Glycated haemoglobin and the incidence of end-stage renal disease in diabetics

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Abstract

Background. The relationship between glycated haemoglobin and the incidence of end-stage renal disease (ESRD) in patients with diabetes remains uncertain, especially in those with decreased glomerular filtration rate (GFR). The aim of this study was to assess the appropriate HbA1c level for diabetics for minimizing the incidence of ESRD and all-cause mortality.

Methods. A cohort of patients aged 25 years or older who had been treated for diabetes was generated from the Seoul National University Bundang Hospital database using diagnosis code and prescribed medication during 2004. The 4474 patients were classified into three groups according to the baseline HbA1c in 2004 (HbA1c <6.50%, 6.50–7.49% and ≥7.50%; termed groups 1, 2 and 3, respectively). The outcomes were extracted from the database of Statistics Korea for mortality and registry in the Korean Society of Nephrology for ESRD incidence.

Results. Ninety patients developed ESRD during 5.29 ± 1.22 years of mean follow-up period. Group 1 patients showed the lowest incidence of ESRD (P = 0.003). Compared with this group, the adjusted hazard ratio of ESRD was 2.915 and 4.219 in groups 2 and 3, respectively. The incidence of ESRD increased in patients with HbA1c ≥6.50% compared with the patients with HbA1c <6.50%, regardless of GFR. However, HbA1c <6.50% showed no benefit on ESRD development in patients older than 80 years and in patients with diabetic duration >10 years. All-cause mortality was not associated with the level of HbA1c.

Conclusions. HbA1c <6.50% was associated with reduced development of ESRD in all patients and later stages of chronic kidney disease.

Keywords: diabetes mellitus; end-stage renal disease; glycosylated; haemoglobin A

Introduction

Diabetes mellitus is the most common cause of end-stage renal disease (ESRD). Diabetic nephropathy was the major cause for 54% of newly developed ESRD patients in the USA [1] and 41.9% in Korea [2]. The main objective for the care of diabetics is to prevent macrovascular and microvascular complications by management of hyperglycaemia. Previous studies reported that intensive glycaemic control reduced the risk of microvascular disease in both type 1 and 2 diabetes [3–6]. Although the effect on macrovascular complication remains uncertain, the association between intensive glycaemic control and microvascular complication, particularly nephropathy, has been consistent [3–10].

However, previous trials evaluating the effect of glucose control have provided conflicting results on the rate of decrease in glomerular filtration rate (GFR) or ESRD in diabetics. The patients in the intensive control group in the United Kingdom Prospective Diabetes Study (UKPDS) exhibited a 67% risk reduction for creatinine doubling at 9 years in type 2 diabetes [4]. In the Epidemiology of Diabetes Interventions and Complications/Diabetes Control and Complications Trial follow-up study, the previously intensive control group was associated with a significantly reduced incidence of serum creatinine level of 2 mg/dL or greater (P = 0.004) [9]. In contrast, the intensive glycaemic control had no significant effect on the doubling of serum creatinine level (P = 0.99) or GFR <15 mL/min (P = 0.35) for 5.6 years of median follow-up in the Veterans Affairs Diabetes Trial (VADT) despite the reduced progression of albuminuria [7]. Similarly, in a follow-up study of the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD) trial, the outcome of ESRD was not significantly different between the intensive and standard glucose control groups (P = 0.7126) [10].

Accordingly, the optimal level of HbA1c to prevent the progression of ESRD in diabetics remained uncertain. In
addition, few studies evaluated the effect of glycaemic control on the progression of ESRD as a primary outcome. Furthermore, very few studies have reported on the effect of intensive glucose control in the later stages of chronic kidney disease (CKD) [11,12]. The Kidney Disease Outcomes Quality Initiative guidelines suggested that lowering the glycated haemoglobin (HbA1c) level to <7.0% might reduce the rate of decrease in renal function; however, the evidence is weak [11]. Therefore, the aim of this study was to assess the appropriate HbA1c level for diabetics for minimizing the incidence of ESRD and all-cause mortality. We also analysed the relationship between strict glucose control and the incidence of ESRD in patients with advanced stages of CKD.

Materials and methods

Patients

Our study population comprised diabetics who visited the Seoul National University Bundang Hospital once or more during 2004 in Korea. We retrospectively selected the patients, aged 25 years or older, who had been diagnosed with diabetes by ICD-10 code (E10–E14) or taken oral hypoglycaemic agents (OHA) or insulin from the electronic health record (EHR) database which had been in operation since the opening of the hospital in 2003. After patient selection, two research nurses reviewed the EHR data for each patient and confirmed the diagnosis and duration of diabetes by 2004. This study was approved by the Institutional Review Board at the Seoul National University Bundang Hospital (IRB number: B-1006-103-103).

Data variables

We gathered data of age, gender, the unique national identification number, which all Koreans have, and the date of the first visit to the hospital in 2004. We also searched all diagnoses, medication and laboratory data that were recorded in 2004 and at the last visit until December 2009. We grouped the ICD-10 diagnosis codes as coronary artery disease (CAD), including I20–I25, cerebrovascular accident (CVA), including G45, G46 and I60–I69, cardiovascular disease (CVD), including CAD and CVA, and cancer including all ‘C’ codes. We defined hypertensive patients as those who had been diagnosed as I10–I15 or taken anti-hypertensive medication. ESRD was defined as patients who need renal replacement therapy or renal transplantation. We calculated the estimated GFR using the abbreviated Modification of Diet in Renal Disease equation [13]. We joined the mortality data from Statistics Korea [14] and the ESRD incidence from the ESRD registry of the Korean Society of Nephrology [15] to our dataset using each individual’s unique identifier as the primary key element. We obtained the mortality data until December 2008 and ESRD until December 2009. The cause of death could not be specified, and only all-cause mortality was examined because the data did not specify individual causes of death.

Analyses

The patients were classified according to the baseline HbA1c level in 2004. The first data in 2004 were used for analyses and, if there were no data during 2004, we defined the data as missing values. Post-index HbA1c was defined as the mean of all recorded HbA1c between the baseline value in 2004 and the respective outcome event (ESRD or death) or censoring point (last recorded value in the database until December 2009). We compared the parameters between groups. All analyses were conducted using SPSS (version 15.0, SPSS, IL, USA). Descriptive statistics were reported as mean ± standard deviation for continuous variables or frequency for categorical variables. Differences in continuous variables were analysed by two-tailed, unpaired t-tests or one-way ANOVA tests and, in categorical variables, by chi-square tests. We compared the cumulative incidence of ESRD and all-cause mortality between patients, categorized into three groups according to baseline HbA1c level, by log-rank test. To determine whether the baseline HbA1c level was independently related to the incidence of outcomes, we used Cox’s hazard proportional analysis adjusted for age, gender and other risk factors assessed by univariate analysis. Two-sided P-values were reported with 0.05 taken as the level of statistical significance.

Results

Characteristics of patients

Of the 4474 identified patients, the mean age was 66.21 ± 11.60 years, 52.5% were male, the mean duration of diabetes was 8.56 years, 1751 (39.1%) patients had been diagnosed as hypertensive and 1605 (35.9%) patients had previously been diagnosed with CVD (Table 1). We classified the patients into three groups according to the baseline HbA1c in 2004. The baseline mean HbA1c of group 1 (HbA1c ≤ 7.50%) was 5.90%, of group 2 (HbA1c 6.50–7.49%) 6.92% and of group 3 (HbA1c ≥ 7.50%) 8.91%. The mean age was the youngest in group 3. The diabetic duration was the shortest in group 1. The serum total cholesterol and fasting blood glucose levels differed significantly among the three groups. Group 1 showed the lowest value of serum cholesterol. Of the medications given, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, OHA and insulin were the most frequently prescribed in group 3. Hypertension and CVA were the most frequent in group 1. However, no significant differences in CAD, CVD and cancer were seen between the groups (Table 1).

Follow-up HbA1c data

All of the recorded HbA1c data were gathered during the follow-up period. During this period, mean post-index HbA1c value was lowered to 7.27 ± 1.15%. Post-index HbA1c showed significant group differences: group 1 was 6.32%, group 2 was 7.05% and group 3 was 8.10%. Most patients remained in their baseline HbA1c group after the reclassification by post-index HbA1c (Table 2).

Clinical outcome

The patients were observed over 5.29 ± 1.22 years for the detection of ESRD incidence and 4.42 ± 0.92 years for mortality. ESRD was developed in 90 (2.0%) patients who had not shown ESRD in 2004. ESRD incidence was directly proportional to the baseline HbA1c level: 1.3% in group 1, 1.8% in group 2 and 2.7% in group 3 (P = 0.017). There were no significant differences between groups for all-cause mortality, with 439 (9.8%) patients dying: 9.4% in group 1, 9.0% in group 2 and 10.8% in group 3 (P = 0.199). Kaplan–Meier curves showed that the time until ESRD occurrence, group 1 showed the lowest incidence of ESRD during follow-up period (log-rank test, P = 0.003) (Figure 1A). All-cause mortality was not different among the three HbA1c groups (log-rank test, P = 0.199) (Figure 1B). With Cox’s proportional hazard analysis for ESRD, after adjustment for age, diabetes duration and univariate risk factors, and compared with group 1 patients, group 2 patients had a 2.915-fold increased risk for ESRD [95%
Table 1. Baseline characteristics stratified by baseline HbA1c group

<table>
<thead>
<tr>
<th>Level of HbA1c (%)</th>
<th>Group 1 (n = 1255)</th>
<th>Group 2 (n = 1438)</th>
<th>Group 3 (n = 1781)</th>
<th>All (n = 4474)</th>
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<tr>
<td>&lt;6.50</td>
<td>5.90 ± 0.42</td>
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<td>6.50–7.49</td>
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<td>≥7.50</td>
<td>638 (50.8)</td>
<td>780 (54.2)</td>
<td>929 (52.2)</td>
<td>2347 (52.5)</td>
</tr>
<tr>
<td>Diabetes duration (year)</td>
<td>6.33 ± 8.08</td>
<td>8.37 ± 8.53*</td>
<td>10.20 ± 8.90 a</td>
<td>8.56 ± 8.71</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.17 ± 1.01</td>
<td>1.14 ± 0.96</td>
<td>1.12 ± 0.96</td>
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<tr>
<td>Cholesterol (mg/dL)</td>
<td>187.85 ± 40.89</td>
<td>191.76 ± 38.55 a</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>79.20 ± 12.12</td>
<td>79.63 ± 12.17</td>
<td>79.38 ± 11.86</td>
<td>79.41 ± 12.03</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>135.64 ± 19.97</td>
<td>135.74 ± 19.27</td>
<td>136.73 ± 20.66</td>
<td>136.11 ± 20.03</td>
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Post-index HbA1c(%)*

| Mean ± SD | 6.32 ± 0.67 | 7.05 ± 0.59 | 8.10 ± 1.16 | 7.27 ± 1.15 |
|<6.5 (%)    | 814 (64.9)  | 173 (12.0)  | 58 (3.3)    | 1045 (23.4) |
|6.50–7.49 (%)| 381 (29.4)  | 1026 (71.3) | 506 (28.4)  | 1913 (42.8) |
|≥7.50 (%)   | 60 (4.8)    | 239 (15.8)  | 1217 (68.3) | 1781 (33.9) |

*Post-index HbA1c was defined as the mean of all recorded HbA1c between the baseline value in 2004 and the respective outcome event (ESRD or death) or censoring point (last recorded value in the database until December 2009).

SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; OHA, oral hypoglycaemic agents; HTN, hypertension; CAD, coronary artery disease; CV A, cerebrovascular accident; CVD, cardiovascular disease (CVA or CAD).

P < 0.05 vs group 1 (baseline HbA1c <6.5%) by ANOVA or chi-square test.

Late stages of CKD and HbA1c

There were 799 patients with a GFR <60 mL/min/1.73 m². The mean age was 77.12 ± 9.75 years, 45.4% were male and the mean duration of diabetes was 12.87 years. ESRD was developed in 22 (2.8%) patients during follow-up period. ESRD incidence was 1.3% in baseline HbA1c <6.50%, 1.7% in HbA1c 6.50–6.99%, 2.3% in HbA1c 7.00–7.99% and 5.4% in HbA1c ≥8.00% (P = 0.043).

We categorized the patients into four groups according to GFR and baseline HbA1c. The baseline mean HbA1c of group A (HbA1c <6.50% and GFR <60 mL/min/1.73 m²) was 5.89%, of group B (HbA1c <6.50% and GFR ≥60 mL/min/1.73 m²) 5.91%, of group C (HbA1c ≥6.50% and GFR <60 mL/min/1.73 m²) 8.03% and of group D (HbA1c ≥6.50% and GFR ≥60 mL/min/1.73 m²) 7.99%. ESRD incidence was 1.1% in group A, 1.3% in group B, 2.9% in group C and 3.4% in group D (P = 0.019) (Figure 2). After adjustment for age, sex, diabetes duration and univariate risk factors, and compared with group A, group C had 3.692-fold increased risk for ESRD (95% CI, 2.369–5.997) (P = 0.001). However, group B did not show a significant relationship compared with group A (P = 0.368).

Age, diabetes duration, cardiovascular risk factors and HbA1c

Among 489 patients older than 80 years, the incidence of ESRD development was 3.8%, 0.7% and 0.5% in groups 1, 2 and 3, respectively (P = 0.034). There was no significant difference in all-cause mortality (P = 0.822).

In the subgroup of patients whose diabetes duration was more than 10 years (n = 1346), 24 patients (1.8%) developed ESRD (1.2%, 0.7% and 2.6% in groups 1, 2 and 3, respectively).
respectively). Patients in group 2 showed a reduction in the incidence of ESRD (P = 0.047). All-cause mortality was not significantly different among the three groups (P = 0.929).

A total of 1592 patients were identified with a CVD history. The overall incidence of ESRD development was 1.8%: 1.1%, 1.2% and 2.7% in groups 1, 2 and 3, respectively (P = 0.063). After adding the patients with a 10-year cardiovascular risk more than 10%, as estimated by Framingham/ATP III point scores [men: age ≥70, systolic blood pressure (SBP) ≥140 mm Hg and serum cholesterol ≥200 mg/dL; women: age ≥75, SBP ≥140 and serum cholesterol ≥200 mg/dL], the incidence of ESRD development was 1.0%, 1.1% and 2.8% in groups 1, 2 and 3, respectively (P = 0.027) [16]. There was no difference in all-cause mortality (P = 0.587).

Discussion and Conclusion

We have shown that HbA1c lower than 6.50% was associated with a reduced incidence of ESRD and that the risk of adverse outcome was also increased as the HbA1c value increased from 6.50%.

Although previous studies had shown consistent results regarding the effect of intensive glucose control on microalbuminuria, the association between intensive glucose control and ESRD incidence was conflicting. Furthermore, in recent studies, the risks appeared to outweigh the benefits in the intensive glycaemic control group [7,17,18]. The ACCORD trial randomized participants with either a history of CVD (35%) or a significant CVD risk, old age and a relatively long duration of diabetes (mean age, 62 years; median diabetes duration, 10 years). The ACCORD trial was discontinued due to increased mortality in the intensive control group after 3.5 years of follow-up [17]. In a recently published retrospective cohort study, low and high mean HbA1c values were related to increased death from all causes and cardiac events [18].

In contrast, intensive glucose control delayed the onset and slowed the progression of microvascular complications in young patients with type 1 diabetes [3]. Similarly, intensive therapy reduced the risk of microvascular complications in newly diagnosed patients with type 2 diabetes (mean age 54 years) [4]. In the post-trial follow-up of UKPDS (UKPDS 80), the emergent risk of myocardial infarction and all-cause mortality was reduced, and the risk of microvascular complication was continuously reduced during 10 years of follow-up, regardless of an early loss of glycaemic differences [19]. Based on these studies, the American Diabetes Association (ADA) guidelines recommend a target HbA1c level of 7.0% or less as the general goal for the prevention of microvascular and macrovascular complications, and an intensive glucose control can be achieved for selected patients with long life expectancy, short duration of diabetes and no significant CVD [20].

However, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, despite the older age (median age 66 years) and high risk of CVD (history of CVD...
the intensive glucose control group showed a 10% relative reduction in the combined outcome of macrovascular and microvascular events [6]. Based on the ADA guidelines, these results were attributed to the shorter diabetes duration (mean 8 years) and lower baseline HbA1c (mean 7.48%). In addition, subset analysis of the ACCORD trial showed that the primary CVD outcome was reduced in participants who had a baseline HbA1c <8% and no previous CVD history [17]. Post-hoc subgroup analysis of VADT suggested that participants with a duration of diabetes of <12 years had a CVD benefit in the intensive glucose control group [21].

Our research supports the findings of the ADVANCE study. The patients had similar baseline characteristics regarding age, CVD risk and average diabetes duration. Although the ADVANCE study had no effect on creatinine doubling but a trend toward a reduction in death from renal cause or need for renal replacement therapy, our results demonstrated that ESRD incidence was reduced significantly in group 1. The baseline serum creatinine level of our study was higher than that of the ADVANCE study (86 ± 24 vs 100 ± 86 μmol/L), which may explain why ESRD incidence was increased in our study during 5.29 years of follow-up. Although we could not analyse cardiovascular mortality, all-cause mortality was not significantly different between the groups. This result was consistent with that of the ADVANCE study. Despite old age and high risks of CVD, HbA1c <6.50% was associated with a reduced ESRD incidence and an unaffected all-cause mortality.

However, in subgroup analysis of the patients aged 80 years or more, the ESRD incidence was the highest in group 1. In addition, in patients with diabetes duration more than 10 years, group 2 showed the lowest ESRD incidence. Very elderly patients or patients with long duration of diabetes in group 1 did not show any reduction in ESRD development. Furthermore, ESRD incidence was significantly reduced in the combined group of CVD history and high CVD risk (P = 0.036). These results suggest that more emphasis should be placed on age and diabetic duration than on CVD risk in the setting of a more stringent goal. In addition, we reanalysed the incidence of ESRD according to the GFR and HbA1c level. Spontaneous hypoglycaemia in patients with established diabetes can occur in later stages of CKD because the renal and hepatic clearance of insulin declines and renal gluconeogenesis also declines [22,23]. In contrast, uncontrolled glycaemia has been noticed as a complication of advanced CKD. Uncontrolled glycaemia might be caused by reduced insulin clearance, diminished insulin production and increased insulin resistance. In addition, the improvement of insulin secretion was documented after administration of vitamin D [24,25]. Because of this complex pathophysiology, the appropriate HbA1c level for CKD diabetics remained unclear. Our study demonstrated that strict HbA1c goal of <6.5% in patients with GFR <60 mL/min/1.73 m² appears to reduce the development of the ESRD without an increase of all-cause mortality. Also, we noticed the incidence of ESRD in patients with HbA1c >6.5% was lower compared with the patients with HbA1c <6.5% in a group more than 6.5%, regardless of GFR. Because of the small number in group B (n = 225), group B did not show significant association compared with group A by Cox’s proportional hazard analysis for ESRD. However, these results suggested that, even in patients with advanced stages of CKD, the role of intensive glucose control is significant on the progression of ESRD.

Our study had several limitations. We classified the patients by baseline HbA1c rather than the mean HbA1c value during follow-up. Therefore, group 1 did not represent the intensive glucose control during the entire follow-up, although most patients (64.9%) remained in the same group after the reclassification by post-index HbA1c. However, due to the limitations of this retrospective study, variability
in the frequency of HbA_1c may have introduced a bias and the HbA_1c level at one point could represent the situation that occurs in actual clinical practice. Second, as we collected all the study data from routine practice, they contained missing data and possibly coding imperfections regarding diagnoses and medication. Third, as our study was not randomized, differences existed between the groups. We adjusted for these factors using Cox’s hazard proportional analysis. Finally, we could not exclude patients who managed diabetes in other hospitals or visited our hospital for problems not directly related to diabetes. This may have caused information bias in the analysis focused on the association between the presence of data and outcomes.

Nevertheless, our study has some significance despite these limitations. There are limited data regarding ESRD as a single primary outcome, and we defined ESRD based on the enrollment from the ESRD registry of the Korean Society of Nephrology. Therefore, we could exclude patients on dialysis due to acute kidney injury and the precise ESRD outcome was reported. Second, few large-scale studies have been reported in Asian populations. Ethnic and racial differences of HbA_1c were documented by previous studies [26,27]. Herman et al. reported that Asian had higher HbA_1c level than whites. However, this study included only 5% Asians of the total patients, and haemoglobin level in Asians was markedly higher than whites in the above study [27].

Recently, an international expert committee demonstrated that HbA_1c value of 6.5% is sensitive and specific to identify patients who are at risk of developing retinopathy in western populations [28]. In comparison, recent studies reported that an HbA_1c threshold of 6.1 and 6.3% was suitable for detecting undiagnosed diabetes in Japanese and Chinese studies, respectively [29,30]. In our study, the baseline HbA_1c level was lower than other reports [3,6,7,17], and strict glucose control was appropriate for reducing the incidence of ESRD; ethnic and racial differences could have influenced these results. Third, we evaluated the effect of strict glucose control on ESRD in patients with later stages of CKD.

In conclusion, our study suggested that an HbA_1c level of <6.50% might be related to a reduced risk of ESRD without an increase of all-cause mortality in diabetics, and patients aged 80 years or older and long-standing diabetics more than 10 years could be suggested with the standards which are applicable for less-stringent HbA_1c goals in clinical settings. In addition, HbA_1c<6.5% also showed benefits on the progression of ESRD in later stages of CKD.

Conflict of interest statement. None declared.

References
Obstructive sleep apnoea: a stand-alone risk factor for chronic kidney disease

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Abstract

Background. Previous studies have found an association between obstructive sleep apnea (OSA) and chronic kidney disease (CKD). However, subjects with confounding factors such as diabetes and hypertension were not excluded. The purpose of the present study was to determine whether patients with OSA without meeting criteria for diabetes or hypertension would also show increased likelihood of CKD.

Methods. We prospectively enrolled adult patients with a chief complaint of habitual snoring. Overnight polysomnography, fasting blood triglyceride, cholesterol, glucose, insulin, creatinine, albumin and hemoglobin A1c, and first voiding urine albumin and creatinine were examined. Estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), homeostatic model assessment–insulin resistance and percentage of CKD were calculated.

Results. The final analyses involved 40 patients who were middle-aged [44.8 (8.6) years] predominantly male (83%), obese [body mass index, 28.2 (5.1) kg/m²] and more severe OSA, with an apnea–hypopnea index (AHI) of 51.6 (39.2)/h. The mean eGFR and UACR were 85.4 (18.3) mL/min/1.73m² and 13.4 (23.4) mg/g, respectively. The prevalence of CKD in severe OSA subjects is 18%. With stepwise multivariate linear regression analysis, AHI and desaturation index were the only independent predictor of UACR (β = 0.26, P = 0.01, R² = 0.17) and eGFR (β = 0.32, P < 0.01, R² = 0.32), respectively.

Conclusions. High prevalence of CKD is present in severe OSA patients without hypertension or diabetes. Significantly positive correlations were found between severity of OSA and renal function impairment.

Keywords: albuminuria; glomerular filtration rate; kidney; obstructive sleep apnea

Introduction

Chronic kidney disease (CKD) affects 10–13% of the general population and is associated with substantial morbidity, including poor health outcome, particularly cardiovascular