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Original Investigation

Diabetes Control and the Risks of ESRD and Mortality in Patients With CKD

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Background: Diabetes is the leading cause of end-stage renal disease (ESRD) and a significant contributor to mortality in the general population. We examined the associations of hemoglobin A_{1c} (HbA_{1c}) levels with ESRD and death in a population with diabetes and chronic kidney disease (CKD).

Study Design: Cohort study.

Setting & Participants: 6,165 patients with diabetes (treated with oral hypoglycemic agents and/or insulin) and CKD stages 1 to 5 at a large health care system.

Predictor: HbA_{1c} level (examined as a categorical and continuous measure).

Outcomes: All-cause and cause-specific mortality ascertained from the Ohio Department of Health mortality files and ESRD ascertained from the US Renal Data System.

Results: During a median 2.3 years of follow-up, 957 patients died (887 pre-ESRD deaths) and 205 patients reached ESRD. In a Cox proportional hazards model, after multivariable adjustment including for kidney function, HbA_{1c} level $< 6\%$ was associated with higher risk for death when compared with HbA_{1c} levels of 6% to 6.9% (HR, 1.23; 95% CI, 1.01-1.50). Similarly, HbA_{1c} level $\geq 9\%$ was associated with higher risk for all-cause death (HR, 1.34; 95% CI, 1.06-1.69). In competing-risk models, baseline HbA_{1c} level was not associated with ESRD. For cause-specific mortality, diabetes accounted for >12% of deaths overall and >19% of deaths among those with HbA_{1c} levels $> 9\%$.

Limitations: Small proportion of participants with advanced kidney disease; single-center population.

Conclusions: In this cohort of patients with CKD with diabetes, HbA_{1c} levels $< 6\%$ and $\geq 9\%$ were associated with higher risk for death. HbA_{1c} levels were not associated with ESRD in this specific CKD population. Diabetes-related deaths increased with higher HbA_{1c} levels.

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INDEX WORDS: Glycated hemoglobin; HbA_{1c}; end stage renal disease (ESRD); diabetes mellitus; diabetes control; incident ESRD; chronic kidney disease (CKD); death and kidney disease; diabetic nephropathy; mortality.

Diabetes is considered as a coronary artery disease equivalent, and the presence of diabetes and chronic kidney disease (CKD) poses the highest risk for death compared to diabetes or CKD alone.[1,2] The prevalence of diabetic kidney disease is also increasing, and diabetic nephropathy is the leading cause of end-stage renal disease (ESRD).[1,3,4] What constitutes an ideal glycated hemoglobin (hemoglobin A_{1c} [HbA_{1c}]) level has been a matter of debate, and some clinical trials in the general population have reported that intensive glycemic control in diabetic patients is associated with adverse outcomes.[5-8] Based on available evidence, the American Diabetes Association has recommended targeting an HbA_{1c} level $< 7\%$ for most nonpregnant adults and $<8\%$ for those at risk for hypoglycemia, extensive comorbid conditions, and long-standing diabetes.[9]

Few studies have evaluated associations between HbA_{1c} levels and clinical outcomes in those with CKD. Shurraw et al[10] reported that HbA_{1c} levels $> 9\%$ were associated with worse clinical outcomes, such as faster kidney disease progression, more cardiovascular events, and increased mortality, among patients with non−dialysis-dependent CKD. In addition, lower HbA_{1c} levels ($<6.5\%$) were associated with higher hazards of death. Findings from a cohort of Taiwanese adults with type 2 diabetes showed that HbA_{1c} levels $> 7.0\%$ were associated with increased risk for ESRD compared with HbA_{1c} levels of 6% to 7%, but HbA_{1c} levels $< 6.0\%$ were also associated

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with increased risk for ESRD.[11] However, a secondary analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial reported that tighter glycemic control in patients with CKD was associated with a significant increase in cardiovascular and all-cause mortality.[12] Although secondary analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) trial reported a reduced risk for ESRD with intense glucose control, no significant effects of intensive glycemic control on ESRD were noted in other studies.[13,14] Patients with CKD are generally at higher risk for hypoglycemia, making a case for avoiding intense glycemic control in this population.[15] Hence, given these inconsistent findings in the literature, we examined associations between HbA_{1c} levels and ESRD and death in a cohort of patients with diabetes and non−dialysis-dependent CKD receiving care in a large US health care system.

METHODS

Overview

We conducted an analysis using a pre-existing electronic medical record (EMR)-based CKD registry. The development and validation of this registry at Cleveland Clinic has been described in detail previously.[16] This study and the CKD registry were approved by the Cleveland Clinic Institutional Review Board (IRB #09-015). Informed consent was not obtained because these data were developed using electronic medical records and Cleveland Clinic has an opt-in policy for collecting data for research purposes using electronic medical records.

Study Population

Patients who were residents of Ohio and had (1) at least 1 outpatient encounter with a Cleveland Clinic health care provider and either 2 estimated glomerular filtration rate (eGFR) values < 60 mL/min/1.73 m^2 more than 90 days apart or *International Classification of Diseases, Ninth Revision* codes for various kidney diseases, (2) diabetes and were using oral hypoglycemic agents and/or insulin, and (3) HbA_{1c} measured in the year prior to the second eGFR < 60 mL/min/1.73 m^2 or a CKD diagnosis were included (Fig S1, available as online supplementary material). Patients younger than 18 years and those who already had ESRD diagnosed (ie, dialysis dependent or having received a kidney transplant) were excluded. Patients who met the inclusion/exclusion criteria from January 1, 2005, to September 15, 2009, were included in this analysis.

Definitions and Outcome Measures

Demographics, Comorbid Conditions, and Laboratory Parameters

Demographic details were extracted from the EMR. Diabetes mellitus, hypertension, coronary artery disease, and other comorbid conditions were defined using prespecified criteria and validated. Relevant outpatient laboratory values were obtained from the EMR. Medication details were obtained from the EMR and were validated in the past. The automated chemistry laboratory at Cleveland Clinic runs HbA_{1c} testing on a Roche Integra 800 platform using a method called TinaQuant Gen2, an immune-based turbidimetric assay. It measures both hemoglobin concentration and HbA_{1c} concentration, then calculates the glycated hemoglobin percentage. The laboratory follows the National Glycohemoglobin Standardization Program guidelines for standardizing these measures. Baseline HbA_{1c} measurements in the year prior to the second eGFR < 60 mL/min/1.73 m^2 or diagnosis of CKD were used in this study, and when multiple measurements were available for a patient, the result closest to the date of diagnosis of CKD was selected for analytical purposes. For the time-dependent repeated-measures analysis, we included the baseline HbA_{1c} value and the first HbA_{1c} value measured each month during study follow-up. We used carry-forward values to fill in data for months when HbA_{1c} data were not available.

Kidney Function Measures

All creatinine measurements were performed by the modified kinetic Jaffé reaction using an Hitachi D 2400 Modular Chemistry Analyzer thereafter (Roche Diagnostics) at the Cleveland Clinic laboratory. In patients who had at least 2 serum creatinine levels measured 90 days apart during January 2005 to September 15, 2009, at the Cleveland Clinic health system,[17] the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation was used to calculate eGFR. Urinary protein studies were not available for the entire study population. Therefore, to be comprehensive and reflect clinical practice, patients who had urine dipstick measurements, urine albumin-creatinine ratio, urine protein-creatinine ratio, and 24-hour urine studies were included to assess whether they had proteinuria. The following cutoffs were considered in determining whether someone had proteinuria: presence of proteinuria $\geq 1+$ in dipstick studies, >30 mg/g in those who had urine albumin-creatinine ratio and urine protein-creatinine ratio studies, and proteinuria with protein excretion $>$ 30 mg in 24-hour studies. Urinalysis chemstrip is performed on the iRICELL 3000 using iChem VELOCITY test strips (both Beckman Coulter) or on the AX-4280 using AUTION 9EB test strips (both ARKRAY).

Urine albumin was measured by immunoturbidimetric assay with antigen excess check, and urine creatinine was measured using a multistep enzymatic procedure that produces a quinone imine chromogen on the Roche Modular platform at the Cleveland Clinic laboratory.

Outcome Measures

The primary outcomes of interest were all-cause mortality and ESRD. ESRD was defined as the need for renal replacement therapy: dialysis or transplantation. Mortality details were ascertained from the Ohio Department of Health mortality files, which also provided cause-specific mortality data[18]; deaths from the Cleveland Clinic EMR were also captured. Incident treated ESRD was ascertained from linkage of our registry with the US Renal Data System (USRDS). Patients were followed up from their date of inclusion in the registry until September 15, 2009.

Statistical Analysis

Baseline characteristics among strata of HbA_{1c} levels ($<$6, 6%-6.9%, 7%-7.9%, 8%-8.9%, and $\geq$9%) were compared using χ^2 and analysis of variance tests for categorical and continuous variables, respectively. These categories were chosen because they are used in clinical practice and other studies. To evaluate whether unadjusted survival and ESRD among persons with CKD was associated with baseline HbA_{1c} levels, we fitted cumulative incidence functions that adjusted for competing risks using the Fine and Gray method with date of second eGFR < 60 mL/min/1.73 m^2 or date of CKD diagnosis as the time of origin. We tabulated causes of death for all deaths (both before and after ESRD).

We evaluated the independent relationship between various baseline HbA_{1c} categories and pre-ESRD mortality using a Cox proportional hazards regression model with HbA_{1c} levels of 6% to 6.9% as the reference group. We also used Fine and Gray's