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Synergistic interaction between prolonged increased glycemic exposure and mildly increased urinary albumin excretion on diabetic retinopathy

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Abstract

The association of mild increase in urinary albumin excretion with diabetic retinopathy (DR) in clinical studies is controversial. The aim of this study is to clarify the interaction between increased glycemic exposure and mild increase in urinary albumin excretion on risk of DR.

Data were collected from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2012. Overall, data from 953 participants without microalbuminuria (477 men and 476 women) were assessed. Logistic regression analysis was constructed to evaluate the association between DR and related clinical parameters, including urinary albumin-creatinine ratio (UACR, mg/g creatinine). The biological interaction of glycemic status and UACR on DR was evaluated by 3 indices: RERI, the relative excess risk due to the interaction; AP, the attributable proportion due to the interaction; and S, the additive interaction index of synergy.

We found that UACR, glycated hemoglobin (HbA1c), and diabetic duration were deeply associated with increased risk of DR (UACR, odds ratio [OR] = 1.04, 95% confidence interval [CI] = 1.02–1.07; HbA1c, OR = 1.16, 95% CI = 1.04–1.30; diabetic duration, OR = 1.06, 95% CI = 1.04–1.07). Furthermore, our interaction analysis demonstrated that synergistic interaction between HbA1c and UACR on development of DR was prominent in participants with diabetic duration of ≥10 years (adjusted RERI = 0.92, 95% CI = 0.10–1.74; adjusted AP = 0.29, 95% CI = −0.82–1.41; adjusted S = 1.76, 95% CI = 1.27–2.25), but not subjects with shorter diabetic duration.

These findings imply that there is the interaction between prolonged hyperglycemic exposure and increased urinary albumin excretion may exert additive synergistic effect on vascular endothelial dysfunction in the eye, even before the appearance of overt diabetic nephropathy.

Keywords: complication, diabetes mellitus, diabetic retinopathy, microalbuminuria, National Health and Nutrition Examination Survey, urinary albumin creatinine ratio

1. Introduction

Diabetes mellitus and related metabolic disturbances are the biggest threats to eye health after adolescence, and diabetic retinopathy (DR) may be responsible for 4.8% of cases of adult blindness worldwide.[1–3] Moreover, because of increased prevalence of diabetes mellitus (DM) and related chronic diseases, increased life expectancy, and improved diagnostic technique, it is expected that the number of patients with DR will steadily increase to 432 million by 2030.[4–8] Thus, identifying subjects at risk for DR is critical to prevent irreversible clinical consequences.

A growing body of evidence has shown that increased glycemic exposure,[3,9–13] uncontrolled blood pressure,[3,12–14] long duration of diabetes,[3,12,13,15] and microalbuminuria[2,16–22] are all potential risk factors for the development and progression of DR. Microalbuminuria is a marker of endothelial dysfunction and may influence on alterations in the microvasculature of retina and kidneys. Recently, some authors argued that a mild increase in urinary albumin excretion, even below the diagnostic threshold of microalbuminuria, is an independent predictor of DR in Asian population.[23,24] However, the studies about this relationship are limited for other ethnic/racial groups and, population-based studies with national representative sample have not been performed yet. Considering that ethnic/racial differences may lead to varying susceptibilities to diabetic microvascular complications, more extensive studies including a larger and more diverse study population are needed. The aim of this study was to clarify the exact association between a mild increase in urinary albumin excretion and DR in a representative sample of the US population.

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2. Methods

2.1. Study population

This was a population-based, retrospective cross-sectional study. The National Health and Nutrition Examination Survey (NHANES) is nationally representative survey conducted by the Centers for Disease Control and Prevention. All participants were volunteers and were selected using a stratified, multistage probability sampling design of non-institutionalized US civilians. Questionnaire-based personal interviews are conducted in participants' homes and health measurements are performed in a mobile examination. More detailed information of sampling design and data collection have been previously described.[25] The NHANES protocol was approved by the human subjects review board, and written informed consent was obtained from all participants.[26] The data in our study were collected from public-use datasets of the NHANES between 2005 and 2012. (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx, last accessed November 1, 2017).

Among a total of 40,790 individuals, the following participants were excluded from this study: participants without DM, patients who had not received any ophthalmologic examination within the past 2 years or whose examination results were missing, patients with estimated glomerular filtration rate (eGFR) with the Modification of Diet in Renal Disease (MDRD) Study equation $<60\,\mathrm{mL}\times\mathrm{min}^{-1}\times1.73\,\mathrm{m}^{-2}$, or patients with urinary albumin-creatinine ratio (UACR) ≥30 mg/g creatinine. The total number of eligible participants was 953 (Fig. 1).

2.2. Measurement

Blood pressure (BP) was measured 3 times in the sitting position after at least 5 minutes of rest. The average of the 3 recorded systolic and diastolic BP values was used in the analyses. Fasting triglycerides and high-density lipoprotein (HDL) cholesterol were measured according to standard procedures using a Hitachi 912 analyzer (Hitachi, Tokyo, Japan) from 2005 to 2006, and a Roche/Hitachi modular P chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany) from 2007 to 2012. Fasting glucose concentrations were measured using a Roche 911 (Roche, Basel, Switzerland) from 2005 to 2006, and a Roche/Hitachi modular P chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany) from 2007 to 2012. For accuracy and consistency in each survey, we followed the Centers for Disease Control and Prevention guidelines that recommend the use of corrected fasting plasma glucose concentration and corrected HDL cholesterol values in the NHANES data. The duration of DM was calculated by the difference between the age at diagnosis and the age at NHANES participation. Those with newly diagnosed DM were given a DM duration of zero years.

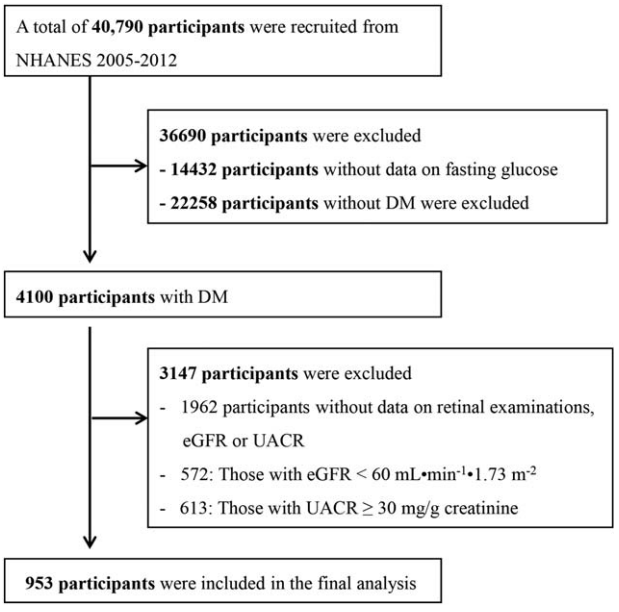

Figure 1. Flow chart for final selection.

All participants completed a structured questionnaire that included health-related questions concerning DR. The questions were as follow:

1. When was the last time you had an eye exam in which the pupils were dilated?
2. Has a doctor ever told you that diabetes has affected your eyes or that you had retinopathy?

Participants who reported to have DR in the questionnaire were classified as DR group. We excluded participants without DR who had not undergone a retinal examination within the past 2 years. Since the NHANES included retinal image data between 2005 and 2008, additional information of DR was available in these cycles. Participants with retinal image were classified as DR group if any following characteristic lesion was present: microaneurysm, blot hemorrhages, retinal exudate, intraretinal microvascular abnormalities, retinal venous beading, retinal new vessels, retinal fibrous proliferation, macular edema, vitreous hemorrhage, or photocoagulation scar. The severity of DR in those with retinal image was presented in supplemental Table 1, http://links.lww.com/MD/C74.

2.3. Statistical analysis

Data, including demographic data, medical condition, anthropometric and clinical measures, and laboratory results, are presented as the median and interquartile range or frequencies and proportions. Normality of the continuous each variable was assessed by use of the Kolmogorov–Smirnov test. Because all continuous variables in the present study showed non-standard normal distribution, Mann–Whitney *U* test was used. Pearson chi-square test was used to compare proportions according to DR. Odds ratios (ORs) with 95% CIs were calculated in multiple logistic regression models according to the presence of DR (case vs control).

The Cochran-Armitage test for trend was used to assess for the presence of an association between diabetic duration, glycated hemoglobin (HbA1c), and UACR on the prevalence of ocular problems. The biological interactive effect between glycemic status and UACR on DR was evaluated in both multiplicative scale and additive scale using logistic regression analysis. The multiplicative interaction analysis was performed by comparing participants with poor glycemic control (HbA1c ≥7.0%), mildly increased UACR (≥8.5 and <30), or both to participants with adequate glycemic control (HbA1c <7.0%) and low UACR. Biological interaction of HbA1c and UACR was evaluated by 3 indices: RERI, the relative excess risk due to the interaction; AP, the attributable proportion due to the interaction; and S, the additive interaction index of synergy. RERI is the excess risk due to interaction relative to the risk without exposure. AP refers to the attributable proportion of disease that is due to interaction

among individuals with both exposures. S is the excess risk from both exposures when there is an additive interaction, relative to the risk from both exposures without interaction. If there was no biological interaction, the 95% CI of RERI and AP included 0, and the CI of S contained 1.

A 2-tailed $P < .05$ was considered statistically significant. Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC) was used for all analyses.

3. Results

3.1. Baseline characteristics

Overall, data from 953 participants (477 men and 495 women) were assessed (Fig. 1). The anthropometric, clinical, and biochemical characteristics of the participants by retinal status are summarized in Table 1. Among the included participants, 20.7% had DR. Compared with controls, participants with DR were more likely to have a long diabetic duration, dyslipidemia, increased glycemic exposure, and a high UACR. However, there were no significant differences between the 2 groups in other baseline characteristics.

3.2. Association of UACR with DR

As shown in Table 2, the multivariate logistic regression analysis demonstrated that UACR (OR, 1.04, 95% CI = 1.02–1.07), diabetic duration (OR, 1.06, 95% CI = 1.04–1.07), and HbA1c (OR, 1.16, 95% CI = 1.04–1.30) were independently associated with DR. In the subgroup analysis for DR determined with a retinal image from NHANES 2005 to 2008, these associations were not attenuated, even after adjustment for age, sex, ethnicity smoking, hypertension, dyslipidemia, body mass index (BMI), estimated glomerular filtration rate (eGFR), systolic blood pressure, and medications of renin-angiotensin system (RAS) inhibitor.

Table 1

Demographic and clinical characteristics according to DR status.

Characteristics	No DR (N = 756)	DR (N = 197)	P
Age, yr	62 (52–70)	61 (50–70)	.656
Sex (% men)	373 (49.3%)	104 (52.8%)	.433
Ethnicity			.131
Hispanic	180 (23.8%)	51 (25.9%)	
Non-Hispanic White	303 (40.1%)	62 (31.5%)	
Non-Hispanic Black	218 (28.8%)	70 (35.5%)	
Other	55 (7.3%)	14 (7.1%)	
Duration of DM, yr*	6 (3–12)	12 (8–20)	<.001
Current smoking (%)	361 (48.0%)	87 (44.2%)	.378
Hypertension (%)	623 (84.1%)	161 (83.9%)	1.000
Dyslipidemia (%)	613 (81.1%)	174 (88.3%)	.023
BMI, kg/m^2	31.4 (27.6–36.5)	30.1 (26.7–35.2)	.025
Systolic BP, mm Hg	126 (115–137)	127 (116–139)	.354
Diastolic BP, mm Hg	69 (61–77)	68 (60–73)	.138
Fasting glucose, mg/dL	134 (11–168)	146.5 (124–191)	.024
HbA1c (%)	6.7 (6.1–7.6)	7.4 (6.5–8.7)	<.001
UACR, mg/g creatinine	8.2 (5.3–13.8)	10.0 (6.7–17.9)	<.001
Triglycerides, mg/dL	126 (90–178)	116 (85–183)	.550
LDL-C, mg/dL	98 (74–123)	104 (78–132)	.116
HDL-C, mg/dL	46 (40–56)	50 (41–58)	.052
eGFR, (mL × min^{-1} × 1.73 m^{-2})†	89.7 (76.7–106.6)	92.3 (77.6–110.5)	.109

Variables are expressed as median (interquartile range) or as frequency (%).
BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, DR = diabetic retinopathy, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, UACR = urinary albumin-creatinine ratio.
* The duration of DM was calculated by the difference between the age at diagnosis and the age at NHANES participation. Those with newly diagnosed DM were given a DM duration of zero years.
† eGFR was calculated using MDRD equation.

Table 2

Multivariate logistic regression analysis for DR.

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Diabetic patients with a questionnaire survey (n = 953)				
UACR	1.04	1.02–1.07	1.04	1.02–1.07
HbA1c	1.29	1.17–1.42	1.16	1.04–1.30
Duration of DM*	1.05	1.04–1.07	1.06	1.04–1.07
Hypertension	0.96	0.61–1.53	1.24	0.69–2.24
Dyslipidemia	1.89	1.17–3.06	1.66	0.97–2.85
Diabetic patients with a retinal image (n = 334)				
UACR	1.07	1.03–1.11	1.07	1.02–1.12
HbA1c	1.46	1.23–1.74	1.30	1.05–1.60
Duration of DM*	1.07	1.04–1.10	1.07	1.04–1.10
Hypertension	1.25	0.52–3.00	1.90	0.61–5.91
Dyslipidemia	1.65	0.82–3.34	1.76	0.76–4.12

Model 1 was adjusted for age, sex, and ethnicity.
Model 2 was adjusted for the variables in Model 1, plus smoking, hypertension, dyslipidemia, BMI, eGFR, systolic blood pressure, RAS inhibitor medication, UACR, HbA1c, and duration of DM.
CI = confidence intervals, DM = diabetes mellitus, DR = diabetic retinopathy, HbA1c = hemoglobin A1c, OR = odds ratio, UACR = urinary albumin-creatinine ratio.
* The duration of DM was calculated by the difference between the age at diagnosis and the age at NHANES participation. Those with newly diagnosed DM were given a DM duration of zero years.

3.3. Synergistic interaction between glycemic exposure and UACR on DR

To determine the association between diabetic duration, HbA1c, and UACR on the development of diabetic ocular problems, we performed the Cochran-Armitage test for trend and found that the prevalence of DR significantly increased in participants with increased UACR and prolonged increased glycemic exposure, suggesting there is possible interaction between UACR and glycemic control on development of DR (Fig. 2).

To examine the interactive effects of glycemic status and UACR on DR, we performed stepwise multiplicative and additive interaction analyses. As shown in Table 3, the multiplicative interaction analysis revealed that participants with a hyperglycemic status and high UACR had a significantly increased risk for

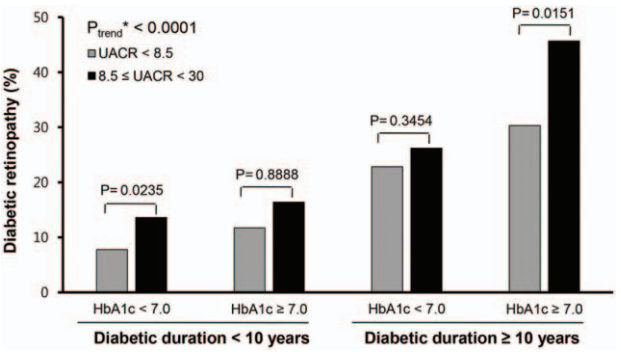

Figure 2. Prevalence of DR according to diabetic duration, HbA1c, and UACR. *Cochran-Armitage test for trend. DR = diabetic retinopathy, HbA1c = glycated hemoglobin; UACR = urinary albumin-creatinine ratio.

Table 3

Interactive effect analysis of glycemic status and UACR.

Categories			Unadjusted		Adjusted	
HbA1c ≥7	UACR ≥8.5	DR/Total (n)	OR	95% CI	OR	95% CI
Total						
(−)	(−)	35/274		Reference		Reference
(−)	(+)	42/231	1.52	0.93–2.47	1.56	0.95–2.55
(+)	(−)	41/193	1.84	1.12–3.02	1.85	1.12–3.04
(+)	(+)	78/249	3.12	2.00–4.86	3.16	2.02–4.94
Duration of DM* <10 yr						
(−)	(−)	14/180		Reference		Reference
(−)	(+)	20/147	1.87	0.91–3.84	1.96	0.94–4.07
(+)	(−)	11/94	1.57	0.68–3.61	1.57	0.68–3.62
(+)	(+)	20/122	2.33	1.13–4.81	2.37	1.14–4.91
Duration of DM* ≥10 yr						
(−)	(−)	21/92		Reference		Reference
(−)	(+)	22/84	1.20	0.60–2.39	1.33	0.66–2.68
(+)	(−)	30/99	1.47	0.76–2.81	1.39	0.72–2.68
(+)	(+)	58/127	2.84	1.56–5.17	2.94	1.60–5.38

Adjusted for age, sex, ethnicity, smoking, hypertension, dyslipidemia, BMI, eGFR, systolic blood pressure, RAS inhibitor medications, UACR, HbA1c, and duration of DM.
CI = confidence intervals, DM = diabetes mellitus, DR = diabetic retinopathy, HbA1c = hemoglobin A1c, OR = odds ratio, UACR = urinary albumin-creatinine ratio.
* The duration of DM was calculated by the difference between the age at diagnosis and the age at NHANES participation. Those with newly diagnosed DM were given a DM duration of zero years.

DR after 10 years of DM (OR, 3.14, 95% CI = 1.59–6.18). Furthermore, additive interaction analysis indicated that there was a significant synergistic effect of hyperglycemic status and high UACR on DR in subjects with prolonged diabetic duration (adjusted RERI = 0.92, 95% CI = 0.10–1.74; adjusted AP = 0.29, 95% CI = −0.82–1.41; adjusted S = 1.76, 95% CI = 1.27–2.25; Table 4).

4. Discussion

In this study, our results demonstrate that a mild increase in urinary albumin excretion, even below the diagnostic threshold of microalbuminuria, is independently associated with an increased risk of DR and suggest that there is a synergistic effect between a prolonged increased glycemic exposure and mildly increased UACR on the development of DR.

Table 4

Indexes of additive biological interactive effect of glycemic status and UACR on DR.

	Unadjusted		Adjusted	
Measure	Estimate	95% CI	Estimate	95% CI
Total				
RERI	0.76	0.16–1.35	0.75	0.15–1.36
AP	0.24	−0.81–1.29	0.24	−0.81–1.29
S	1.56	1.15–1.96	1.54	1.12–1.95
Duration of DM* <10 yr				
RERI	−0.11	−1.05–0.82	–	–
AP	−0.05	−1.70–1.61	–	–
S	0.92	0.65–1.20	–	–
Duration of DM* ≥10 yr				
RERI	1.17	0.50–1.41	1.21	0.52–1.92
AP	0.41	−0.58–1.41	0.42	−0.55–1.38
S	2.75	2.25–3.25	2.70	2.16–3.24

Adjusted for age, sex, ethnicity, smoking, hypertension, dyslipidemia, BMI, eGFR, systolic blood pressure, RAS inhibitor medications, UACR, HbA1c, and duration of DM.
AP = the attributable proportion because of the interaction, CI = confidence intervals, DR = diabetic retinopathy, RERI = the relative excess risk because of the interaction, S = the synergy index, UACR = urinary albumin-creatinine ratio. If there was no biological interaction, the CI of RERI and AP include 0, and the CI of S contains 1.
* The duration of DM was calculated by the difference between the age at diagnosis and the age at NHANES participation. Those with newly diagnosed DM were given a DM duration of zero years.

Microalbuminuria indicates a small increase in leakage of albumin into urine, and it usually implicates the presence of glomerular filtration barrier dysfunction, a significant feature of microvascular complications in patients with DM.[27] In line with earlier evidence, previous epidemiologic studies demonstrated that a small increase in UACR was frequently observed in a diabetic population that went on to develop macro- or microvascular complications,[21,27–29] and that was a strong predictor of increased cardiovascular morbidity and mortality.[30–32] However, the clinical significance of this finding on the initiation and progression of diabetic ocular problems has been overlooked to this point.

In this study, we found that a mild increase in UACR was related to DR, even in subjects without diabetic nephropathy. Many clinical and experimental studies had proved that DR is the most important ocular manifestation of metabolic disturbance in patients with DM,[33–36] and microalbuminuria is a strong predictor of vascular changes in the eyes.[2,16–22] Recently, Ra et al[23] and Chen et al[24] demonstrated that 24-hour urinary albumin excretion >10.7 mg/24 h could predict the development of severe ocular problems in patients with type 2 DM and suggested that the relative risk of DR may be increased with a gradual increase in UACR, long before the appearance of diabetic nephropathy. Furthermore, other population-based studies have reported that increased urinary albumin excretion is associated with other components of metabolic syndrome, increased incidence of cardiovascular diseases, and increased cardiovascular morbidity and mortality, suggesting that a mildly increased UACR, even below the diagnostic criteria for microalbuminuria, may be an indicator of potential vascular dysfunction related to DM.[32,37–39] Such findings indicate that small increases in UACR may indicate the initial development of vascular complications of DM in the eye.

In addition to UACR, we demonstrated that its synergistic interaction with prolonged increased glycemic exposure increased risk of microvascular complications of DM. Experimental studies on the mechanism of initiation of diabetic vascular

complications have proved that long-standing glycemic exposure of the vascular endothelium may cause dysregulation of its protective mechanism, resulting in various forms of diabetic vascular complications.[40,41] Although previous clinical studies found that HbA1c and duration of diabetes has been reported as risk factors for either diabetic nephropathy or DR,[3,9–13,15] they did not support experimental evidence on a potential interaction between metabolic disturbances and endothelial dysfunction in the initiation of microvascular complications because previous studies included subjects with microalbuminuria and overt proteinuria. Thus, our results add clinical evidence on the biologic interaction of increased glycemic exposure and endothelial dysfunction on the initiation of vascular endothelial damage in the eye.

The present study has some limitations. First, the number of subjects who met the inclusion criteria was relatively small as it was a retrospective cross-sectional study. However, this study was larger and included a more diverse population than earlier studies that identified this association. Thus, further large-scale prospective studies are needed in the future. Second, because of the self-reporting of medical history, medication, and use of tobacco and alcohol, a social-desirability bias could not be ruled out. It may have been responsible for results and conclusions that conflicted with previous research. Third, as with any observational study, this analysis may not be free from various confounding factors, selection bias, and attribution bias. Finally, participants may have forgotten relevant details.

5. Conclusions

Our results imply that mildly increased UACR, even below the diagnostic criteria for microalbuminuria, appears to be associated with DR, and could be a valuable early predictor of diabetic microvascular complications. However, for more definite clarification of this association, more research including a large population-based prospective study should be conducted.

6. Author contributions

S. Moon contributed to the design and conduct of the study, data analysis, data interpretation, and manuscript writing. H.J. Yoo, Y.H. Ahn, G.H. Kim contributed to the study design and data interpretation. J.M. Yu and J.S. Park contributed to study design and conduct of the study, data analysis, and data interpretation. All authors read, revised, and approved the manuscript.

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