Glycaemic variability and progression of chronic kidney disease in people with diabetes and comorbid kidney disease: Retrospective cohort study

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ABSTRACT

Aim: To investigate the association between glycaemic variability and the development of End-Stage-Kidney-Disease (ESKD) among individuals with diabetes and chronic kidney disease.
Methods: A cohort study using UK electronic primary care health records from the Clinical Practice Research Datalink. Glycaemic variability was assessed using a variability score and intra-individual coefficient of variation (CV) of HbA1c. We calculated sub-distribution hazard ratios (sHR) for developing ESKD using competing risk regression analysis.
Results: There were 37,222 eligible participants (45.5 % male), with a mean age of 76.4 years (SD ± 9.2), and a mean baseline eGFR 40.7 (±10.7) ml/min/1.73 m^2. There were 5,086 incidents of ESKD in the follow-up period. The adjusted sHR (95 %CI) for each variability score group, were as follows: 21–40, 1.38 (1.27–1.50); 41–60, 1.54 (1.41–1.68); 61–80, 1.61 (1.45–1.79); and 81–100, 1.42 (1.19–1.68), compared with the group (score 0–20) with least variability. The adjusted sHR for CV were as follows: 6.7–9.9, 1.29 (1.15–1.45); 10.0–13.9, 1.55 (1.39–1.74); 14.0–20.1, 1.79 (1.60–2.01) and ≥20.2, 2.10 (1.88–2.34) compared to reference group 0–6.6.
Conclusions: Glycaemic variability was strongly associated with the development of ESKD in people with diabetes and CKD.

1. Introduction

Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [1,2]. Kidney disease develops in approximately 30–40 % of people with diabetes [3] and is associated with elevated mortality and morbidity [4–6]. There is compelling evidence that reducing glucose exposure lowers the risk of microvascular and macrovascular complications, including kidney disease [7–9]. There are national and international guidelines on diabetes management for patients with CKD that advocate a bi-annual screening review of CKD status in people with diabetes [10–12]. However, despite clinical guidelines for screening and preventing the advancement of CKD in people with diabetes, a significant proportion of people with diabetes progress to ESKD. While elevated glycaemic control is strongly association with CKD progression, there is also emerging evidence that glycaemic variability may be a significant risk factor for kidney disease [13].

A meta-analysis of eight studies reported that higher glycaemic variability increased the risk of developing CKD among people with Type 1 (Hazard ratio (HR) 1.70, 95 % CI, 1.41–2.05) and Type 2 (HR 1.20, 95 % CI, 1.12–1.28) diabetes [10]. In two more recent studies, Yan et al. [14] reported that glycaemic variability defined using three methods (HbA1c-SD, HbA1c-AUC, and an HbA1c variability score) was significantly associated with the development of microalbuminuria; and Lee et al. [15] reported that higher glycaemic variability (HbA1c-CV) was associated with the increased decline in the estimated glomeruli filtration rate (eGFR). However, these studies were limited as they were conducted in people without CKD and did not consider how variability might impact on progression to ESKD. Hence, currently little is known about the association between glycaemic variability and the clinical prognosis of people with CKD. The few studies that examined the association between glycaemic variability and progression to ESKD show

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mixed results. Chiu et al. [16,17] found that higher glycaemic variability based on the standard deviation (SD) of HbA1c over 6 years, was associated with an increased risk of progressing to macroalbuminuria. Conversely, Lee et al. [18] who used tertiles of SD in HbA1c found that participants with CKD stage 3–4 and an HbA1c ≥7.0 % (≥53.0 mmol/mol) in the highest HbA1c SD tertile, had a lower risk of progression to dialysis. While studies have shown an association between glycaemic variability and chronic kidney disease (CKD) in people with diabetes, the data on the relationship between glycaemic variability and the development of End-Stage-Kidney-Disease (ESKD) are limited in this population [19].

Therefore, more information on the association between glycaemic variability in CKD progression is needed, particularly in people with stages 3–5 CKD [19]. In this study, we investigated whether variability in HbA1c levels was associated with the development of ESKD among individuals with diabetes and CKD at baseline.

2. Methods

We undertook a retrospective cohort study using the Clinical Practice Research Datalink (CPRD), which is a nationwide United Kingdom (UK) primary care dataset. CPRD has been shown to be representative of the general UK population in terms of age, gender, and ethnicity [20]. Data are collected longitudinally from a patient's first registration with their general practice until they transfer out or die. The dataset contains patient-level factors, consultations, clinical information, test results, prescribed therapies, and diagnostic information, using Read Codes (these are the standard clinical codes used in the UK). CPRD patient records are linked to other routine datasets such as Hospital Episode Statistics (HES) and Index of Multiple Deprivation (IMD). We used practice-level IMD scores as a measure of deprivation in our analysis.

The study protocol was approved by the Independent Scientific Advisory Committee of CPRD (Protocol 20_011) and the London School of Hygiene and Tropical Medicine Ethics Committee (LSHTM reference 26594).

2.1. Study population

The study population consisted of adults (age ≥18 years) with a diagnostic code for diabetes recorded between 1st January 2007 to 31st December 2009 and who had CKD stage ≥3 defined by Read code or based on serum creatinine and estimated glomerular filtration rate (eGFR) during the baseline period (1st January 2007 to 31st December 2009).

Individuals were included in the study if all the following criteria were met:

(1) Diagnosed with diabetes before 2010.
(2) CKD stage ≥3 (defined as two measurements of eGFR <60 mL/min/1.73 m^2 during the baseline period).
(3) The earliest of last practice data collection, date of death, or transfer out of CPRD must have occurred after 31/12/2009; and the patient must have met CPRD standards from 1/1/2007 until the patient's date of the last follow-up.

Diabetes status was confirmed from Read diagnostic codes using a previously developed algorithm [21] (see supplemental file 1). Patients with comorbid CKD were identified based on two measures of eGFR during the baseline period >3 months apart. We calculated eGFR for each patient from serum creatinine records using the CKD Epidemiology Collaboration equation (*EPI*-CKD 2021) [22–24]. CKD status was not adjusted for Black ethnicity in accordance with the latest guideline from the UK's National Institute of Clinical Excellence (NICE) [11,23]. For records before 2014 the serum creatinine measurements on file were multiplied by 0.95 to allow for the absence of reporting of correctly calibrated creatinine results prior to that date.

Exclusions included:

- Patients <18 years of age with diabetes.
- Those with gestational diabetes; and.
- Patients with a history of kidney transplantation or renal replacement therapy are defined by Read Codes prior to the baseline period (see supplemental file 3).

2.2. Primary exposure

The primary exposure of interest were glycaemic control and glycaemic variability during the baseline observation period from 1st January 2007 to 31st December 2009. Two methods were used to determine glycaemic variability: method A used a glycaemic variability score, and method B used the coefficient of variation (CV) of HbA1c; both methods required a minimum of four or more measurements to be calculated.

The glycaemic variability score calculation (method A) was developed as part of a previous study [15]. This method uses the number of times consecutive HbA1c records differed by ≥0.5 % (5.5 mmol/mol), divided by the number of comparisons and multiplied by 100, providing a score range from 0 to 100 (lowest to highest variability). Scores were grouped into five categories in order of variability from lowest to highest: 0–20, 21–40, 41–60, 61–80, and 81–100.

For method B, the intrapersonal mean and SDs of all HbA1c measurements (HbA1c -SD) were calculated. As the number of HbA1c measurements affects the standard deviation (having fewer HbA1c measurements is likely to overestimate SD), we adjusted according to the formula $SD/\sqrt{[n/(n-1)]}$, where n is the number of HbA1c measurements. We divided the adjusted HbA1c-SD by the mean HbA1c and multiplied by 100 to obtain HbA1c-CV, these values were then grouped into quintiles. The mean of the annual mean HbA1c values (baseline mean HbA1c) during the baseline period was also considered as an exposure and were grouped as follows: < 6.5 % (<48 mmol/mol), 6.5 to <7.0 % (48 to <53 mmol/mol), 7.0 to <7.5 % (53 to <58 mmol/mol), 7.5 to <8.1 % (58 to <65 mmol/mol) and ≥8.1 % (≥65 mmol/mol).

2.3. Outcomes

The primary outcome variable was time to the development of ESKD, defined as requiring dialysis or transplantation or a sustained eGFR <15 mL per minute per 1.73 m^2, according to the last available eGFR result. Changes in eGFR from baseline to final follow-up point were calculated as a secondary outcome excluding those that had reached ESKD. To avoid misclassification due to delayed recording of ESKD in the GP record, participants who experienced the primary outcome of interest in the first year of follow-up were excluded.

2.4. Covariates

The analysis was adjusted for the following covariates: age, sex, ethnicity, IMD (deprivation), duration of diabetes, body mass index (BMI), systolic blood pressure, total cholesterol, baseline mean HbA1c, baseline CKD, polypharmacy and comorbidity count (asthma, arterial fibrillation, cancer, chronic obstructive pulmonary disease, dementia, epilepsy, chronic liver disease, hypertension, heart failure, ischaemic heart disease, myocardial infarction, peripheral vascular disease, polycystic kidney disease, rheumatoid arthritis, stroke, thyroid disease, and severe mental health disorders (including bipolar and schizophrenia)) (see Read Code for all comorbidities supplemental file 2). Self-reported ethnicity identified using Read Codes based on the 2001 & 2011 UK census data were used to derive a four-category variable (White, Black, Asian, Mixed). If ethnicity records were not found in CPRD, the Hospital episode statistics (HES) records were used. Patients who did not have ethnic information in CPRD or HES were categorised as "White", as per previous CPRD studies [17], although we also undertook a sensitivity

analysis excluding the ethnicity variable.

A drug was counted for polypharmacy purposes if it had been prescribed ≥3 times between 1st January 2009 and 31 December 2009 and for at least six months without any gaps of three months or more. Polypharmacy was categorized into four groups (0–2, 3–4, 5–6, and ≥7 medicines meeting the above criteria), as per previous studies [21]. Duration of diabetes was categorized into five groups <5, 5 to <10, 10 to <15, 15 to <20 and ≥20 years [21]. Other continuous variables such as age, blood pressure, and total cholesterol were also grouped into ordinal categories. Smoking was categorised as never smoked, ex-smoker, or current smoker. Practice level IMD was used as a measure of deprivation.

2.5. Statistical analysis

Time to event analyses were conducted to evaluate the effect of glycaemic variability on time to ESKD. Follow-up time and person-years were calculated as the time elapsed from the date of enrolment until the date of ESKD, date of death, patient leaving the practice, last data collection from the practice, renal replacement therapy (kidney transplant or dialysis) or the end of follow-up (31st December 2018) whichever came first. The competing risk of death was accommodated by fitting sub-distribution hazard models to the data. The incidence of ESKD was estimated for each category of the glycaemic variability score (method A) with the group representing patients with the least variability (0–20) as the reference, and for the quintiles of the HbA1c-CV, the quintile representing least variability was used as the reference (method B). Sub hazard ratios (sHR) with 95 % confidence interval for the association between the primary exposures and time to the development of ESKD were estimated.

Three models were used to test the association between the primary exposures (glycaemic variability and baseline mean HbA1c) and the development of ESKD:

- Model 1 - Crude analysis
- Model 2 - Multivariable associations (adjusted): glycaemic variability score (method A), and covariates.
- Model 3 - Multivariable associations (adjusted): coefficient variation (CV) (method B), and covariates.

Unadjusted and adjusted sub-hazard ratios (sHR) were used to examine whether glycaemic variability (methods A and B), baseline mean HbA1c, baseline CKD stage (3a, 3b 4), or other covariates were associated with the development of ESKD. The covariate variables were age, sex, ethnicity, IMD, duration of diabetes, BMI, hypertension, SBP, total cholesterol, polypharmacy, and comorbidity count. Collinearity between the independent variables was assessed using variance inflation factors (VIFs). These indicated low collinearity between independent variables.

The percentage of patients with any missing data in variables other than ethnicity was very low (<1%), hence we undertook a complete cases analysis. Individuals with missing ethnicity data were retained in the analysis by assigning them to the White ethnicity category.

We undertook four sensitivity analyses using a fully adjusted model 1) excluding ethnicity to assess its impact on model estimates and to consider any potential bias caused by missing ethnicity data; 2) excluding those with a type 1 diabetes Read code to assess whether the impact of glycaemic variability differed by type of diabetes. 3) adjusting for baseline albuminuria for patients with baseline u ACR results (N = 25,984); 4) by replacing baseline CKD stage with mean baseline eGFR.

We also explored the nature of the variability observed to consider how the variability related to bi-directional fluctuations or an increasing or declining trend. The first step in this analysis was to consider the distribution of variation observed by generating an indicator which showed variability on a score ranging from 1.0 to −1.0 (scores nearer to 0 indicate fluctuations that are in equal proportions of increases or

decreases, whereas scores toward 1.0 indicate an increasing trend and scores toward −1.0 suggest a decreasing trend). The variability indicator was calculated using the following formular:

$(TicN/TcN) – (TdcN/TcN)$ = variability indicator
$TicN$ = the total number of increases ≥5.5 mmol/mol.
$TdcN$ = the total number of decreases ≥5.5 mmol/mol
TcN = the total number of changes ≥5.5 mmol/mol.

The variability indicator enabled us to look at the distributions of variability in the sample over the observation period. To ensure reliable estimates only patient records with ≥10 changes ≥5.5 mmol/mol were included in this analysis. A Chi-squared test was used to examine whether the glycaemic variability indicator was associated with the development of ESKD. The ESKD risk associated with a variability indicator ≥0.25 and then a variability indicator of ≤−0.25 was assessed using logistic regression by comparing each of these two groups with the group of patients who had a variability indicator of zero. All analyses were undertaken using Stata, version 16.0.

3. Results

There were 37,222 individuals with diabetes and chronic kidney disease between 1st January 2007 to 31st December 2009 in the dataset. We excluded individuals who developed ESKD within the first year of follow-up (n = 430) and those with any missing data (n = 370) for variables other than ethnicity, leaving a total of 36,422 participants for analysis. The breakdown of exclusions from the source data file are summarised in a figure provided in supplemental file 4.

3.1. Sample characteristics

The mean age of the participants was 76.4 (SD ± 9.2) years, with a mean diabetes duration of 8.2 (±6.8) years, and mean baseline HbA1c 56.3 (±13.4) mmol/mol. Mean baseline eGFR was 40.7 (±10.7) mL/min/1.73 m^2 and the mean number of HbA1c measurements per participant was 13.8 (±7.3). The characteristics of the baseline variables by glycaemic variability score groups are presented in Table 1.

The mean follow-up period was 6.8 (±2.9) years, the total person-time at risk was 248,146 days, and 5,086 developed ESKD during the follow-up period. Follow-up was shorter among individuals who developed ESKD (6.9 [±3.1] years compared to those who did not (7.4 ± 2.4) years. The profile of the ESKD events for the observation period in terms of person-years (in 1000 s) of follow-up and incidence per 1000 person-years (95 % CI) for the exposure variables are presented in Table 2.

3.2. Model 1 crude analysis

A crude analysis for each of the baseline variables was undertaken to estimate their individual hazards for progression to ESKD (see supplemental file 5). In summary, the analysis showed that male gender and Asian ethnicity were associated with an increased risk of ESKD. Polypharmacy conferred the greatest risk with those in the highest category (≥7 agents) having a 36 % increased risk of ESKD in the adjusted analysis when compared to the reference group (0–2 agents). Systolic blood pressure and BMI categories were incrementally associated with an increased risk of ESKD. In the unadjusted analysis the risks observed in the glycaemic variability score groups were 46 % higher in the 21–40 group and approximately doubled in the other groups (highest in the 61–80 group), compared with the lowest group (scores 0–20) (see Table 3). Risk increased incrementally in relation HbA1c-CV quintiles, with a 2.5-fold increase in the highest quintile compared to the lowest quintile.

Table 1
Descriptive distribution of baseline variables by glycaemic variability score category.

Variables	Categories	Missing (%)	Glycaemic variability score categories N (Column%)					N (column %)
			0–20	21–40	41–60	61–80	81–100	Total
Age in years	<70		1,526 (13)	2,054 (20)	2,193 (25)	1,305 (28)	347 (30)	7,425 (21)
	70–74		1,760 (15)	1,833 (18)	1,628 (19)	806 (17)	176 (15)	6,203 (17)
	75–79		2,700 (24)	2,395 (23)	1,985 (23)	988 (21)	211 (18)	8,279 (23)
	80–84		2,834 (25)	2,196 (21)	1,694 (19)	864 (18)	221 (19)	7,809 (21)
	≥85		2,680 (23)	1,790 (17)	1,250 (14)	755 (16)	231 (20)	6,706 (18)
Sex	Female		6,725 (58)	5,583 (54)	4,503 (52)	2,426 (51)	624 (53)	19,861 (55)
	Male		4,775 (42)	4,685 (46)	4,247 (48)	2,292 (49)	562 (47)	16,561 (45)
Ethnicity	White	18.9 %	10,390 (90)	9,204 (90)	7,828(90)	4,174 (89)	1,052 (89)	32,648 (90)
	Black		75 (0.7)	91 (0.9)	69 (0.8)	62 (1.3)	16 (1.4)	313 (0.9)
	Asian		195 (2)	221 (2)	216 (3)	144 (3)	36 (3)	812 (2)
	Mixed		840 (7)	752 (7)	637 (7)	338 (7)	82 (7)	2,649 (7)
IMD	1 (least deprived)	0.04 %	1,746 (15)	1,568 (15)	1,291(15)	687 (14)	167 (14)	5,459 (15)
	2		1,890 (16)	1,613 (16)	1,421 (16)	727 (15)	175 (15)	5,826 (16)
	3		2,211 (19)	2,116 (21)	1,710 (20)	969 (21)	246 (21)	7,252 (20)
	4		2,521 (22)	2,259 (22)	1,946 (22)	1,057 (22)	266 (28)	8,049 (22)
	5 (Most deprived)		3,132 (27)	2,712 (26)	2,382 (27)	1,278 (27)	332 (27)	9,836 (27)
Smoking status	Never Smoked	0.18 %	4,037 (35)	3,678 (36)	2,902 (33)	1,597 (34)	379 (32)	12,593 (35)
	Ex-smoker		6,631(58)	5,901 (58)	5,224 (58)	2,752 (58)	698 (58)	21,206 (58)
	Current smoker		832 (7)	689 (7)	624 (7)	369 (8)	109 (9)	2,623 (7)
BMI	<25	0.61 %	2,825 (25)	2,110 (21)	1,581 (18)	915 (19)	247 (21)	7,678 (21)
	25–29.9		4,433 (39)	3,833 (37)	3,048 (35)	1,526 (32)	391 (33)	13,231 (36)
	≥30		4,242 (37)	4,325 (42)	4,121 (47)	2,277 (48)	548 (46)	15,513 (43)
Duration of diabetes in years	<5		4,302 (37)	3,244 (32)	2,562 (29)	1,375 (29)	356 (30)	11,839 (33)
	5 to <10		4,916 (43)	4,080 (40)	3,211 (37)	1,706 (36)	411(35)	14,324 (39)
	≥10		2,282 (20)	2,944 (29)	2,977 (34)	1,637 (35)	419 (35)	10,259 (28)
Polypharmacy	0–2		1,048 (9)	633 (6)	339 (4)	226 (5)	66 (6)	2,312 (6)
	3–4		3,433 (30)	2,187 (21)	1,499 (17)	809 (17)	192 (16)	8,120 (23)
	5–6		4,094 (36)	3,680 (36)	3,050 (35)	1,575 (33)	378 (32)	12,777 (35)
	≥7		2,925 (25)	3,768 (37)	3,862 (44)	2,108 (45)	550 (46)	13,213 (36)
Comorbidity count	0		570 (5)	580 (6)	492 (6)	279 (6)	76 (6)	1,997 (6)
	1		3,883 (34)	3,271 (32)	2,669 (31)	1,327 (28)	325 (27)	11,475 (32)
	2		3,341 (29)	2,950 (29)	2,442 (28)	1,240 (26)	300 (25)	10,273 (28)
	3		2,056 (18)	1,845(18)	1,614 (19)	922 (20)	232 (20)	6,669 (18)
	≥4		1,650 (14)	1,622 (16)	1,533 (18)	950 (20)	253 (21)	6,008 (17)
Total cholesterol	<3	0.18 %	416 (4)	474 (5)	421 (5)	231 (5)	51 (4)	1,593 (4)
	3–3.99		4,265 (37)	4,132 (40)	3,470 (40)	1,804 (38)	412 (35)	14,083 (39)
	4–4.99		5,093 (44)	4,323 (42)	3,685 (42)	1,969 (42)	489 (41)	15,559 (43)
	≥5		1,726 (15)	1,339 (13)	1,174 (13)	714 (13)	234 (20)	5,187 (14)
Mean systolic blood pressure	<130	0.14 %	1,623 (14)	1,596 (16)	1,444 (17)	808 (17)	206 (17)	5,677 (16)
	130–139		3,094 (27)	2,993 (29)	2,450 (28)	1,313 (28)	331 (28)	10,181 (28)
	140–149		3,944 (34)	3,419 (33)	2,892 (33)	1,468 (31)	319 (27)	12,042 (33)
	≥150		2,839 (25)	2,260 (22)	1,964 (22)	1,129 (24)	330 (28)	8,522 (23)
Baseline CKD stages	CKD Stage 3a		4,633 (40)	4,015 (39)	3,246 (37)	1,620 (34)	357 (30)	13,871 (38)
	CKD Stage 3b		5,009 (44)	4,384 (43)	3,674 (42)	2,079 (44)	556 (47)	6,849 (19)
	CKD Stage 4		1,858 (16)	1,869 (18)	1,830 (21)	1,019 (22)	273 (23)	15,702 (43)
Baseline mean HbA1c (%, mmol/mol)	<6.5 % (<48)		6,213 (54)	2,537 (25)	1,126 (13)	368 (8)	60 (5)	10,304 (28)
	6.5–7.0 % (48 to <53)		2,767 (24)	2,318 (23)	1,296 (15)	412 (9)	74 (6)	6,867 (19)
	7.0–7.5 % (53 to <58)		1,545 (13)	2,233 (22)	1,591 (18)	618 (13)	119 (10)	6,106 (17)
	7.5–8.1 % (58 to <65)		624 (5)	1,604 (16)	1,732 (20)	805 (17)	179 (15)	4,944 (14)
	≥8.1 % (≥65)		351 (3)	1,576 (15)	3,005 (34)	2,515 (53)	754 (64)	8,201 (22)

3.3. Model 2 and 3 analyses

When adjusting for all covariates, the association between glycaemic variability (both methods A&B) and developing ESKD was attenuated but the overall association remained strong (see Table 3). The sHRs (95 % CI) were 1.38 (95 % CI 1.27–1.50), 1.54 (1.41–1.68), 1.61 (1.45–1.79) and 1.42 (1.19–1.68) for the variability score groups 21–40, 41–60, 61–80, 81–100 respectively compared with the reference group (scores 0–20). In the HbA1c-CV model, the association remained incremental with a sHR of 2.10 (1.88–2.34) in the highest compared to the lowest quintile. In relation to mean baseline HbA1c there was evidence of an association between higher HbA1c (values >7.5 %) > 58 mmol/mol) and ESKD in the crude analysis. In the adjusted analysis, there was a moderate reduction in the risk of ESKD for those within the HbA1c groups ranging from 7.0 to <7.5 % (53 to <58mmols/mol), compared to those with values <6.5 % (<48 mmol/mol) in the fully adjusted models. The data for the adjusted exposure models are presented graphically in Fig. 1.

3.4. Sensitivity analysis

We undertook an exploratory analysis to understand the type of variability observed, in those with ≥10 changes of ≥0.5 % (5.5 mmol/mol, n = 4,764). In this sub-group, 1,301(27.3 %) developed ESKD, and the distribution of the variability indicator showed that most of the variability was expressed as fluctuations (see supplemental file 6) with a mean score of 0.01 (±0.17). The directionality risk analysis showed those patients with scores ≥0.25 (increasing trend, n = 364) had a lower risk (OR 0.80, 95 % CI 0.62–1.02) whilst those with a score ≤−0.25 (decreasing trend, n = 321) had a higher risk (OR 1.58, 95 % CI 1.23–2.04) when compared with patients scoring 0.0 (n = 1,004). The sensitivity analysis to assess the missing data in the ethnicity variable, showed marginal differences from the main analysis when ethnicity was excluded (see Supplemental File 7). Results remained unchanged in both models after adjusting for baseline albuminuria (see Supplemental file 11). Excluding patients with type 1 diabetes Read codes produced similar results (see supplemental file 12). Findings also remained similar

Table 2

Events, person years and crude incidence of ESKD by mean HbA1c, glycaemic variability and HbA1c- coefficient of variation categories at baseline.

Baseline mean HbA1c Categories (%, mmol/mol)	N (column %)	ESKD events (n)	Person years (in 1000 s) of follow-up	Incidence per 1000 person-years (95 % CI)
<6.5 %(<48)	10,304 (28.29)	1261	70.85	17.80 (16.84–18.81)
6.5 to <7 % (48 to <53)	6,867 (18.85)	871	47.69	18.26 (17.09–19.52)
7 to <7.5 % (53 to <58)	6,106 (16.76)	768	42.30	18.16 (16.92–19.48)
7.5 to <8.1 % (58 to <65)	4,944 (13.57)	748	33.71	22.19 (20.65–23.84)
≥8.1 % (≥65)	8,201 (22.52)	1438	53.24	27.01 (25.65–28.44)
Glycaemic variability Categories				
0–20	11,500 (31.57)	1036	76.08	13.61 (12.81–14.47)
21–40	10,268 (28.19)	1471	72.59	20.27 (19.26–21.33)
41–60	8,750 (24.02)	1577	62.76	25.13 (23.92–26.40)
61–80	4,718 (12.95)	832	30.32	27.44 (25.63–29.37)
81–100	1,186 (3.26)	176	6.40	27.52 (23.73–31.90)
HbA1c-Coefficient of variation				
0–6.6	7,247 (19.90)	468	42.44	11.03 (10.07–12.07)
6.7–9.9	7,396 (20.31)	749	49.21	15.22 (14.17–16.35)
10.0–13.9	7,339 (20.15)	1015	51.62	19.66 (18.49–20.91)
14.0–20.1	7,232 (19.86)	1291	52.39	24.64 (23.33–26.02)
≥20.2	7,208 (19.79)	1569	52.49	29.89 (28.45–31.41)

when the baseline CKD stage was replaced in models 2&3 by baseline mean eGFR (see supplemental 15).

4. Discussion

Our findings demonstrated that in a cohort of people with diabetes

and CKD stage 3 or 4 the proportion of clinically significant changes in HbA1c was strongly associated with progression to ESKD. Although the level of risk peaked in the 61–80 variability group and then declined in the 81–100 group to a level similar to the 21–40 group, the data suggest that glycaemic variability is a potentially important risk indicator of ESKD progression in patients. Our data showed a stronger association between HbA1c CV and ESKD than was reported in previous studies of people with Type 2 diabetes. Yang et al. [17] examined the association between HbA1c CV and ESKD in a large dataset of people with Type 2 diabetes (n = 31,204) with a 10-year follow-up, and reported modest increased risk with HR of 1.15 (95 % CI 1.06–1.15) and 1.23 (95 % CI 1.13–1.34) in the two highest quintiles for HbA1c CV, compared with the lowest quintile. The more modest risk observed by Yang and colleagues is likely to be related to their inclusion of patients without significant CKD, with a mean eGFR of 74 mL/min/1.73 m^2 at baseline. In a similar study Chui et al. [25], assessed whether glycaemic variability (SD of HbA1c) contributed to the progression of macroalbuminuria in a much smaller sample of people with Type 2 diabetes with (n = 70) or without (n = 40) established microalbuminuria. While they reported higher progression in those with microalbuminuria and higher SD of HbA1c, the limited sample size and study design make these findings inconclusive. Our findings are in contrast to the study of Lee et al. [18], which reported lower risk in people with CKD with higher glycaemic variability. However, that study was limited by a relatively small sample size (n = 380), a follow-up of only three years, and lower eGFR levels at a baseline of 26 mL/min/1.73 m^2. Hence, we are confident that our study provides more robust estimates of the impact of glycaemic variability in people with CKD ≥stage 3, compared to those studies.

Our study has also added a more specific examination of the risk of glycaemic variability, by using clinically significant changes in HbA1c (≥0.5 %, 5.5 mmol/mol) which provides a potentially more valid estimate of variation compared to the SD or CV of the HbA1c which can be inflated by modest changes between tests over time. Furthermore, using clinical changes in HbA1c rather than average variability enabled us to consider the pattern and directionality of variation. These data showed that glycaemic variability, at the patient level, was mainly comprised of similar numbers of positive and negative changes that were ≥0.5 % (5.5 mmol/mol) in HbA1c. While we reported this distribution of changes in those with >10 changes in the findings, the distribution was consistent in those with 4, 6, or 8 changes (see supplemental file 5). In terms of

Table 3

Unadjusted & adjusted sub-Hazard Ratios (sHR) for ESKD and their 95 % Confidence intervals (95 %CI) by mean HbA1c, glycaemic variability scores, and HbA1c – coefficient of variation categories at baseline.

Variables	Categories	Model 1 (unadjusted)[†] sHR of ESKD (95 % CI)	Model 2 (adjusted)[‡] sHR of ESKD (95 % CI)	Model 3 (adjusted)[§] sHR of ESKD (95 % CI)
Baseline mean HbA1c (%, mmol/mol)	<6.5 % (<48)	1.00	1.000.93	1.000.93
	6.5 to <7 % (48 to <53)	1.031.02	(0.85–1.01)	(0.85–1.02)
	7.0 to <7.5 % (53 to <58)	(0.93–1.11)	**0.85 (0.77–0.93)**	**0.87 (0.79–0.95)**0.92
	7.5 to <8.1 % (58 to <65)	**1.25 (1.14–1.36)**	**0.90 (0.82–0.99)**0.98	(0.84–1.02)1.00
	≥8.1 % (≥65)	**1.53 (1.42–1.65)**	(0.90–1.08)	(0.92–1.09)
Glycaemic variability score	0–20	1.00	1.00	-
	21–40	**1.46 (1.35–1.58)**	**1.38 (1.27–1.50)**	-
	41–60	**1.80 (1.67–1.94)**	**1.54 (1.41–1.68)**	-
	61–80	**1.96 (1.79–2.14)**	**1.61 (1.45–1.79)**	-
	81–100	**1.93 (1.64–2.25)**	**1.42 (1.19–1.68)**	-
HbA1c-CV	0–6.6	1.00	-	1.00
	6.7–9.9	**1.33 (1.19–1.49)**	-	**1.29 (1.15–1.45)**
	10.0–13.9	**1.68 (1.51–1.88)**	-	**1.55 (1.39–1.74)**
	14.0–20.1	**2.10 (1.89–2.33)**	-	**1.79 (1.60–2.01)**
	≥ 20.2	**2.53 (2.28–2.80)**	-	**2.10 (1.88–2.34)**

sHR (95 % CI) shown in **bold** indicates that the 95 % CI does not include 1.

[†] Model 1 Crude association.

[‡] Model 2 Glycaemic variability score adjusted for age, sex, ethnicity, IMD, BMI, baseline CKD, baseline mean HbA1c, total cholesterol, systolic blood pressure, comorbidity count, polypharmacy, smoking status, and duration of diabetes.
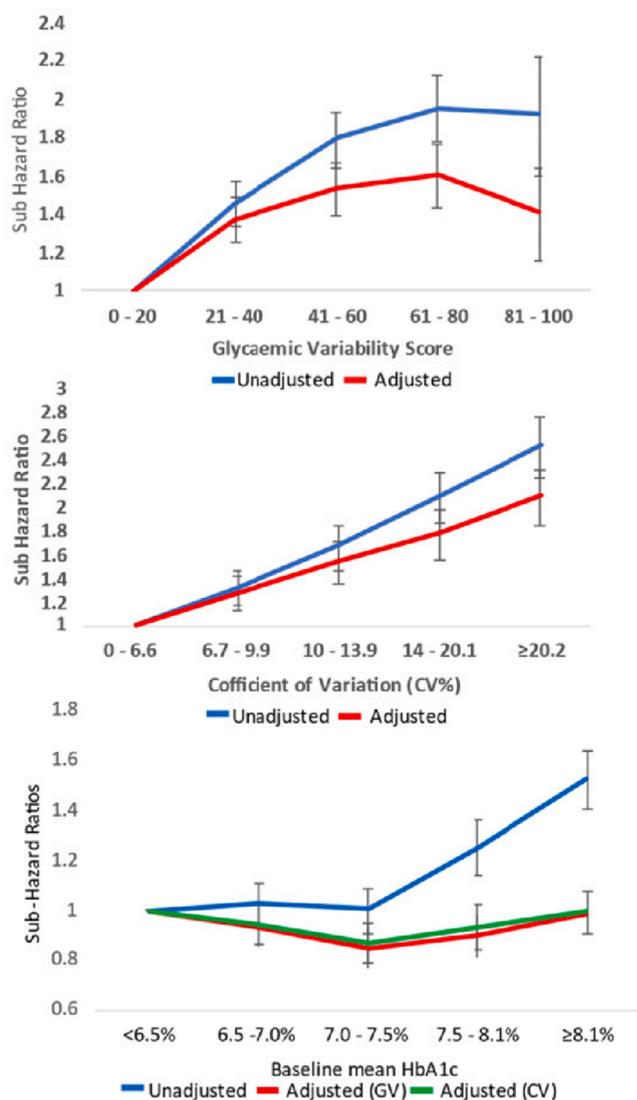
[§] Model 3 HbA1c – Coefficient variation (CV%) adjusted for age, sex, ethnicity, IMD, BMI, baseline CKD, baseline mean HbA1c, total cholesterol, systolic blood pressure, comorbidity count, polypharmacy, smoking status and duration of diabetes.

Fig. 1. Adjusted/Unadjusted sub-HRs glycaemic variability and baseline HbA1c. Adjusted sub-hazard ratios were obtained from the multivariable model containing either glycaemic variability (GV) score or HbA1c coefficient of variation (CV) and age, sex, ethnicity, IMD, BMI, baseline CKD, baseline HbA1c, total cholesterol, systolic blood pressure, comorbidity count polypharmacy smoking status, and duration of diabetes.

directionality, while the number of observations was limited, the risk of ESKD was greatest in those with a decreasing trend. An observation that is most likely explained by the fact that declining kidney function, is associated with a decline in HbA1c levels [18]. Finally, our data suggest that variability was a much more significant predictor of progression when compared to the baseline level of HbA1c levels which showed only very modest associations, with the greatest reduction in risk found in those with an HbA1c ranging from 7.0 to <7.5 % (53 to <58 mmol/mol).

Clinically our findings suggest that when monitoring glycaemic trends in diabetes patients with CKD, it is important to consider not only the absolute level of HbA1c, but also fluctuations in HbA1c over time as a potential risk predictor. Future studies are now needed to establish whether the association between glycaemic variability and progression to ESKD is causal and if so, what the mechanisms might be. It is also possible that the association is bidirectional, with declining kidney function contributing to variability by impacting on insulin excretion rates and erythrocyte survival [26]; and with glucose fluctuations driving the inflammatory process that causes kidney disease by

damaging microvascular structures and impeding endothelial function [27,28]. Patient level factors such as their self-management performance or different combinations of hypoglycaemic agents may also be important mediators of both glycaemic variability and kidney disease. Understanding these mechanisms, particularly those that may be modifiable, could be useful in developing ESKD risk reduction interventions for people with established CKD. Finally, another possible interpretation of our observations is that HbA1c becomes a less reliable measure of glycaemia with declining kidney function, again this needs further investigation.

The study participants with higher glycaemic variability were male; were of Asian ethnicity; were obese (BMI ≥ 30); had higher mean systolic blood pressure; had a longer duration of diabetes and had a high polypharmacy load (≥7 agents). Many of these characteristics that were reported previously to be associated with insulin resistance and adverse cardiovascular outcomes [29] have also been found to be associated with glycaemic variability [13]. GV was positively associated with changes in blood pressure [30,31]. Participants with higher glycaemic variability therefore might have an increased risk of CVD. Although studies report a higher CKD prevalence in females than males, the risk of progression to ESRD appears to be higher among males [32]. Polypharmacy is associated with adverse health outcomes such as increased mortality, falls and adverse drug interactions [33]. Mansnoon et al. (2017) found the risk of adverse effects and harm rises with increasing polypharmacy load [33,34].

4.1. Study limitations

The main limitation of this study is one that is common to all observational studies, and that is it can only provide information on associations and not causality. Nevertheless, we hope by highlighting the association between glycaemic variability and kidney disease progression, we will promote future studies to explore possible causal mechanisms and identify/test compensating treatment models to reduce the hazard or ways of incorporating variability in assessing risk. A further limitation is the use of secondary data via electronic medical records, where there may be issues with data accuracy and completeness [20,35,36]. However, clinical recording in the United Kingdom is supported by performance incentives and the selected study populations are highly monitored within that framework, which requires patients with diabetes to have regular assessment of kidney function. An exception to this was ACR data which was excluded as a confounder because it is no longer adequately reported in UK primary care data. This test for diabetics is no longer part of the department of health's current remuneration scheme for GPs. The CPRD dataset has been shown to be representative of the UK population and has been used in multiple previous studies on both diabetes and kidney disease [20]. An additional point to consider was whether using an accumulative mean HbA1c over the observation period may have provided a more progressive estimate of the interaction of HbA1c on progression compared to the baseline HbA1c. The reason we did not consider this was the complex nature of time-dependent confounding and the high level of mortality in the observation period with 36 % of patients dying during the follow-up. Finally, a further limitation to consider was that it was not possible to distinguish between patients with Type 1 or Type 2 diabetes in the analysis. While we acknowledge that the impact of glycaemic variability may vary somewhat between diabetes types, reliably differentiating them in large primary care datasets is problematic as highlighted in previous analyses of coding reliability in primary care [37,38]. We can broadly assume that 90 % of participants included in the analysis had Type 2 diabetes. We have also included a supplemental analysis where we excluded those with codes for Type 1 diabetes and this did not impact on the findings (see supplemental file 10). Future research examining the association between progression of CKD and glycaemic variability should consider separating patients into either Type 1 or Type 2 diabetics.

In conclusion, this study has demonstrated the association between glycaemic variability (based on either the proportion of clinically significant changes between consecutive records or the coefficient of variation of a patient's HbA1c records), and the risk of developing ESKD. The pattern of glycaemic variability observed was one of fluctuation rather than an increasing or declining trend. Glycaemic variability has a stronger association with kidney disease progression than mean baseline HbA1c. Therefore, more studies are required to explore the potential causes of this association, so we can better understand how to interpret glycaemic variability and kidney disease progression.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110117.

References

[1] Limkunakul C, de Boer IH, Kestenbaum BR, Himmelfarb J, Ikizler TA, Robinson-Cohen C. The association of glycated hemoglobin with mortality and ESKD among persons with diabetes and chronic kidney disease. J Diabetes Complicat 2019;33 (4):296–301.

[2] Reutens AT. Epidemiology of diabetic kidney disease. Med Clin North Am 2013;97 (1):1–18.

[3] Bhansali A, Gogate Y. Clinical rounds in endocrinology volume I - adult endocrinology. New Delhi: Springer India; 2015. p. XVII, 469 p. 161 illus., 114 illus. in color.

[4] McBrien, K.A., et al., Health Care Costs in People With Diabetes and Their Association With Glycemic Control and Kidney Function. 2013. p. 1172-1180.

[5] Helou N, Dwyer A, Shaha M, Zanchi A. Multidisciplinary management of diabetic kidney disease: a systematic review and meta-analysis. JBI Database Syst Rev Implement Rep 2016;14(7):169–207.

[6] Afkarian M, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24(2):302–8.

[7] Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? J Diabetes Complicat 2005;19(3):178–81.

[8] Hanefeld M. Postprandial hyperglycaemia: noxious effects on the vessel wall. Int J Clin Pract Suppl 2002;129:45–50.

[9] Stratton IM, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321(7258):405–12.

[10] ADAPP ADA Committee. 11. Chronic kidney disease and risk management: standards of medical care in diabetes—2022. Diabetes Care 2021;45(Suppl. 1): S175–84.

[11] NICE. Chronic kidney disease: assessment and management. UK: National Institute Clinical Excellence; 2021.

[12] KDIGO. Clinical practice guideline for diabetes management in chronic kidney disease. KDIGO; 2020.

[13] Cheng D et al. HbA1C variability and the risk of renal status progression in diabetes mellitus: a meta-analysis. PLoS ONE 2014;9(12):e115509.

[14] Yan Y, et al. Predictive ability of visit-to-visit variability of HbA1c measurements for the development of diabetic kidney disease: a retrospective longitudinal observational study. J Diabetes Res 2022;2022:6934188.

[15] Lee,CL et al. The variability of glycated hemoglobin is associated with renal function decline in patients with type 2 diabetes. Ther Adv Chronic Dis 2020;11: 2040622319898370.

[16] Luk AOY, et al. Risk association of HbA1c variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: Prospective analysis of the Hong Kong diabetes registry. Diabetes/Metabolism Res Rev 2013;29(5):384–90.

[17] Yang Y-F et al. Visit-to-visit glucose variability predicts the development of end-stage renal disease in type 2 diabetes: 10-year follow-up of Taiwan diabetes study. Medicine 2015;94(44):e1804.

[18] Lee M-Y, et al. Association of HbA1C variability and renal progression in patients with type 2 diabetes with chronic kidney disease stages 3–4. Int J Mol Sci 2018;19 (12):4116.

[19] Habte-Asres HH, Wheeler DC, Forbes A. The association between glycaemic variability and progression of chronic kidney disease: a systematic review. SN Compreh Clin Med 2022;4(1):102.

[20] Herrett E, et al. Data resource profile: clinical practice research datalink (CPRD). Int J Epidemiol 2015;44(3):827–36.

[21] Forbes A, et al. Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. Lancet Diabetes Endocrinol 2018;6(6):476–86.

[22] Vos T, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet 2017; 390(10100):1211–59.

[23] Meeusen JW, et al. Clinical impact of the refit CKD-EPI 2021 creatinine-based eGFR equation. Clin Chem 2022;68(4):534–9.

[24] Inker LA, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385(19):1737–49.

[25] Chiu W-C, et al. HbA1C variability is strongly associated with development of macroalbuminuria in normal or microalbuminuria in patients with type 2 diabetes mellitus: a six-year follow-up study. Biomed Res Int 2020;2020:7462158.

[26] Runesson B, 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(8):1425–35.

[27] Costantino S, et al. Impact of glycemic variability on chromatin remodeling, oxidative stress, and endothelial dysfunction in patients with type 2 diabetes and with target HbA1c levels. Diabetes 2017;66(9):2472–82.

[28] Moen MF, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 2009;4(6):1121–7.

[29] Jang JY, et al. Visit-to-visit HbA1c and glucose variability and the risks of macrovascular and microvascular events in the general population. Sci Rep 2019;9 (1):1374.

[30] Kilpatrick ES, Rigby AS, Atkin SL. Mean blood glucose compared with HbA1c in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia 2008;51(2):365–71.

[31] Gordin D et al. Glucose variability, blood pressure and arterial stiffness in type 1 diabetes. Diabetes Res Clin Pract 2008;80(3):e4–7.

[32] Giandalia A, et al. Gender differences in diabetic kidney disease: focus on hormonal, genetic and clinical factors. Int J Mol Sci 2021;22(11):5808.

[33] Masnoon N, et al. What is polypharmacy? A systematic review of definitions. BMC Geriatrics 2017;17(1):230.

[34] Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf 2014;13(1):57–65.

[35] Menachemi N, Collum TH. Benefits and drawbacks of electronic health record systems. Risk Manag Healthc Policy 2011;4:47–55.

[36] Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 2010;60(572): e128–36.

[37] de Lusignan S, et al. Miscoding, misclassification and misdiagnosis of diabetes in primary care. Diabet Med 2012;29(2):181–9.

[38] Tate AR et al. Quality of recording of diabetes in the UK: how does the GP's method of coding clinical data affect incidence estimates? Cross-sectional study using the CPRD database. BMJ Open 2017;7(1):e012905.