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The Association of Glycated Hemoglobin with Mortality and ESKD among Persons with Diabetes and Chronic Kidney Disease

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Abstract

Context: Diabetic kidney disease (DKD) is the leading cause of end stage kidney disease (ESKD) and is associated with a considerably shortened lifespan. While glucose-lowering therapy targeting glycated hemoglobin (HbA1c) <7% is proven to reduce the risk of developing DKD, its effects on complications of DKD are unclear.

Objective: We examined the associations of HbA1c with risks of progression to ESKD and death within a clinic-based study of CKD. We hypothesized that higher HbA1c concentrations would be associated with increased risks of ESKD and death.

Design and Setting: We studied 618 participants from the Seattle Kidney Study (mean eGFR 42ml/min), 308 of whom had diabetes, and tested associations of baseline HbA1c with time to a composite outcome of initiation of renal replacement therapy or death.

Results: During a median follow-up of 4.2 years, there were 343 instances of the composite outcome (11.5 per 100 person-years). Among participants with diabetes, in both crude and adjusted analyses, higher HbA1c levels (examined continuously or categorically) were not associated with the risk of the composite outcome (HR (95% CI): 0.99 (0.88, 1.10) per 1% additional HbA1c, p=0.79). HbA1c was not associated with ESKD or mortality when the outcomes were examined separately, nor when stratified between insulin users and non-users.

Conclusion: In a referred population of established DKD, higher HbA1c was not associated with higher risk of ESKD or death. These data support current recommendations to be

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conservative with glycemic control among patients with advanced diabetes complications, such as CKD.

Keywords

chronic kidney disease; diabetes; HbA1c

Introduction

Chronic kidney disease (CKD), manifesting as albuminuria or impaired glomerular filtration rate (eGFR <60 ml/min/1.73m²), present for 3 months or longer, is a common and morbid complication of diabetes.^{1–3} The prevalence of diabetic kidney disease (DKD) has grown substantially over the past 20 years, driven by the rising underlying prevalence of obesity and diabetes.⁴ Moreover, persons with diabetes and CKD are at high risk of adverse clinical outcomes, including progression to ESKD and death.^{5,6}

Intensive glucose-lowering therapy is proven to reduce the risk of developing DKD.^{7–9} However, the effects of intensive glucose-lowering therapy on progression of existing DKD are unclear. In particular, beneficial effects of intensive glucose-lowering manifest over many years of follow-up – beyond the time frame required for some patients at imminent risk of progressive disease – and hyperglycemia may contribute less to the fibrotic process leading to progressive loss of GFR than to the injuries initiating diabetic glomerulopathy. Moreover, the effects of intensive glucose-lowering on cardiovascular disease (CVD), which commonly complicates DKD, are controversial. For example, in the ACCORD trial, an intensive glucose-lowering strategy targeting glycated hemoglobin (HbA1c) $<6.5\%$ increased the risk of death.¹⁰ Risks of intensive glucose-lowering therapy may be increased in patients with established DKD due to impaired clearance of drug used to lower blood glucose, an impaired counter-regulatory response, and an increased burden of co-morbidity.

In order to help define the risk-benefit balance of tight glycemic control among persons with diabetes and established CKD, we examined the associations of HbA1c with risks of progression to ESKD and death in a well-characterized Nephrology clinic-based cohort. We hypothesized that higher HbA1c concentrations would be associated with increased risks of ESKD and death.

Materials and Methods

Study population

The Seattle Kidney Study (SKS) is a prospective cohort study recruited from nephrology clinics associated with the University of Washington, Seattle, WA, including: the Puget Sound Veterans Affairs Health Care System, Harborview Medical Center, and the University of Washington Medical Center.^{11,12} The SKS began recruiting in 2004 and is currently ongoing. Inclusion criteria are age ≥ 18 years and either an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m² or a urinary protein to creatinine ratio ≥ 30 mg/g. Exclusion criteria are dialysis, previous kidney transplant, inability to provide informed consent, and expectation of dialysis initiation within 3 months. Of the 693 participants

enrolled through May 23, 2017, this study excludes 75 participants for whom no HbA1c was measured as part of a routine study visit. This study was approved by the University of Washington Institutional Review Board.

Hemoglobin A1c

HbA1c was measured at baseline from fresh whole blood using high performance liquid chromatography, certified by the National Glycohemoglobin Standardization Program (NGSP). Diabetes was defined as HbA1c $\geq$ 6.5% or use of glucose-lowering medications.¹³

Study outcomes

Study coordinators screened for major events (hospitalizations, procedures, and dialysis) in 2 ways: annual study examinations and interim (at 6 months) telephone interviews. Death and ESKD were also ascertained during follow-up through linkage with the National Death Index and the United States Renal Data System (USRDS). The primary study outcome was a composite of ESKD or death. This composite was chosen to reflect endpoints that are clinically relevant to patients with DKD and which reduce the potential for competing risks in outcome ascertainment. ESKD was defined as the initiation of maintenance dialysis or kidney transplantation. ESKD and death were also evaluated individually as secondary outcomes.

Covariates

All covariates were ascertained concurrently with HbA1c measurement. Blood samples were collected after an overnight fast and urine was collected as timed overnight voids. Other than HbA1c, which was measured on fresh blood, serum, plasma, and urine were stored at -80°C until analysis. Glomerular filtration rate was estimated from serum creatinine and serum cystatin C using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) combined equation.¹⁴ Concentrations of albumin, low density lipoprotein (LDL) cholesterol, C-reactive protein (CRP) were measured in serum. Urine albumin-to-creatinine ratio (ACR) was measured in spot morning or overnight urine collections. Smoking status (current, former, or never), and previous medical disease history were ascertained by health questionnaire. Medications were ascertained from the computerized pharmacy database or by direct transcription of medication bottle labels. Blood pressure was measured 3 times 5 minutes apart on an automated sphygmomanometer, with the last two measurements averaged for analysis. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or use of antihypertensive medications.¹⁵ Prevalent coronary artery disease (CAD) was defined as a self-reported history of myocardial infarction, cardiac arrest, coronary artery bypass graft, or percutaneous coronary intervention.

Statistical analysis

We tabulated participant characteristics with respect to diabetes status and HbA1c category. Participants were considered at risk from the date of their baseline exam until the first occurrence of the primary outcome, or their data were censored due to loss to follow-up, or

end of data collection, defined as January 22, 2018. In models assessing only ESKD as an outcome, participants were censored for death, but not vice versa.

We calculated unadjusted incidence rates as the number of events divided by person-years at risk. We used Cox proportional hazards regression to estimate the relative hazard of an event after adjustment for covariates selected *a priori* based on suspicion that they may confound the association between HbA1c and the combined event. The first, basic model included age (continuous), sex, and race. The second model added eGFR and log-transformed ACR. The third model additionally included smoking status, body mass index, systolic blood pressure, LDL, prevalent CAD, albumin, and log-transformed CRP. A final model additionally included use of oral hypoglycemic medications (yes/no) and insulin (yes/no).

Approximately 7% or less of the study participants were missing data on urine ACR, smoking status, body mass index, albumin, or CRP. For the regression analyses, these participants' values were multiply imputed using chained equations.¹⁶ The multiple analyses over the imputations were combined using Rubin's rules to account for the variability in the imputation procedure.¹⁷

All participants had at least two longitudinal measures of HbA1c. We conducted a secondary analysis in which we used the time-updated HbA1c as the exposure of interest. Because insulin use may increase the risk of hypoglycemia, we performed a sensitivity analysis among diabetics comparing the association of HbA1c with study outcomes among insulin users and non-users. All p-values were two-tailed ($\alpha=0.05$) and analyses were conducted using STATA version 15.1 (College Station, TX).

Results

Patient characteristics

The study population was characterized by a mean age of 60 years, 67% of patients were men. Compared to participants without diabetes, those with diabetes were older, were more likely to have prevalent coronary artery disease (34% vs. 25%) and were characterized by higher body mass index and systolic blood pressure, and lower eGFR. Among participants with diabetes, higher HbA1c did not appear to be linearly correlated with any of the examined baseline characteristics (Table 1).

Composite outcome

During a median follow-up of 4.2 years (interquartile range 2.3 to 7.2 years), there were 343 instances of the composite outcome (11.5 per 100 person-years), of which the first event was death in 158 individuals. Participants with diabetes had higher unadjusted incidence rates of the composite outcome within any category of baseline HbA1c, compared to individuals without baseline diabetes: range 12.4 – 20.1 *versus* 8.2 per 100 person-years (Figure 1). Among participants with diabetes, in both crude and adjusted analyses, higher HbA1c levels were not associated with the risk of the composite outcome (in fully adjusted analyses: 1% lower risk of composite outcome per 1% higher HbA1c, 95% CI: 12% lower to 10% higher, $p=0.79$) (Table 2).

End stage kidney disease outcome

Median follow-up for initiation of dialysis or kidney transplantation was 4.4 years (interquartile range 2.4 to 7.4 years). Progression to ESKD occurred in 185 participants (6.07 per 100 person-years), 73 in non-diabetics (4.41 per 100 person-years) and 112 in diabetics (8.04 per 100 person-years). This higher rate of ESKD among diabetics was present across all categories of HbA1c (Figure 1). Among participants with diabetes, HbA1c was not associated with risk of ESKD (fully adjusted model, per 1% higher HbA1c: HR (95% CI): 1.06 (0.90, 1.25), $p=0.46$) (Table 2).

Mortality outcome

During a median follow-up of 5.0 years (interquartile range 3.1 to 8.7 years), there were 232 deaths (6.48 per 100 person-years), predominantly in men (200 deaths in men (7.7 deaths per 100 person-years) and 32 in women (3.3 deaths per 100 person-years)). Unadjusted mortality rates were higher among participants with diabetes (8.78 per 100 person-years in diabetic participants *versus* 4.43 per 100 person-years in non-diabetics), within any category of baseline HbA1c (Figure 1). HbA1c levels were not associated with mortality among diabetic participants and were not materially altered with adjustment for potential confounding factors (Table 2).

Associations among subgroups

Among participants with diabetes who were receiving insulin therapy, HbA1c was not associated with risk of ESKD, death, or the combined outcome (Table 3). Similarly, among participants with diabetes who were not receiving insulin therapy, HbA1c was not associated with the risk of any examined event.

Discussion

Limited studies have focused on the relevance of control of hyperglycemia, as measured by HbA1c, among people with diabetes and CKD. In our clinic-based CKD population, circulating levels of HbA1c were not associated with reduced risk of a composite outcome of ESKD and death.

Several studies have demonstrated that HbA1c levels are associated with adverse outcomes in individuals with early-stage CKD. A large population-based study from Alberta, Canada, of 23,296 people with $eGFR < 60 \text{ ml/min/1.73}$ and diabetes, found that higher HbA1c levels were strongly and independently associated with death, progression of kidney disease, cardiovascular events, and all-cause hospitalization.¹⁹ However, mean $eGFR$ in these individuals was higher than in our clinic-based cohort, and the authors reported an attenuated association of HbA1c with outcomes at lower baseline $eGFR$.¹⁹ Similarly, a recent study from Taiwan found associations of higher HbA1c with a combined outcome of ESKD, all-cause mortality, and combined cardiovascular events among individuals with mild-moderate, but not severe CKD.²⁰

Recent studies have also reported U-shaped associations between HbA1c and mortality.^{19,21} In our study, individuals with $HbA1c < 6.5\%$ had the highest mortality rates, although this

difference was not statistically significant. Observed associations of low HbA1c (<6.5%) with increased risks of death may be due to confounding, non-glycemic causes of low HbA1c, true adverse effects of low glucose concentrations, or adverse effects of the treatments used to attain low glucose concentrations. Comorbidity and poor nutritional status could potentially lead to low HbA1c and confound the association of HbA1c with and death. However, we noted no strong association of these clinical characteristics with HbA1c in our population at baseline, and adjustment for comorbidities did not substantially affect our results. Erythropoietin treatment can reduce HbA1c without changing blood glucose, potentially introducing confounding by anemia and its treatment, but excluding participants using erythropoietin also did not affect our results.

Hypoglycemia occurs more commonly in advanced CKD as a consequence of the altered sensitivity to or clearance of insulin and prolonged insulin half-life resulting in absolute or relative insulin excess and/or combination of compromised glucose counter regulation.^{22–28} Mechanistic studies directly investigating the link between hypoglycemia and progression of CKD are lacking. Hypothetically, however, recurrent hypoglycemia may lead to worse progression of underlying kidney disease via the aggravation of micro-vascular complications attributable to the subclinical inflammatory response shown to occur after induction of hypoglycemic conditions.^{29–31} Recent data also show that hypoglycemia can provoke immediate oxidative stress through generation of free radicals and toxin products and inhibition of antioxidants enzymes.³² Low glucose exposure rapidly impairs nitric oxide (NO) bioavailability and endothelial function in the human endothelium and might explain why recurrent hypoglycemia might worsen the triad of oxidative stress, endothelial dysfunction and inflammation in patients with DKD. In addition, a greater increase in the concentration of von Willebrand factor has also been observed during hypoglycemia, which might reduce intraglomerular perfusion in diabetic patients.³³ Hypoglycemia could induce several counterregulatory responses including sympathoadrenargic response with increased catecholamine release.³⁴ Hypoglycemia is also associated with cardiac arrhythmia, impaired cardiovascular autonomic function which may increase with mortality among rigorous glycemic control.^{35–38}

Notably, due to the time-frame of the study, none of the participants in the SKS cohort were using SGLT2-inhibitors or GL1R agonists. Among participants using these medications, the findings may be different, either by allowing safer glucose-lowering or by providing non-glycemic benefits that go along with HbA1c lowering with those drugs but not the drugs used in this cohort.

The clinical and research implication of our study is that among CKD patients with established diabetes mellitus our results point out the need for cautious approach. A more customized approach to target HbA1c levels might be necessary to prevent the adverse effects of over treatment in these patients. Long term diabetes may cause autonomic dysfunction and “hypoglycemic un-awareness”³⁹ and “self-monitoring glucose” should be emphasized and routinely done in diabetic CKD to prevent subclinical hypoglycemic episodes. Finally, these data suggest that glycemic control alone may be insufficient to account for the progression of diabetic complications, especially in diabetic CKD patients.

Other metabolic abnormalities such as oxidative stress, inflammation, and deranged HDL metabolism could be in effect to explain the variability in kidney disease onset.

This study has certain strengths and limitations. The strengths of our study were the prospective cohort, the data collected by the protocol and designed with a validated method. The most important limitation of our study is that it is observational and causality cannot be inferred from the results. While we adjusted for an extensive list of variables, there still might residual confounding influencing the results. Most patients had only a single HbA1c measurement available, and the follow-up time for adverse events was relatively short for the effects of glycemic control. It is also possible that HbA1c assay may not be the most reliable marker of glycemic control in CKD patients, especially in later stages. While glycosylated albumin is proposed to be a better marker in CKD patients, its validity as a reliable marker in CKD is not established either. Finally, our study is performed in a tertiary care clinic with intensive and careful data collection. The patient population was mostly male and white and the results cannot be readily generalized to all populations. Accordingly, the data presented in this study must be interpreted with caution.

In conclusion, in a referred population of established DKD, higher HbA1c was not associated with higher risk of ESKD or death. The safety of intensive glycemic control (HbA1c <7%) in patients with DKD should be reassessed by future prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Incidence of the primary composite outcome of end stage kidney disease or death and each of its components by diabetes status and hemoglobin A1c

Table 1.

Baseline Characteristics of Seattle Kidney Study Participants (n=618)

	No DM	Participants with diabetes, HbA1c (%)		
		<7	[7–8)	≥8
N	310	142	81	85
Age at baseline (years)	57.6 (+15.0)	64.0 (+11.3)	61.9 (+12.1)	58.2 (+13.0)
Male gender	190 (61.3)	102 (71.8)	62 (76.5)	63 (74.1)
White Race	202 (65.2)	93 (65.5)	51 (63.0)	42 (49.4)
Current smoking	58 (19.4)	17 (12.4)	14 (17.7)	15 (18.1)
College education or higher	100 (34.1)	37 (27.6)	25 (32.1)	16 (21.6)
Body mass index (kg/m ²)	29.8 (+7.0)	33.1 (+7.7)	33.5 (+8.5)	32.4 (+7.7)
Systolic blood pressure (mmHg)	129.1 (+21.2)	136.7 (+23.4)	138.3 (+22.0)	135.7 (+23.0)
<i>Labs</i>				
Albumin (g/dL)	3.8 (+0.6)	3.8 (+0.6)	3.7 (+0.6)	3.6 (+0.6)
Creatinine (mg/dL)	2.0 (+1.2)	2.3 (+1.4)	2.2 (+1.1)	2.2 (+1.3)
C-reactive protein (mg/L)	4.7 (+9.5)	5.5 (+10.0)	5.1 (+7.8)	4.4 (+5.7)
Cystatin C (mg/L)	1.7 (+0.7)	2.0 (+0.8)	1.9 (+0.7)	2.0 (+0.9)
Glucose (mg/dL)	98.4 (+28.0)	129.3 (+51.8)	143.6 (+61.0)	192.3 (+90.9)
Hemoglobin (g/dL)	12.9 (+1.9)	12.2 (+1.8)	12.4 (+1.8)	12.4 (+2.0)
Hemoglobin a1c (%)	5.6 (+0.6)	6.3 (+0.5)	7.4 (+0.3)	9.4 (+1.5)
Albumin to creatinine ratio (mg/g)	105 (16, 399)	329 (34, 1385)	425 (33, 1851)	418 (97, 1191)
Estimated GFR, ml/min/1.73m ²	45.4 (+25.1)	36.8 (+18.8)	38.5 (+22.6)	40.1 (+22.2)
<i>Medications</i>				
Ace Inhibitor Use	135 (43.5)	82 (57.7)	42 (51.9)	47 (55.3)
ARBs use	79 (25.5)	46 (32.4)	41 (50.6)	37 (43.5)
Statin use	139 (44.8)	103 (72.5)	53 (65.4)	64 (75.3)
Erythropoietin Use	9 (2.9)	14 (9.9)	7 (8.6)	1 (1.2)
<i>Diabetes medication</i>				
Oral	0 (0.0)	38 (62.3)	38 (48.1)	20 (42.6)
Insulin	0 (0.0)	59 (41.5)	44 (54.3)	61 (71.8)
<i>Prevalent Disease</i>				
Any coronary artery disease	77 (24.8)	51 (35.9)	27 (33.3)	26 (30.6)
Any hypertension	280 (90.3)	140 (98.6)	81 (100.0)	83 (97.6)

Data are crude means ±SD or median (IQR) for continuous variables and number (proportion) for categorical variable.

Associations of hemoglobin A1c with the primary composite outcome of end stage kidney disease or death and with each of its components among participants with diabetes and chronic kidney disease.

Table 2:

	Number of Events (IR, per100p-y)	Adjusted HR (95% CI)			
		Model 1	Model 2	Model 3	Model 4
Composite outcome					
<i>Hemoglobin A1c category</i>					
<7%	88 (14.9)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
7–8%	57 (17.1)	1.01 (0.72,1.40)	1.15 (0.81,1.65)	1.06 (0.72,1.58)	1.01 (0.68,1.52)
8%	64 (15.5)	1.15 (0.82,1.61)	1.24 (0.86,1.78)	1.21 (0.81,1.79)	1.18 (0.79,1.75)
<i>Continuous hemoglobin A1c, per 1% higher</i>		0.98 (0.89,1.07)	1.03 (0.93,1.13)	1.00 (0.90,1.11)	0.99 (0.88,1.10)
p-value		0.63	0.57	0.99	0.79
End stage kidney disease					
<i>Hemoglobin A1c category</i>					
<7%	47 (7.4)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
7–8%	32 (9.4)	0.85 (0.54,1.35)	1.15 (0.68,1.94)	1.00 (0.55,1.81)	0.93 (0.51,1.71)
8%	33 (7.9)	1.10 (0.70,1.73)	0.95 (0.56,1.60)	1.01 (0.57,1.80)	1.05 (0.59,1.87)
<i>Continuous hemoglobin A1c, per 1% higher</i>		0.92 (0.81,1.05)	1.08 (0.93,1.25)	1.08 (0.92,1.27)	1.06 (0.90,1.25)
p-value		0.21	0.29	0.33	0.46
Death					
<i>Hemoglobin A1c category</i>					
<7%	65 (8.7)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
7–8%	38 (8.6)	1.25 (0.85,1.85)	1.38 (0.92,2.06)	1.37 (0.87,2.14)	1.40 (0.88,2.20)
8%	45 (9.0)	1.05 (0.70,1.57)	1.02 (0.67,1.56)	1.15 (0.74,1.80)	1.15 (0.73,1.80)
<i>Continuous hemoglobin A1c, per 1% higher</i>		1.06 (0.95,1.18)	1.08 (0.97,1.21)	1.05 (0.93,1.19)	1.06 (0.93,1.20)
p-value		0.31	0.16	0.41	0.38

Model 1 included age, sex, and race; Model 2 additionally adjusted for eGFR (CKD-EPI) and log ACR; Model 3 additionally adjusted for prevalent CAD, smoking status, BMI, systolic blood pressure, albumin, LDL, and log CRP; Model 4 added use of oral hypoglycemic medications and insulin.

Table 3:

Associations of hemoglobin A1c with the primary composite outcome of end stage kidney disease or death and with each of its components among participants with diabetes and chronic kidney disease, by insulin medication use.

	Diabetic insulin users (n=162)		Diabetic insulin non-users (n=144)	
Composite outcome	Number of Events (IR, per 100 p-y)	Adjusted HR (95% CI)	Number of Events (IR, per 100 p-y)	Adjusted HR (95% CI)
<i>Hemoglobin A1c category</i>				
<7%	42 (22.5)	1.00 (Ref.)	46 (11.4)	1.00 (Ref.)
7–8%	34 (20.0)	1.20 (0.70,2.05)	23 (14.1)	1.14(0.64,2.03)
8%	43 (15.5)	0.92 (0.55,1–55)	21 (15.4)	1.18 (0.65,2.15)
<i>Continuous hemoglobin A1c, per 1% higher</i>		0.94 (0.82,1–08)		1.08 (0.90,1.29)
p-value		0.39		0.43
End stage kidney disease				
<i>Hemoglobin A1c category</i>				
<7%	27 (13.6)	1.00 (Ref.)	20 (4.6)	1.00 (Ref.)
7–8%	22 (12.8)	1.17 (0.56,2.43)	10 (5.9)	0.87 (0.35,2.17)
8%	25 (9.0)	0.91 (0.45,1.85)	8 (5.7)	1.09 (0.38,3.08)
<i>Continuous hemoglobin A1c, per 1% higher</i>		1.05 (0.87,1.26)		1.10 (0.82,1.49)
p-value		0.61		0.52
Death				
<i>Hemoglobin A1c category</i>				
<7%	28 (10.0)	1.00 (Ref.)	37 (7.9)	1.00 (Ref.)
7–8%	20 (8.0)	1.24 (0.65,2.35)	18 (9.5)	1.07 (0.56,2.04)
8%	29 (8.4)	1.30 (0.69,2.44)	15 (10.5)	1.52 (0.80,2.90)
<i>Continuous hemoglobin A1c, per 1% higher</i>		1.03 (0.88,1.20)		1.12 (0.90,1.39)
p-value		0.72		0.32

* adjusted for age (continuous), sex, and race, GFR (CKD-EPI), log ACR