HbA_{1c} in a primary care cohort with diabetes and chronic kidney disease: the East and North Hertfordshire Institute of Diabetes and Endocrinology (ENHIDE) Diabetes Renal Telehealth Project

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Abstract

Aim: **Diabetes mellitus and chronic kidney disease (CKD) commonly co-occur. Control of glycaemia is nuanced, and should be individualised. The Diabetes Renal Telehealth Project identified 2,356 adults with diabetes and CKD, and evaluated determinants and patterns of HbA_{1c} in order to identify under-treatment or potential over-treatment of glycaemia.**

Method: **Comprehensive review of GP diabetes registers by the clinical investigators.**

Results: **The study subjects (52% male, 48% female) were aged 77 years (range 19–103) with median estimated glomerular filtration rate 52 (range 3–171) mL/min and median albumin to creatinine ratio 34 (range <0.05–1428) mg/mmol. 81% were solely managed in primary care. Median HbA_{1c} was 57 (range 10–148) mmol/mol (7.4% (3.1–15.7%)) and at the 58 mmol/mol target in 64%. Anaemia was present in 31%. 22% were solely on dietary management, 29% on insulin therapy (6 in 10 of whom were also on additional agents) and 19% were on sulfonylurea (8 in 10 of whom were on additional agents excluding insulin). Patterns of HbA_{1c} over 2 years were stable for 44%, variable in 19%, rising in 12% and improved in 8%. The 13% initially considered at increased hypoglycaemic risk based on HbA_{1c} measures alone had worse renal function and were more frequently anaemic (both p<0.0005), and 83% were treated with insulin and/or sulfonylureas. Hypoglycaemia hospital admissions were low with 10 people admitted over the study period. There was a reduction in age with increasing quintiles of HbA_{1c}, and those with HbA_{1c} >75 mmol/mol (9.0%) were youngest (mean age 68 years, p<0.001).**

Conclusions: **The majority of people with diabetes and CKD are elderly and managed in primary care, with anaemia in 31%, potentially affecting HbA_{1c} interpretation. Iatrogenic hypoglycaemic risk was identified in 10%, with suboptimal glycaemic control (HbA_{1c} >9% (75 mmol/mol)) through under-treatment in 9%. This study uncovered unmet clinical need, requiring both escalation and de-escalation of glycaemic therapies.**

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Key words: diabetes, chronic kidney disease (CKD), glycaemia, haemoglobin A1c, anaemia, hypoglycaemia, ageing

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Introduction

Diabetes mellitus is the commonest accompaniment of chronic kidney disease (CKD) that progresses to end stage renal failure, with increasing incidence through the impact of obesity and ageing.[1-3] Classification of CKD that takes account of declining estimated glomerular filtration rates (eGFR) (G1–5) and increasing urinary albumin creatinine ratios (ACR) (A1–3) has been widely adopted (Figure 1).[4] Management of hyperglycaemia in diabetes with CKD is complex.[5] Outside the documented benefit of sustained improvements in glycaemic control in type 1 diabetes on renal outcomes, there is evidence that intensive glycaemic control with insulin and insulin secretagogues in type 2 diabetes may be associated with increased mortality, especially in CKD.[6,7] Assessment of integrated glycaemic control relies on measurement of glycated haemoglobin (HbA_{1c}). At a population level the impact of anaemia and renal disease on interpretation of HbA_{1c} may be less than had been presumed.[8] However, HbA_{1c} levels are reduced with shortened red cell half-life, and this and more advanced CKD (G3b or worse) may limit interpre-

Figure 1. Classification of chronic kidney disease (CKD). Patients are classified as G1–G5, based on the eGFR, and A1–A3 based on the ACR. eGFR estimated glomerular filtration rate; ACR, albumin to creatinine ratio. Adapted from: NICE. Chronic Kidney Disease (Partial Update): Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care. London: National Institute for Health and Care Excellence, 2014. Available at: http:/www.nice.org.uk/cg182.

				Albuminuria stage, description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<3 mg/mmol	3-29 mg/mmol	≥30mg/mmol
GFR stages, descriptions and range (ml/min per 1.73m²)	Stage 1 (G1)	Normal or High	≥90			
	Stage 2 (G2)	Mildly decreased	60-90			
	Stage 3 (G3a)	Mildly to moderate decreased	45-59			
	Stage 3 (G3b)	Moderately to severely decreased	30-44			
	Stage 4 (G4)	Severely decreased	15-29			
	Stage 5 (G5)	Kidney failure	<15			

tation of HbA_{1c}.[9-11] Treatment with iron and erythropoietin may reduce HbA_{1c} with no changes in glycaemic control.[12] In elderly patients aged >75 years where CKD is more common, low HbA_{1c} levels may be a marker of malnutrition and frailty, both of which increase mortality.[13] Advanced renal disease may promote spontaneous hypoglycaemia with reduced renal gluconeogenesis and/or malnutrition.[14] The risk of severe hypoglycaemia is increased in elderly patients with CKD,[15,16] who have increased mortality rates.[17] The majority of ambulance hypoglycaemia call outs are amongst elderly people on insulin and, to a lesser extent, sulfonylureas.[18,19] Over-treatment with insulin and sulfonylureas carries an increased risk for hypoglycaemia when eGFR is reduced in the elderly requiring effective dose reduction,[20] and newer classes of therapy promoted with renal benefit are currently not licensed in more advanced CKD, particularly sodium glucose co-transporter 2 inhibitors (SGLT 2 inhibitors). Appropriate target HbA_{1c} among people with diabetes and CKD requires a more cautious approach for those with diabetes and CKD aged >75 years.[21]

The last English National Diabetes Audit (NDA) that focused on renal function in more than 800,000 people with type 2 diabetes dates back to 2007–2008. Over 42% had renal dysfunction, based on reduced eGFR <60 mL/min and increased albumin creatinine ratios (>3 mg/mmol).[22] The mean recorded HbA_{1c} fell with progressive renal insufficiency from 65 mmol/mol (8.1%) with normal renal function to 53 mmol/mol (7.0%) at stage 5 CKD. The current HbA_{1c} Quality and Outcome Framework (QOF) target for primary care in the UK of 58 mmol/mol (7.5%)[23] was achieved in 68% overall but increased to 77% attainment at stage 5A2 CKD.[21]

The majority of diabetes management currently takes place in primary care, and this is likely to include the bulk of those with CKD given that the majority of older people with CKD are managed in that setting.[24]

The ENHIDE diabetes renal telehealth project was a 2-year pilot project that set out to establish the feasibility of data extraction from primary care diabetes registers of those with CKD, with subsequent telehealth virtual review and primary care education. One specific objective was to evaluate the extent of unmet clinical need across a range of biomedical metrics, including glycaemia management.[24]

The current study examines the distribution of HbA_{1c} across a primary care diabetes cohort, and the relationship with age, anaemia and degree of renal impairment. One objective was to identify the frequency of individuals on treatment with the greatest hypoglycaemia potential where HbA_{1c} values might indicate enhanced hypoglycaemia risk. We also assessed the extent of unequivocally chronic hyperglycaemic status and examined HbA_{1c} patterns over a period of 2 years.

Methods

The ENHIDE diabetes renal telehealth project has been outlined in detail elsewhere[24] (see Appendix at www.bjd-abcd.com). Information from diabetes registers was extracted from all those with eGFR <60 mL/min and/or ACR >10 by individual practices and compiled by the project manager, with subsequent diabetes consultant clinical review. The ACR threshold was selected to identify unambiguous abnormal albuminuria excretion within the CKD A2 category. East and North Hertfordshire is a relatively affluent part of England with pockets of deprivation. The popu-

lation is currently supported by 55 separate general practices. We initially identified 20 practices that covered the six localities with a spread of deprivation index to ensure the study cohort was representative of the wider population. The deprivation score was available for practice localities based on the Index of Multiple Deprivation (IMD) 2015 scores from Public Health England's National General Practice Profiles.[25] The IMD in East and North Hertfordshire ranged from 6.7 to 27.1 (mean 13.3) and practices in the ENHIDE renal diabetes study had deprivation scores ranging from 7 to 21. In the current study, 16 practices with the most comprehensive available data were analysed as the other four used different laboratories and information systems.

The most contemporary HbA_{1c}, eGFR, ACR, haemoglobin (Hb) and assessment for anaemia was used to categorise individuals, and up to 2 years data prior to the most recent measures. In addition, diabetes medications and any treatment for anaemia were recorded up to 3 months prior to the most contemporary HbA_{1c} measurement through review of information on the practice downloads or through access to Summary Care Records.

We categorised clinically significant changes if HbA_{1c} had consistently increased or decreased by more than 10% in the antecedent 2 years compared with the most up-to-date result. If such a change had taken place inconsistently, this was categorised as variable glycaemic control. If HbA_{1c} had ranged within 10% or less of the most up-to-date value, glycaemia control was considered stable. The change of 10% took account of biological and analytical variability and recognition this was clinically meaningful. At least three measures were used to make this judgement, and at least 3 months had to have elapsed between the most contemporary and previous measurement. HbA_{1c} values were separated into categories to identify potential extremes of glycaemic control.

Potential hypoglycaemia risk was categorised for those on insulin and/or insulin secretagogues whose most recent HbA_{1c} value was <50 mmol/mol (6.7%) and/or where the HbA_{1c} value was <40 mmol/L (5.8%) regardless of diabetes treatment, unless there was an identified analytical basis for the low HbA_{1c}.

The population was categorised into five quintiles of HbA_{1c} and the characteristics of those with HbA_{1c} >75 mmol/mol (9.0%) were studied in more detail.

Anaemia was documented as contemporary Hb <110 g/L. If Hb had been recorded at this value in the previous 2 years but treated with a rise to >110 g /L, this was recorded as treated anaemia.

Hospital admissions with hypoglycaemia over the 2 years before baseline measures were recorded using the hospital administration system in East and North Hertfordshire NHS Trust (Bed In-patient Management System (BIMS)). In addition, subsequent hospital admissions up to 2 years after baseline were recorded in those identified with potential hypoglycaemia risk.

Ethical approval

This pilot was approved by the Clinical Commissioning Group (CCG) Caldecott Guardian. Ethical approval was not required given this was an extension of clinical care to implement national guidelines and part of commissioned integrated diabetes services.

Results

Diabetes and CKD (contemporary eGFR <60 mL/min and/or ACR >10 mg/mmol from initial case review) were identified in 23% (n=2,356) of adults on the practice diabetes registers. Of these, 81% were solely managed in primary care, 14% attended the hospital or community specialist diabetes services (2% of whom also attended specialist renal services) and 5% only attended the specialist renal services in East and North Hertfordshire NHS Trust. The vast majority (n=2,236 (95%)) were coded as type 2 diabetes, 106 (4.4%) as type 1 diabetes, one with mitochondrial diabetes and 13 (0.6%) had no diagnostic coding for the type of diabetes. Separation of those without type 2 diabetes did not alter the findings and have been included in the analyses. Of the 2,356 identified initially, only 7% were subsequently found to have eGFR >60 mL/min and ACR <10 mg/mol, with marginal changes outside the initial thresholds for categorisation as CKD.

Complete basic demographic and HbA_{1c} data including 2-year trends were available in 95–99.8%, with blood pressure measures available in 91% and albuminuria measures in 70%. HbA_{1c} data were not available in four cases, eGFR in 42 cases and trends in HbA_{1c} and eGFR were not available in 92 and 679 cases, respectively.

The median age of the cohort was 77 years (mean 75, range 19–103), 52% were male, 48% were female, eGFR was 52 (3–171) ml/min and ACR was 34 (<0.05–1428 mg/mmol). Within the overall cohort, 48% had a body mass index (BMI) >30, Hb was 128 (47–177) and was <110 g/L in 15%. A further 16% had recorded anaemia on treatment and the most up-to-date Hb was >110 g/dL. Thus, 31% had documented anaemia.

There were 310 (13%) with 'normal' GFR >60 mL/min whose ACR was >10 mg/mmol, 1,127 (48%) with CKD 3a and either normal or raised ACR >10 mg/mmol, 516 (22%) with CKD3b and either normal or raised ACR, and 245 (10%) with CKD 4 or worse. A small proportion (n=165 (7%)) were identified by practices as suitable for inclusion based on previous eGFR and/or ACR, but at the time of data review had eGFR >60 mL/min and/or ACR <10 mg/mmol. For the purposes of data analysis, they were included in this current report given variable renal function within the category for original inclusion. Trends in eGFR were available for 1,677 cases over 2 years and were judged to be deteriorating in 23%, improving in 9%, stable in 35% and variable in 33%.

Median HbA_{1c} was 57 (range 10–148) mmol/mol) (7.4% (3.1–15.7%). The low value of 10 mmol/mol (3.1%) was in an individual with progressive autoimmune haemolytic anaemia. The current UK National QoF target (58 mmol/mol (7.5%)) was attained in 64%. Those with HbA_{1c} <50 mmol/mol (6.7%) were more likely to be under primary care (89% vs 59–86% in the other HbA_{1c} categories ($p<0.001$, Table 1).

The average deprivation index value for England of 12.5 was considered as a threshold, and 10 of the participating practices had an IMD score >12.5 (mean 13.7). Using the IMD deprivation index as a grouping variable by practice in the regression modelling, we found no effect on HbA_{1c}, eGFR and BMI.

Table 1 Care setting by HbA_{1c} category (n=2,352)

	<49 mmol/mol (n=849)	50-58 mmol/mol (n=644)	59–67 mmol/mol (n=388)	68–75 mmol/mol (n=190)	>75 mmol/mol (n=281)
Hospital specialist team (Diabetes/Renal)	10% (85)	13% (81)	21% (80)	27% (52)	29% (83)
Community-led services	1% (7)	1% (8)	4% (15)	5% (9)	12% (33)
Primary care	89% (757)*	86% (555)	75% (293)	68% (129)	59% (165)

Four had no HbA_{1c} recorded. *p<0.001 compared with other categories.

Table 2 Treatment of 2,356 individuals with diabetes and CKD

Treatment	No	%
Diet alone	508	22%
Insulin ± additional therapies	690	29%
Metformin ± additional therapies (excluding insulin or SU)	615	26%
SU ± additional therapies (excluding insulin)	458	19%
DPP4 inhibitors ± SGLT2I	75	3%
Other (monotherapy pioglitazone, GLP-1, SGLT2I)	10	0%

CKD, chronic kidney disease; SU, sulfonylurea; SGLT2I, sodium glucose co-transporter 2 inhibitors; GLP-1, glucagon-like peptide-1, DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors.

When considering the regression modelling of HbA_{1c}, only age showed consistently in the model (p<0.001). The overall goodness of fit was 8.3% with age alone and 9.3% when BMI, cholesterol and eGFR were included in the model (p=0.006). Thus, age was the main predictor of HbA_{1c}, with a clear inverse relationship.

The breakdown of treatment for diabetes is shown in Table 2. Diet therapy alone was significantly more frequent in the cohort with HbA_{1c} <50 mmol/mol (6.7%) (47% vs 0.7–14%; p<0.001).

Of those on insulin, 40% were on no other treatment, 37% were on additional metformin and/or dipeptidyl peptidase 4 (DPP 4) inhibitors and, less commonly, pioglitazone or SGLT 2 inhibitors, 15% were on sulfonylureas (usually with additional oral therapy) and 8% were also on glucagon-like peptide-1 (GLP-1) analogue therapy (usually with additional oral therapy).

Of those on sulfonylureas without insulin, this was monotherapy in 18%, dual oral therapy in 41%, triple or quadruple oral therapy in 36% and in addition to GLP-1 analogue therapy (usually with other oral agents) in 5%.

There was no difference in mean Hb levels across the HbA_{1c} categories; 46% of anaemic people with an HbA_{1c} <50 mmol/mol were managed with diet alone and 25% received insulin and/or sulfonylurea therapy. There was an inverse relationship between HbA_{1c} and age, which was lowest in the cohort with HbA_{1c} >75 (9.0%) (age 68 years), representing 281 (12%) of the total population studied (p≤0.001; Figure 2).

Glycaemic control was judged stable in 44%, variable in 19%, rising in 12%, improved in 8% and 13% initially considered at increased hypoglycaemic risk. Due to lack of comparative HbA_{1c} data, trends were not possible to determine in 4%.

Figure 2. HbA_{1c} distribution and mean age in 2,352 patients with diabetes and chronic kidney disease

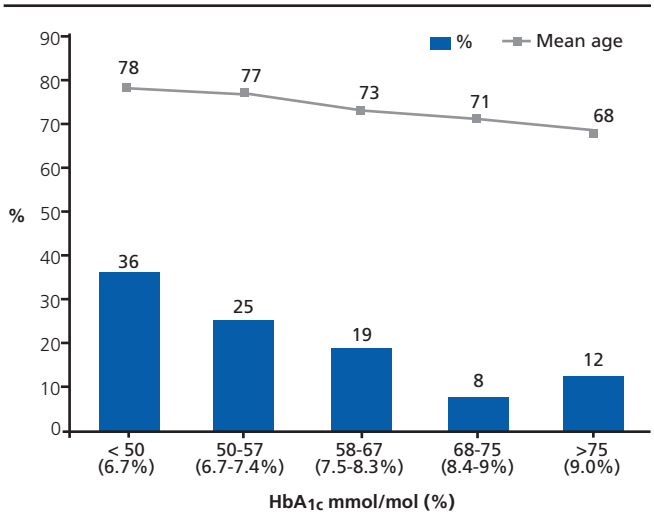

Table 3 Treatment among potential hypoglycaemia subgroup (n=308)

Treatment	No	%
Diet alone	32	10%
Insulin ± additional therapies (including SU)	145	47%
Metformin ± additional therapies (excluding insulin or SU)	19	6%
SU ± additional therapies (excluding insulin)	110	36%
DPP4 inhibitors ± SGLT2I	2	1%

SU, sulfonylurea; SGLT2I, sodium glucose co-transporter 2 inhibitors; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors.

The 13% (n=308) considered to have an increased hypoglycaemia risk were predominantly managed with insulin and/or sulfonylureas in 83% of cases (Table 3). Those identified with 'increased hypoglycaemic risk' had significantly worse renal function and were more frequently anaemic (both p<0.0005). Their median age was 77 years and the proportion with more advanced CKD (3b or worse = 44%) was significantly higher than the overall group (32%) (mean eGFR in hypoglycaemia risk group vs others 46.2 vs 52.9 mL/min, p<0.001), and. 0.5% had CKD 5. Anaemia was pre-

Table 4 Treatment regime among those managed in specialist care with HbA_{1c} ≥75 mmol/mol (9.0%)

Treatment (under specialist care)	N=116	%
Diet	0	0%
Insulin alone and or other therapies	96	83%
Metformin plus other therapies (but not on insulin or SU)	6	5%
SU plus other therapies (but not insulin)	13	11%
DPP-4 inhibitors	1	1%

SU, sulfonylurea; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors.

Table 5 Medication among those managed in primary care with HbA_{1c} ≥75 mmol/mol (9.0%)

Treatment (under primary care)	N=165	%
Diet	2	1%
DPP-4 inhibitor and/or SGLT2I	3	2%
Insulin alone and/or other therapies	75	45%
Metformin plus other therapies (but not on insulin or SU)	26	16%
SU plus other therapies (but not insulin)	59	36%

SU, sulfonylurea; DPP4 inhibitors, dipeptidyl peptidase-4 inhibitors; SGLT2I, sodium glucose co-transporter 2 inhibitors.

sent in 123 (40%) of those considered at hypoglycaemia risk, and 0.1% had Hb ≤80 g/L. 46% were managed with diet alone for at least 3 months prior to the relevant HbA_{1c} measure and 25% were on insulin and/or sulfonylurea therapy. Consequently, no more than 10% of the overall study group were considered at iatrogenic hypoglycaemic risk from insulin and/or sulfonylureas.

The cohort of 281 people whose HbA_{1c} was >75 mmol/mol (9.0%) were more frequently under specialist care than those with other categories of HbA_{1c} (41% vs 11–32%, p<0.001). Diabetes care for 30% of this high-risk group was provided by the hospital specialist diabetes team, 11% by the community diabetes specialist nurse-led team and 59% were managed by primary care. The breakdown of therapy by location of care is shown in Tables 4 and 5. Slightly fewer than 34% (n=92) of these had anaemia (Figure 3), but detailed evaluation of iron status was not available. However, 60% (n=55) of these cases were on treatment that included iron supplements leading to corrected Hb values >110 g/L. The management of the cohort differed by location of care with more on insulin (71% vs 37.5%) and fewer on sulfonylureas (11% vs 36%) if under specialist care (both p<0.001). The majority had BMI >30 (56%), but only 7% were receiving treatment with a GLP-1 analogue and 11% were on SGLT2 inhibitors.

There was a difference in CKD classification across the range of HbA_{1c} groupings, driven by those with HbA_{1c} >75 mmol/mol (9.0%), where the proportion with less advanced CKD was highest (p<0.001). Regardless of HbA_{1c} status, the majority in each HbA_{1c} band were managed solely in primary care (81%). Those with more

Figure 3. Haemoglobin distribution (g/L) among patients with HbA_{1c} >75 mmol/mol (9.0%)

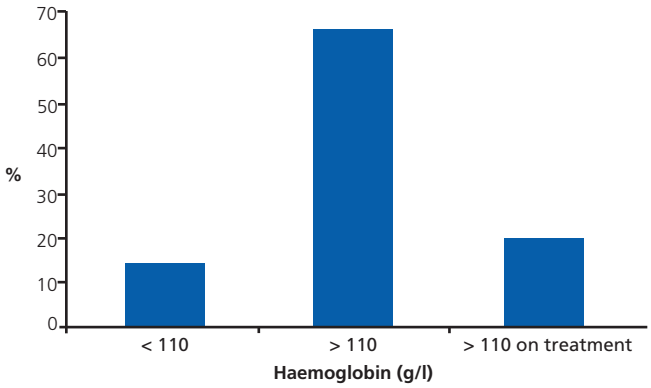

Table 6 eGFR CKD category by setting of care (n=2,314)

	CKD 1+2 (n=426)	CKD 3a (n=1,127)	CKD 3b (n=516)	CKD 4+5 (n=245)
Hospital specialist team (Diabetes/Renal)	19% (81)	7% (78)	17% (88)	53% (129)
Community-led services	4% (16)	2% (26)	4% (22)	3% (7)
Primary care	77% (329)	91% (1,023)	79% (406)	44% (109)

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

advanced CKD (G3b or worse) were managed more frequently in primary care than in specialist care (68% vs 32%, p<0.001), especially those with CKD stage 3b (Table 6).

Hospitalisation with hypoglycaemia over the 2 years before and after data capture was identified in 20 (0.8%) individuals (24 episodes) of the total cohort of 2,356. Of these, only 10 were identified as having an increased hypoglycaemia risk on the basis of HbA_{1c}, five were considered to have stable HbA_{1c}, two were felt to have improving HbA_{1c}, two variable and one rising values.

Discussion

This study offers an insight into factors underlying patterns of HbA_{1c} in a cohort with diabetes and CKD predominantly under primary care. A previous study suggested that only 30% of people with CKD and diabetes are managed in primary care.[26] With comorbidity more common amongst the elderly, it is not surprising that the majority (81%) were managed in this setting in the current study.

The current cross-sectional study records contemporary care in a geographically defined area with fairly comprehensive data capture and retrospective records for up to 2 years. Individualised patient review was enabled through this approach. The absence of comprehensive information in four general practices is unlikely to have materially altered the findings.

We identified two important subgroups who required de-escalation or alternatively intensification of glycaemia management

– namely, those with a potential risk of hypoglycaemia and those with excessively high levels of HbA_{1c}.

To our knowledge this approach has not been undertaken previously, although can be compared with renal data from the NDA.[19] In that report 42% of the population had renal dysfunction. In the current study the prevalence was 23%, using a higher cut-off for ACR, to ensure only unambiguous abnormal albumin excretion was identified.

Comparison of current data with the earlier NDA data demonstrates no greater HbA_{1c} QoF target attainment over 10 years, although levels of HbA_{1c} fell with reducing eGFR in both studies. Several factors may account for these observations, which are exclusive to the notion that the lower values reflect 'better' glycaemic control. Frailty and malnutrition can lead to lower levels of HbA_{1c}.[13] The mean age was 66 years in the NDA study and 75 years in the current study. This may have been a factor in the observed numbers with low HbA_{1c}. Assessment for hypoglycaemia unawareness was not recorded in primary care records.

The impact of anaemia on HbA_{1c} values is relevant. The prevalence of treated and untreated anaemia in the current study totalled 31%, in line with previous reports.[8–10] Anaemia in CKD can lead to lower HbA_{1c} values through increased red cell turnover, although iron deficiency anaemia is associated with higher levels of HbA_{1c}.[12] We found that anaemia and lower HbA_{1c} values were more prevalent amongst the older cohort aged >75 years. Often anaemic people with an HbA_{1c} <50 mmol/mol were managed with diet alone (46%). Only 25% were on insulin and/or sulfonylurea therapy, suggesting low HbA_{1c} values were not reflective of iatrogenic hypoglycaemia in most cases, although detailed information on the type of anaemia was lacking. It is more likely that, unless there was hypoglycaemia as a consequence of frailty, malnutrition and reduced gluconeogenesis, the majority were close to normoglycaemic values as only 0.5% had CKD 5 where spontaneous hypoglycaemia can occur. An earlier report suggested that, at a population level, HbA_{1c} may be misleadingly low as a result of that level of anaemia and CKD in less than 1%,[8] and only 0.1% had Hb ≤80 g/L in this current study.

The HbA_{1c} threshold of 50 mmol/mol (6.7%) to identify possible hypoglycaemia risk took account of the targets for type 1 and type 2 diabetes in the Association of British Clinical Diabetologists (ABCD) Renal Association (RA) guidelines for managing glycaemia in kidney disease.[20] Although the risk of hypoglycaemia is not solely identified through low HbA_{1c} values, marked glycaemic variability and hypoglycaemia with high HbA_{1c} values are more reflective of type 1 diabetes, who were a small minority in the current study.

The primary concern with older people with CKD is of vulnerability to iatrogenic hypoglycaemia without de-escalation of therapy. This is reflected in the preponderance of older people requiring ambulance assistance for hypoglycaemia through insulin treatment and, to a lesser extent, sulfonylureas.[15–19] In the current study, overall 49% were on insulin and/or sulfonylureas, often with the majority on additional diabetes therapy. Only 122 (5%) of these had HbA_{1c} <50 mmol/mol and were considered at risk of hypoglycaemia. Dose reduction to mitigate this risk is an important consideration.

All cases were evaluated to enable detailed glycaemic review with expectation of de-escalation of therapy to reduce the risk of hypoglycaemia and attainment of HbA_{1c} values >50 mmol/mol (6.7%). This is in contrast to reports that have evaluated established hypoglycaemia and/or hypoglycaemia ambulance call outs, who more often were elderly with CKD.[18,19] Without clearly defining the therapeutic regime and other factors such as anaemia and whether on diet alone, the individualised approach recommended in the 2018 ABCD RA guidelines[20] will not target those at highest hypoglycaemia risk by relying solely on HbA_{1c}. We did not identify a major burden of hypoglycaemia admissions through HbA_{1c} values alone. Integrated diabetes care in East and North Hertfordshire since 2010 has focused on potential hypoglycaemia risk. This may have encouraged some de-escalation of therapy to minimise the risk of ambulance hypoglycaemia call outs.

However, documentation on discharge summaries of hospitalisation with hypoglycaemia is not accurate, and there may have been additional cases not coded for such an outcome.[18] We only recorded admissions within our own acute trust. In addition, many patients with ambulance call outs for hypoglycaemia are not conveyed to hospital.[19]

The 2018 ABCD RA guidelines[20] do not emphasise that HbA_{1c} targets of <50 mmol/mol (7.5%) may be appropriate in older people with CKD who are solely managed by diet, with corroborative blood glucose monitoring data to provide reassurance there is no hypoglycaemia.

HbA_{1c} values over 2 years frequently plateaued, but clinically significant variability was identified in 19%, highlighting the need for repeat measures for optimal management. By contrast, 12% had worsening and 8% improved HbA_{1c} patterns.

We also identified 281 people (12%) whose HbA_{1c} was higher than 75 mmol/mol (9.0%) Most were not anaemic and were the youngest cohort overall, in whom current guidelines recommend additional efforts to improve glycaemia to an HbA_{1c} target of <68 mmol/mol.[20] The majority were solely under primary care with a clear unmet need, reflecting previously reported therapeutic inertia.[27] The majority had BMI >30 (56%) but only 7% were receiving treatment with a GLP-1 analogue and 11% were on SGLT2 inhibitors. Glycaemic management in CKD is recognised as challenging, with contraindications, dosing and current licensing limitations.[20] Recommendations for wider use of SGLT2 inhibitors should change in the future in light of evidence of renoprotection, independent of glycaemic-lowering effects.

Diabetes, ageing and obesity can all lead to falsely lower eGFR than true GFR measurement, potentially leading to over diagnosis of CKD,[28,29,30] with implications for restrictions in certain diabetes therapies.

The NDA in 2008 and subsequent years has reported a wide spectrum of socioeconomic deprivation, which can increase adverse metabolic and renal measures.[3,21,31] In the current report there was no relationship between these measures and those practices with higher deprivation index, but without individual deprivation status we cannot conclusively conclude that deprivation did not impact on the findings.

We did not document frailty status, and the impact of this and

Key messages

- The assessment of glycaemic control by measurement of HbA_{1c} in people with diabetes and kidney disease must be interpreted taking consideration of anaemia and diabetes medication
- Up to one in five people with diabetes and chronic kidney disease require escalation or de-escalation of their diabetes medication

related low HbA_{1c} values on mortality cannot reliably be examined in a cross-sectional study. However, it is recognised that low HbA_{1c} is common in advanced CKD where there is a U-shaped mortality curve potentially explained by hypoglycaemia.[32] Very low HbA_{1c} (<40 mmol/mol) (5.8%)), regardless of whether attributable to iatrogenic or spontaneous hypoglycaemia, malnutrition, frailty, anaemia or advancing CKD, carries a poor prognosis.

Based on the need to address hyperglycaemia and avoid hypoglycaemia, we identified an important unmet clinical need in current practice in almost 20% with diabetes and CKD within this study cohort. The changing patterns of HbA_{1c} and identified potential hypoglycaemia risk demonstrated the requirement for regular surveillance of glycaemic management plans, not least when renal function deteriorates, necessitating changes in either dosage or class of diabetes therapies.

In summary, this approach to data collection and individual virtual review enabled a more focused assessment of glycaemic control. Given the challenge of providing care to very large numbers, alternative models better using clinical information are required to risk stratify care, recognising that glycaemic management is just one requirement for holistic individualised care of the complex multimorbid nature of diabetes with CKD.[5]

Conflict of interest: PHW has received honoraria for delivering educational meetings and/or attending advisory boards for Astra Zeneca, BI, Eli Lilly, MSD, Napp, Sanofi, Novo and Vifor Pharmaceuticals.

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Appendix: Biochemical Measures and Statistical Analysis

Study design and assessments
East and North Hertfordshire is a relatively affluent part of England with pockets of deprivation. The population is currently supported by 55 separate general practices. We initially identified 20 practices that covered the six localities with a spread of deprivation index to ensure the study cohort was representative of the wider population. The deprivation score was available for practice localities based on the Index of Multiple Deprivation (IMD) 2015 scores from Public Health England's National General Practice Profiles. This IMD in East and North Hertfordshire ranged from 6.7 to 27.1 (mean 13.3) and practices in the ENHIDE renal diabetes study had deprivation scores ranging from 7 to 21.

Biochemical measures
eGFR was recorded using the Modification of Diet in Renal Disease (MDRD) formula with a transition after 6 months to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with the change in laboratory reporting. For the purposes of the Diabetes Renal Telehealth Project, we did not differentiate the two methodologies, given recognition that both estimates underestimate true GFR in diabetes, but that both perform equally in that regard.

Urine albumin creatinine ratios (ACR) were measured using standard polyethylene glycol enhanced immuno-turbidimetric assay for albumin and a standard enzymatic assay for urine creatinine, based on a requested early morning urine sample.

HbA_{1c} was measured in a UKAS (United Kingdom Accreditation Service) laboratory by high performance liquid chromatography methodology. The assay imprecision was <3% across an HbA_{1c} range of 11–133 mmol/mol (3.2–14.3%). External quality assurance data reported minimal bias (attaining acceptable performance as assessed by the Welsh External Quality Assessment Scheme (WEQAS)).

Statistical analysis
Statistical analysis was undertaken using IBM SPSS v 25. Categorical variables are presented as frequencies and continuous variables summarised using means and standard deviations. Independent sample t-tests were performed on continuous variables. Standard measures of statistical association (χ^2 and Fisher's exact test) were performed on categorised HbA_{1c} and renal measures. Cholesterol, HbA_{1c} and eGFR had a non-normal distribution (positive skewed), consequently these variables, apart from eGFR, were successfully log transformed. Linear multiple regression analysis was performed to build potential predictive models of HbA_{1c} against age, BMI, cholesterol and eGFR. This followed exclusion of Hb and ACR as predictive on univariate analysis. The overall goodness of fit was measured by R-squared. ANOVA was employed to examine differences across HbA_{1c} and age ranges.

Final regression models were used as predictors for HbA_{1c} status. Binary variables were chosen if continuous variables were not normally distributed to allow effect of a eGFR cut-off as individuals were included on the basis of eGFR <60 or significant albuminuria. Thus, those evaluated with eGFR >60 were only included on the basis of raised albuminuria status.