Glycosylated Hemoglobin and Mortality in Patients with Nondiabetic Chronic Kidney Disease

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In the general population, hyperglycemia in the absence of diabetes may be associated with increased risk for mortality. Hyperglycemia is prevalent in chronic kidney disease; however, the relationship between glycosylated hemoglobin (HbA1c) as a marker of chronic hyperglycemia and outcomes has not been studied in nondiabetic chronic kidney disease. HbA1c was measured at baseline in the randomized cohort of the Modification of Diet in Renal Disease Study (n = 840). Participants with diabetes (n = 43), fasting glucose levels >126 mg/dl (n = 20), or missing HbA1c levels (n = 9) were excluded. Survival status until December 2000 was obtained from the National Death Index. Death was classified as cardiovascular (CVD) when the primary cause was International Classification of Disease, Ninth Revision codes 390 to 459. Cox models were performed to assess the relationship of HbA1c with all-cause and CVD mortality. Mean (SD) age was 52 (12) years, and mean (SD) GFR was 32 (12) ml/min per 1.73 m². Eighty-six percent of participants were white, and 61% were male. Mean (SD) HbA1c was 5.6% (0.5). A total of 169 (22%) patients died, 96 (13%) from CVD. After adjustment for randomization assignments and demographic, CVD, and kidney disease factors, HbA1c was a predictor of all-cause mortality (hazard ratio per 1% increase 1.73; 95% confidence interval 1.24 to 2.41; P = 0.001). There was a trend toward statistical significance in the relationship between HbA1c and CVD mortality (hazard ratio per 1% increase 1.53; 95% confidence interval 0.96 to 2.43; P = 0.07). HbA1c is associated with increased mortality in nondiabetic kidney disease. Hyperglycemia may be a potential therapeutic target and HbA1c may be important as a risk stratification tool in this high-risk population.


D iabetes is an established cardiovascular (CVD) risk factor; however, a growing literature indicates that the relationship between glucose levels and CVD may extend below the threshold currently defined as diabetes. Impairments in glucose metabolism, manifest as hyperglycemia, are associated with poor prognosis in the general population, in the absence of diabetes (1–5).

Chronic kidney disease (CKD) is a growing public health problem of epidemic proportions; currently approximately 9 million people in the United States have GFR of <60 ml/min per 1.73 m² (6). Reduced kidney function is now recognized as a powerful and independent risk factor for CVD morbidity and mortality (7,8). The relationship between CKD and CVD does not seem to be fully explained by traditional CVD risk factors (9,10).

Disorders of glucose homeostasis are common in CKD. Two studies using data from the Third National Health and Nutrition Examination Survey found a high prevalence of impaired fasting glucose levels (defined as >110 mg/dl) among individuals with reduced GFR and those with microalbuminuria (11,12). That kidney disease is characterized by hyperglycemia raises the possibility that impaired glucose metabolism may be an important contributor to the excess CVD risk seen in this population. No prospective studies, however, have evaluated the relationship between hyperglycemia and outcomes among nondiabetic patients with CKD.

Glycosylated hemoglobin (HbA1c), a measure of chronic hyperglycemia, is a sensitive and reliable marker of impaired glucose metabolism (13,14). Some studies have shown HbA1c to be a predictor of future CVD events among nondiabetic patients in the general population (15,16), whereas others have found no association (17) or an association only in women (13,18). Using data from the randomized cohort of the Modification of Diet in Renal Disease (MDRD) Study, we performed longitudinal analyses to test the hypothesis that HbA1c is an independent predictor of all-cause and CVD mortality in non-diabetic men and women with CKD before reaching kidney failure.

Materials and Methods

The MDRD Study, conducted from 1989 to 1993, was a randomized, controlled trial to study the effect of dietary protein restriction and strict BP control on the progression of kidney disease (19). A total of 585 patients with a baseline GFR of 25 to 55 ml/min per 1.73 m² were randomized into study A, and 235 patients with a baseline GFR of 13 to 24 ml/min per 1.73 m² were randomized to study B. Patients in study...
A and study B were combined for these analyses. We excluded participants with diagnosed diabetes \((n = 43)\), those with fasting glucose levels \(>126 \text{ mg/dl} \) \((n = 20)\), and missing HbA\(_{1c}\) levels \((n = 9)\). Thus, our effective study sample size was 768. GFR was assessed by the kidney clearance of \(^{125}\)I-iothalamate. HbA\(_{1c}\) was assessed in the central laboratory, in fasting samples obtained during baseline study visits using HPLC (Bio-Rad Diamat Automated Glycosylated Hemoglobin Analyzer).

Survival status and date and cause of death were ascertained from the National Death Index. A death was ascribed to CVD when the primary cause of death was International Classification of Diseases, Ninth Revision codes 390 to 459 \((n = 85)\) or when kidney disease was listed as the primary cause of death and CVD was the secondary cause \((n = 11)\). Survival time was defined as time from randomization to death or end of follow-up (December 31, 2000). Data collection procedures were approved by the Cleveland Clinic and Tufts-New England Medical Center Institutional Review Boards.

**Statistical Analyses**

Summary statistics, according to quartiles of HbA\(_{1c}\), are presented as percentages for categorical data, mean (±SD) for approximately normally distributed continuous variables, and median (interquartile range) for skewed continuous variables. Differences between the groups were tested using the \(\chi^2\) test, one-way ANOVA, and the Kruskall-Wallis test as appropriate.

Incidence rates for mortality were calculated for quartiles of HbA\(_{1c}\). Differences in survival between the quartiles of HbA\(_{1c}\) were compared using Kaplan-Meier survival plots. Cox proportional hazards models were used to evaluate the relationship between HbA\(_{1c}\) and all-cause and CVD mortality initially without adjustment and subsequently adjusting for several groups of a priori defined confounding variables. Studies A and B were combined for these analyses; however, the Cox models were stratified by study to allow different baseline hazard rates in the two studies. Model 1 adjusted for randomization assignments to protein diets and BP strata, age, gender, and race. Model 2 adjusted for history of coronary disease as well as CVD risk factors, namely smoking status, body mass index, systolic BP, LDL and HDL cholesterol, and C-reactive protein (CRP), in addition to the variables in model 1. Model 3 adjusted for variables in model 2 as well as the kidney disease factors proteinuria and cause of kidney disease. The univariate and fully adjusted Cox models were repeated using quartiles of HbA\(_{1c}\). The models were repeated replacing HbA\(_{1c}\) with fasting glucose as a continuous variable.

Hazard ratios (HR) are presented per unit (1%) increase in HbA\(_{1c}\), and 95% confidence intervals (CI) were calculated for the HR. Proportional hazards assumptions were tested using log minus log survival plots and using plots of Schoenfeld residuals versus survival time.

**Sensitivity Analyses and Interactions**

Because stratifying by study may not fully adjust for level of kidney function, we repeated the multivariable Cox models adjusting for baseline GFR as a continuous variable. Hematocrit, use of angiotensin-converting enzyme inhibitors, and aspirin may be potential confounders of the association between HbA\(_{1c}\) and mortality. We therefore repeated the final regression model with the addition of hematocrit and baseline medication use.

The American Diabetes Association recommends that the goal of therapy in type 2 diabetes is an HbA\(_{1c}\) level of \(<7\% \) \((20)\). Whereas HbA\(_{1c}\) levels of 4 to 6% are considered normal, levels \(>6.4\%\) have been used as a cutoff indicative of elevated HbA\(_{1c}\) \((17)\). We therefore performed additional analyses after excluding patients with HbA\(_{1c}\) \(>6.4\%\) \((n = 32)\) to specifically investigate the association between HbA\(_{1c}\) and mortality when HbA\(_{1c}\) is below currently defined thresholds of normal \((n = 32)\).

We evaluated an interaction between HbA\(_{1c}\) and gender on the basis of data from previous studies that have suggested that the association between HbA\(_{1c}\) and mortality (or CVD) is present only in women \((13,18,21)\) or is stronger in women than in men \((22)\). We also evaluated an interaction between HbA\(_{1c}\) and study to assess for differential effects according to severity of kidney disease.

**Results**

**Baseline Characteristics**

The study cohort had mean ± SD age of 52 ± 12 yr, GFR 32 ± 12 ml/min per 1.73 m\(^2\), and HbA\(_{1c}\) 5.6 ± 0.5%. The sample was predominantly white (86%), 61% were male, and 10% were current smokers. Higher HbA\(_{1c}\) was associated with older age, black race, and a worse CVD risk profile with higher body mass index and higher levels of systolic BP, total cholesterol, LDL cholesterol, and CRP and higher baseline aspirin use (Table 1). GFR was lower in the higher HbA\(_{1c}\) groups; however, there were no differences in the other kidney disease–related factors.

**Outcomes**

Median follow-up for analyses of survival was 125 mo. All-cause mortality was 22% \((n = 169)\), and CVD mortality was 13% \((n = 96)\). Incidence rates for all-cause/CVD mortality were 14/9 per 1000 person-years in quartile 1, 14/7 per 1000 person-years in quartile 2, 27/17 per 1000 person-years in quartile 3, and 38/19 per 1000 person-years in quartile 4. Kaplan-Meier curves demonstrated differences in survival between quartiles of HbA\(_{1c}\) (Figure 1).

In univariate analysis, a 1% higher HbA\(_{1c}\) was associated with a greater than two-fold increase in the risk for all-cause and CVD mortality (Table 2). After adjustment for randomization assignments, demographic, CVD, and kidney disease factors, a 1% increase in HbA\(_{1c}\) was associated with a 73% increase in the risk for all-cause mortality. In multivariable analyses, there was a trend toward statistical significance in the relationship between HbA\(_{1c}\) and CVD mortality.

Our prespecified analysis relating mortality hazard to HbA\(_{1c}\) assumed a linear model. However, the quartiles analysis of incidence rates and the Kaplan-Meier curves suggests the possibility of a threshold in risk for the relationship between HbA\(_{1c}\) and all-cause and CVD mortality. Therefore, we present the multivariate Cox regression analysis using quartiles of HbA\(_{1c}\); however, it must be acknowledged that our sample size is too small to make definitive statements regarding these thresholds. Table 3 presents the results of these analyses. In univariate analysis, quartiles 3 and 4 of HbA\(_{1c}\) were associated with increased risk for all-cause and CVD mortality relative to quartile 1. After adjustment for randomization assignments, demographic, CVD, and kidney disease factors, only quartile 4 (HR, 1.80; 95% CI, 1.07 to 3.02; \(P = 0.03\)) of HbA\(_{1c}\) was associated with increased risk for all-cause mortality relative to quartile 1. There was no difference in HR for CVD mortality for the three highest HbA\(_{1c}\) quartiles compared with the lowest quartile.

Fasting glucose levels were associated with all-cause (HR per
Table 1. Baseline characteristics by quartiles of HbA1c

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1 (3.8 to 5.2%; n = 176)</th>
<th>Quartile 2 (5.3 to 5.5%; n = 189)</th>
<th>Quartile 3 (5.6 to 5.9%; n = 231)</th>
<th>Quartile 4 (6.0 to 7.2%; n = 172)</th>
<th>P</th>
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<tbody>
<tr>
<td>HbA1c (%)b</td>
<td>5.0 ± 0.3</td>
<td>5.4 ± 0.1</td>
<td>5.7 ± 0.1</td>
<td>6.3 ± 0.3</td>
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<td>Demographic factors</td>
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<td>age (y)b</td>
<td>47.1 ± 12.1</td>
<td>49.3 ± 12.6</td>
<td>51.6 ± 12.8</td>
<td>56.5 ± 9.6</td>
<td>&lt;0.001</td>
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<td>male (%)</td>
<td>60</td>
<td>60</td>
<td>61</td>
<td>64</td>
<td>0.85</td>
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<td>white (%)</td>
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<td>83</td>
<td>77</td>
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<td>current smoker (%)</td>
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<td>CVD risk factors</td>
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<td>history of coronary artery disease</td>
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<td>7</td>
<td>10</td>
<td>12</td>
<td>0.21</td>
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<tr>
<td>BMI (kg/m²)b</td>
<td>26.2 ± 3.9</td>
<td>26.8 ± 4.3</td>
<td>27.0 ± 4.5</td>
<td>27.6 ± 4.7</td>
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<td>systolic BP (mmHg)b</td>
<td>128.0 ± 16.1</td>
<td>130.4 ± 18.1</td>
<td>131.8 ± 16.2</td>
<td>132.5 ± 17.6</td>
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<tr>
<td>diastolic BP (mmHg)b</td>
<td>81.3 ± 9.0</td>
<td>81.7 ± 10.7</td>
<td>80.9 ± 10.3</td>
<td>80.5 ± 10.2</td>
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<tr>
<td>total cholesterol (mg/dl)b</td>
<td>203.0 ± 41.9</td>
<td>216.2 ± 42.8</td>
<td>218.8 ± 42.9</td>
<td>224.5 ± 46.1</td>
<td>&lt;0.001</td>
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<td>triglycerides (mg/dl)b</td>
<td>167.9 ± 136.3</td>
<td>166.1 ± 112.1</td>
<td>165.6 ± 125.1</td>
<td>173.4 ± 124.5</td>
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<td>LDL cholesterol (mg/dl)b</td>
<td>133.5 ± 39.0</td>
<td>148.3 ± 39.4</td>
<td>150.7 ± 39.3</td>
<td>154.3 ± 41.3</td>
<td>&lt;0.001</td>
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<td>HDL cholesterol (mg/dl)b</td>
<td>40.1 ± 14.4</td>
<td>40.0 ± 14.9</td>
<td>40.1 ± 13.9</td>
<td>40.1 ± 13.6</td>
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<td>CRP (mg/L)c</td>
<td>0.18 (0.38)</td>
<td>0.23 (0.47)</td>
<td>0.21 (0.49)</td>
<td>0.29 (0.54)</td>
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<td>ACE inhibitor (%)</td>
<td>34</td>
<td>35</td>
<td>37</td>
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<td>aspirin (%)</td>
<td>6</td>
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<td>11</td>
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<td>GFR (ml/min per 1.73 m²)b</td>
<td>36.5 ± 12.1</td>
<td>32.9 ± 12.4</td>
<td>30.0 ± 11.6</td>
<td>30.5 ± 11.1</td>
<td>&lt;0.001</td>
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<td>serum creatinine (mg/dl)b</td>
<td>2.1 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>2.6 ± 1.0</td>
<td>2.6 ± 1.0</td>
<td>&lt;0.001</td>
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<td>proteinuria (g/d)c</td>
<td>0.22 (1.06)</td>
<td>0.24 (1.18)</td>
<td>0.33 (1.23)</td>
<td>0.31 (1.31)</td>
<td>0.68</td>
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<td>albumin (g/dl)b</td>
<td>4.04 ± 0.3</td>
<td>4.02 ± 0.3</td>
<td>4.04 ± 0.4</td>
<td>4.0 ± 0.3</td>
<td>0.60</td>
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<td>Kidney disease category (%)</td>
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<tr>
<td>glomerular disease</td>
<td>26</td>
<td>25</td>
<td>27</td>
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<td>polycystic kidney disease</td>
<td>31</td>
<td>28</td>
<td>29</td>
<td>33</td>
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<td>other</td>
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<td>47</td>
<td>44</td>
<td>45</td>
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<tr>
<td>hematocrit (%)b</td>
<td>39.3 ± 5.1</td>
<td>38.9 ± 5.0</td>
<td>38.3 ± 5.2</td>
<td>38.5 ± 5.1</td>
<td>0.22</td>
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<td>Metabolic factors</td>
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<td>glucose (mg/dl)b</td>
<td>83.3 ± 11.2</td>
<td>86.1 ± 10.8</td>
<td>87.1 ± 13.4</td>
<td>93.8 ± 13.5</td>
<td>&lt;0.001</td>
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aHbA1c, glycated hemoglobin; CVD, cardiovascular disease; BMI, body mass index; CRP, C-reactive protein; ACE, angiotensin-converting enzyme.
bMean ± SD.
cMedian (interquartile range).

1-mg/dl increase in glucose, 1.02; 95% CI, 1.01 to 1.03; P < 0.001 and CVD (HR, 1.03; 95% CI, 1.01 to 1.04; P = 0.001) mortality in unadjusted Cox models. However, these associations were attenuated for both all-cause (HR, 1.01; 95% CI, 0.99 to 1.02; P = 0.34) and CVD (HR, 1.01; 95% CI, 0.99 to 1.03; P = 0.11) mortality after adjustment for previously described co-variables.

Sensitivity Analysis
With the inclusion of GFR in the multivariable Cox models, HbA1c remained a significant predictor of all-cause mortality (HR, 1.67; 95% CI, 1.19 to 2.34), and the relationship with CVD mortality was essentially unchanged (HR, 1.47; 95% CI, 0.92 to 2.35). The addition of hematocrit did not appreciably alter the HR for HbA1c as a continuous variable in models that examined all-cause (HR, 1.66; 95% CI, 1.18 to 2.33) or CVD (HR, 1.48; 95% CI, 0.93 to 2.35) mortality. Similarly, the HR for HbA1c remained relatively unchanged with the addition of baseline aspirin and angiotensin-converting enzyme inhibitor use for both all-cause (HR, 1.70; 95% CI, 1.22 to 2.39) and CVD mortality (HR, 1.50; 95% CI, 0.92 to 2.37). After exclusion of patients with elevated HbA1c (defined as HbA1c > 6.4%), HbA1c remained a significant predictor of all-cause mortality (HR, 1.60; 95% CI, 1.04 to 2.46), and the relationship with CVD was essentially unchanged (HR, 1.55; 95% CI, 0.87 to 2.77).

Interactions
The interaction between gender and HbA1c was NS in models that examined all-cause (P = 0.35) or CVD mortality (P = 0.15). There was no interaction between study as a marker of severity of kidney disease and HbA1c in models that examined all-cause (P = 0.60) or CVD mortality (P = 0.87).
Discussion

In this large cohort of nondiabetic patients with CKD, HbA1c, a marker of impaired glucose metabolism, is a significant predictor of all-cause mortality and shows a trend toward being associated with CVD mortality. HbA1c concentration reflects average blood glucose concentration over 3 mo and is a sensitive and reliable marker of glucose metabolism (14). Cross-sectional studies in nondiabetic individuals have shown a relationship between HbA1c and prevalent coronary artery disease as well as markers of subclinical atherosclerosis (18,23,24). Population-based prospective studies have also demonstrated an association between HbA1c values in the non-diabetic range and CVD mortality (3,15,16). Conversely, a nested case-control analysis derived from the Women’s Health Study cohort found that although HbA1c was a strong predictor of a composite outcome of fatal and nonfatal CVD events, this relationship was NS after adjustment for other CVD risk factors. The failure to show a relationship between HbA1c and CVD mortality may be due to inadequate statistical power because there were fewer CVD events.

Previous studies using Third National Health and Nutrition Examination Survey data have shown a high prevalence of hyperglycemia in individuals with GFR < 60 ml/min per 1.73 m² or microalbuminuria (11,12). Our results therefore suggest that “relative” hyperglycemia may be an important risk factor contributing to the excess risk of CVD seen in nondiabetic CKD. Furthermore, the persistence of the association between HbA1c and mortality after exclusion of patients with HbA1c > 6.4% suggests that in CKD, hyperglycemia below currently defined thresholds may be associated with adverse outcomes.

Several studies have suggested a gender difference in the association between HbA1c and mortality. Analyses from the Framingham Heart Study and the Rancho Bernardo Study found that HbA1c levels in the nondiabetic range were related to CVD in women but not in men (13,18). In the MDRD Study cohort, there was no interaction between gender and all-cause or CVD mortality with HbA1c. Although we cannot be sure, differences between the study populations in factors such as number of postmenopausal women, CVD risk profile, and presence of kidney disease itself may account for the inconsistency of the results. It is also possible that we had limited power to detect the interaction of HbA1c and gender.

Several pathophysiologic mechanisms may mediate the toxic effects of chronic hyperglycemia. A growing body of evidence suggests a link between chronic hyperglycemia and oxidative stress, endothelial dysfunction, and inflammation. HbA1c is a target for intracellular glycoxidation and peroxidation reactions that result in the formation of advanced glycation end products (AGE) (25). These AGE have been implicated in the initiation

<table>
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<th>Table 2. Relationship of HbA1c with all-cause and CVD mortalitya</th>
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<td>Unadjusted</td>
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<tr>
<td>model 1b</td>
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<td>model 2c</td>
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<td>model 3d</td>
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aHR, hazard ratio; CI, confidence interval. HR are presented for each 1% increase in HbA1c.
bStratified by study and adjusted for age, gender, race, BP, and protein diet randomization assignments.
cAdjusted for model 1 covariates + current smoking, history of coronary artery disease, LDL and HDL cholesterol, BMI, systolic BP, and C-reactive protein.
dAdjusted for model 2 covariates + proteinuria and cause of kidney disease.

Figure 1. Kaplan-Meier survival curves showed that higher glycosylated hemoglobin levels were associated with higher all-cause mortality (log rank test \( P < 0.0001 \)).
and progression of atherosclerosis. Chronic hyperglycemia has also been associated with increased circulating levels of oxidized LDL, a highly atherogenic form of LDL cholesterol (26). In a population-based study, moderate elevations in glucose levels were associated with abnormalities of cellular antioxidant mechanisms (27). In a study of young healthy Chinese subjects, glucose levels at the higher end of the normal range were associated with impaired endothelial function and higher carotid intima-media thickness (28). Impaired glucose tolerance has also been associated with an elevated white cell count, which may be a surrogate for chronic inflammation (29). In a cross-sectional study of patients with coronary atherosclerosis, HbA1c levels in the high normal range were associated with higher levels of several inflammatory markers, including CRP, erythrocyte sedimentation rate, and white blood cell count (30), although in our study, the relationship of HbA1c with mortality was independent of CRP.

Alternatively, there may be residual confounding from the known clustering of hyperglycemia with CVD risk factors and other components of the metabolic syndrome, including dyslipidemia, obesity, and hypertension. It is also possible that high baseline HbA1c represents patients who are at higher risk for developing diabetes in the future and that this accounts for the association between HbA1c and mortality. We do not have data on diabetic status during long-term follow-up and therefore are unable to assess this hypothesis. However, this does not preclude the use of HbA1c as a risk stratification tool for the early identification of high-risk individuals.

In addition to its relationship with CVD mortality, the association between HbA1c and all-cause mortality may reflect the relationship between abnormalities of glucose metabolism and cancer. Several population-based studies have shown an association of impaired glucose tolerance and diabetes with mortality from cancers of the breast, prostate, colon, pancreas, liver, and gallbladder (31–34). The biologic link between hyperglycemia and the development of cancer may involve stimulation of IGF-1, which has been shown to promote tumor cell growth (35,36).

HbA1c has a few advantages over fasting plasma glucose as a marker of hyperglycemia. First, measurement of HbA1c does not require fasting or glucose load. Second, HbA1c provides a more comprehensive picture of glycemic status and is more indicative of chronic hyperglycemia than a single plasma glucose measurement. Third, HbA1c reflects both fasting and postprandial hyperglycemia. Several studies have shown that the latter may be a better prognostic marker than fasting hyperglycemia (37,38). Fourth, HbA1c is not subject to the wide variations that are inherent in single measures of blood glucose (14).

The strengths of this study include the large number of patients with nondiabetic kidney disease, long-term follow-up, low prevalence of CVD at baseline, detailed ascertainment of potentially confounding variables, and precise measurement of GFR as a marker of kidney function. The main limitations are lack of follow-up HbA1c measurements and the potential misclassification of cause of deaths; however, the latter should not influence the relationship between HbA1c and all-cause mortality. In addition, it must be acknowledged that the use of the HPLC method to measure HbA1c may result in overestimation of HbA1c levels in uremia as a result of interference with carbamylated hemoglobin (39). However, it has been shown that carbamylated hemoglobin constitutes a small fraction of HbA1c in dialysis patients (40).

### Conclusions

In summary, HbA1c is an independent predictor of all-cause mortality in nondiabetic CKD. The association between HbA1c and CVD mortality needs further assessment in this population. Larger studies will allow the evaluation of a threshold in the relationship between level of HbA1c and risk for all-cause and CVD mortality. The results of this study may have important implications: (1) The high prevalence of dysglycemia in CKD may partly explain the high risk for CVD in CKD, (2) the current definitions for normal glycemic status may not be appropriate for this population, (3) there may be a role for HbA1c in risk stratification and early identification of patients who have nondiabetic CKD and are at high risk for CVD, and (4) hyperglycemia may be a potential therapeutic target to reduce CVD risk in this patient population.

### Acknowledgments

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