regarding baseline questions related to the preceding 12 months. Fourth, our analysis encompassed individuals with both type 1 and type 2 diabetes. However, it is essential to interpret the stratified prevalence of IAH by the type of diabetes cautiously, given the limited sample size. We acknowledge that the impact of severe hypoglycemia and IAH differs between people with type 1 and type 2 diabetes. Nonetheless, our results demonstrate that individuals with diabetes on hemodialysis arguably face an elevated risk of hypoglycemia and IAH regardless of the type of diabetes. Fifth, we observed no association between IAH and sociodemographic or clinical factors, and it is possible that the study design and population size may have influenced this result. Another limitation includes the accuracy of HbA1c in the assessment of glycemic status in people with diabetes on hemodialysis. Finally, there was considerable variation in the level of self-monitoring glucose monitoring in this group, suggesting that greater efforts need to be made to engage and ensure that this group has access to technology.

On the other hand, one of the study's strengths includes the use of a validated tool for measuring IAH. Our research provides new insights into the prevalence of IAH in people with diabetes on hemodialysis and quantifies the fear of hypoglycemia and the number of severe hypoglycemic events in this population.

Our study confirms the relationship between IAH, frequency of severe hypoglycemia and fear of hypoglycemia in people with diabetes on hemodialysis in North Central London. Despite the high prevalence and known risk factors for severe hypoglycemia, this group is poorly served by diabetes technology. This observation reflects the known disparity of access to diabetes technology for minority ethnic groups and deprived populations, and that this group does not have access to diabetes technology that could prevent severe hypoglycemia. IAH was more prevalent in people who reported a fear of hypoglycemia and had a history of severe hypoglycemia episodes.

Acknowledgements We thank all the participants in this study. We also express our gratitude to Dr Sally Hamour, Divisional Clinical Director of Nephrology, Urology, Transplantation, and Alisha Ai, Deputy Director of Nursing, for their support.

Contributors HHH-A conducted a comprehensive review of the background literature, formulated the research question, designed and executed the data analysis, synthesized the results, and prepared the manuscript. YJ contributed to identifying background literature, administered the Clarke questionnaire, extracted and tabulated data, assisted in data analysis, and synthesized the results. MR provided expert input in data analysis, reviewed the analysis, and contributed to paper revisions. DCW, as the guarantor, supervised the research process, validated data extraction and analysis, guided paper preparation, and assisted in revisions. DCW, as the guarantor, takes full responsibility for the work, study conduct, had access to the data, and controlled the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests HHH-A received speaker honoraria from AstraZeneca and Bayer. MR received speaker honoraria from AstraZeneca. DCW has an ongoing consultancy contract with AstraZeneca. He has received payments for consultancy working and/or speaking activities from Amgen, Astellas, Bayer, Boehringer Ingelheim, Eledon, GSK, Galderma, Gilead, Janssen, Mundipharma, Menarini, MSD, Novo Nordisk, Pharmacosmos, Tricida and Vifor.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Royal Free London Foundation Trust's Audit Board (approval number: RFH_66422/23). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Hellena Hailu Habte-Asres http://orcid.org/0000-0001-8141-1423
David Collins Wheeler http://orcid.org/0000-0003-0745-3478

REFERENCES

1 Rhee CM, Kalantar-Zadeh K, Tuttle KR. Novel approaches to Hypoglycemia and burnt-out diabetes in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2022;31:72–81.
2 Alwafi H, Alsharif AA, Wei L, *et al*. Incidence and prevalence of Hypoglycaemia in type 1 and type 2 diabetes individuals: A systematic review and meta-analysis. *Diabetes Res Clin Pract* 2020;170:108522.
3 JBDS. *Management of adults with diabetes on dialysis*. UK, 2023.
4 Hsiao C-C, Tu H-T, Lin C-H, *et al*. Temporal trends of severe Hypoglycemia and subsequent mortality in patients with advanced diabetic kidney diseases Transitioning to dialysis. *J Clin Med* 2019;8:420.
5 Runesson B, Xu Y, Qureshi AR, *et al*. Association between reduced kidney function and incident Hypoglycaemia in people with diabetes: the Stockholm creatinine measurements (SCREAM) project. *Diabetes Obes Metab* 2020;22:1425–35.
6 Hodge M, McArthur E, Garg AX, *et al*. Hypoglycemia incidence in older adults by estimated GFR. *Am J Kidney Dis* 2017;70:59–68.
7 Zhong VW, Juhaeri J, Cole SR, *et al*. Incidence and trends in Hypoglycemia hospitalization in adults with type 1 and type 2 diabetes in England, 1998–2013: A retrospective cohort study. *Diabetes Care* 2017;40:1651–60.
8 Gianchandani RY, Neupane S, Heung M. Hypoglycemia in hospitalized Hemodialysis patients with diabetes: an observational study. *J Diabetes Sci Technol* 2018;12:33–8.
9 Alsahli M, Gerich JE. Hypoglycemia, chronic kidney disease, and diabetes mellitus. *Mayo Clin Proc* 2014;89:1564–71.
10 Rhee CM, Kovesdy CP, You AS, *et al*. Hypoglycemia-related hospitalizations and mortality among patients with diabetes Transitioning to dialysis. *Am J Kidney Dis* 2018;72:701–10.
11 McCoy RG, Van Houten HK, Ziegenfuss JY, *et al*. Increased mortality of patients with diabetes reporting severe Hypoglycemia. *Diabetes Care* 2012;35:1897–901.
12 Zoungas S, Patel A, Chalmers J, *et al*. Severe Hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–8.
13 Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol* 2014;10:711–22.
14 Martín-Timón I, Del Cañizo-Gómez FJ. Mechanisms of Hypoglycemia unawareness and implications in diabetic patients. *World J Diabetes* 2015;6:912–26.
15 Hatle H, Bjørgaas MR, Skrivarhaug T, *et al*. Assessing awareness of Hypoglycemia in children and adolescents with type 1 diabetes: evaluation of established questionnaires. *Pediatr Diabetes* 2020;21:300–9.
16 Yu X, Fan M, Zhao X, *et al*. Prevalence of impaired awareness of Hypoglycaemia in people with diabetes mellitus: A systematic review and meta-analysis from 21 countries and regions. *Diabet Med* 2023;40:e15129.
17 Gold AE, MacLeod KM, Frier BM. Frequency of severe Hypoglycemia in patients with type I diabetes with impaired awareness of Hypoglycemia. *Diabetes Care* 1994;17:697–703.
18 Clarke WL, Cox DJ, Gonder-Frederick LA, *et al*. Reduced awareness of Hypoglycemia in adults with IDDM. A prospective study of Hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;18:517–22.
19 Habte-Asres HH, Murrells T, Nitsch D, *et al*. Glycaemic variability and progression of chronic kidney disease in people with diabetes and comorbid kidney disease: retrospective cohort study. *Diabetes Res Clin Pract* 2022;193:110117.
20 Anderbro T, Gonder-Frederick L, Bolinder J, *et al*. Fear of Hypoglycemia: relationship to Hypoglycemic risk and psychological factors. *Acta Diabetol* 2015;52:581–9.
21 Gonder-Frederick LA, Schmidt KM, Vajda KA, *et al*. Psychometric properties of the Hypoglycemia fear survey-II for adults with type 1 diabetes. *Diabetes Care* 2011;34:801–6.
22 Haboosh S, Eid H, Onyema M, *et al*. Burden of Hypoglycaemia in people with diabetes on peritoneal dialysis in 2022. ABCD Conference; UK: ABCD, 2022
23 Hayashi A, Shimizu N, Suzuki A, *et al*. Hemodialysis-related Glycemic disarray proven by continuous glucose monitoring; Glycemic markers and Hypoglycemia. *Diabetes Care* 2021;44:1647–56.
24 Chu Y-W, Lin H-M, Wang J-J, *et al*. Epidemiology and outcomes of Hypoglycemia in patients with advanced diabetic kidney disease on dialysis: A national cohort study. *PLOS ONE* 2017;12:e0174601.
25 Epidemiology of severe Hypoglycemia in the diabetes control and complications trial. *The American Journal of Medicine* 1991;90:450–9.
26 Amiel SA, Potts L, Goldsmith K, *et al*. A parallel randomised controlled trial of the Hypoglycaemia awareness restoration programme for adults with type 1 diabetes and problematic Hypoglycaemia despite Optimised self-care (Harpdoc). *Nat Commun* 2022;13:2229.
27 NICE. *Type 2 diabetes in adults: management*. UK, 2022.
28 Deshmukh H, Wilmot EG, Gregory R, *et al*. Effect of flash glucose monitoring on Glycemic control, Hypoglycemia, diabetes-related distress, and resource utilization in the Association of British clinical Diabetologists (ABCD). *Diabetes Care* 2020;43:2153–60.