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Retinal Nerve Fiber Layer Loss Is Associated with Urinary Albuimin Excretion in Patients with Type 2 Diabetes

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Objectives: To identify the factors associated with retinal nerve fiber layer (RNFL) loss in patients with type 2 diabetes.

Design: Cross-sectional study.

Participants: Ninety-six nonglaucomatous patients with type 2 diabetes without renal impairment (estimated glomerular filtration rate, ≥60 ml/minute per 1.73 m^2).

Methods: Eyes were divided into 2 groups based on the presence or absence of RNFL defects detected by red-free retinal fundus photography. All participants underwent an eye fundus examination, and the urinary albumin-to-creatinine ratio (ACR) was determined. A cardiovascular autonomic function test was performed using the following heart rate variability parameters: expiration-to-inspiration ratio, response to the Valsalva maneuver, and standing. Multiple logistic regression analyses were performed to determine potential risk factors related to the presence of RNFL defects in these patients.

Main Outcomes and Measures: The association between RNFL defects and diabetic complications.

Results: Among the patients, 43 (44.8%) had localized RNFL defects (group 1), whereas the others (55.2%) did not (group 2). The RNFL defects occurred more frequently on the superior side (75.6% and 71.0% in right and left eyes, respectively) compared with the inferior side (13.8% and 0.0% in right and left eyes, respectively). Patients with RNFL defects (group 1) had significantly higher rates of diabetic retinopathy (60.5%) compared with those without RNFL defects (group 2; 32.1%; $P = 0.007$). The urinary ACR was significantly higher in patients with RNFL defects than in those without defects (45.3±72.1 μg/mg vs. 15.4±17.3 μg/mg creatinine, respectively; $P = 0.015$), whereas autonomic function test grading was similar between the groups. The urinary ACR was the only factor related to visual field defect location in both univariate ($P = 0.021$) and multivariate ($P = 0.036$) logistic regression analyses after adjusting for age; gender; presence of diabetic retinopathy; diabetes duration; smoking; statin use; and antiplatelet, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment.

Conclusions: Urinary albumin excretion was associated with nerve fiber layer loss in patients with type 2 diabetes. Careful examination of the optic nerve head may be necessary, particularly in patients with type 2 diabetes exhibiting albuminuria. *Ophthalmology 2015;■:1–6 © 2015 by the American Academy of Ophthalmology.*

Retinal nerve fiber layer (RNFL) loss, a manifestation of diabetic optic neuropathy, occurs frequently in patients with diabetes.[1–5] Diabetic optic neuropathy, represented by RNFL loss, is well distinguished from glaucomatous optic nerve damage.[6] Nerve fiber loss in patients with diabetes is thought to be caused by various mechanisms, including ischemia, accumulation of advanced glycation end products around the optic nerve head,[7] and impaired retrograde axonal transport.[8,9] Numerous studies have focused on the effect of diabetes on retinal vessels. However, relatively few studies are available on its effect on retinal neurons.

Diabetic retinopathy (DR) is associated with RNFL loss in patients with type 1 and 2 diabetes,[1,2,5] and RNFL loss is followed by cotton wool spots.[2,10] However, diabetes-associated RNFL defects develop during the early stages of vascular retinopathy, even before the onset of retinopathy.[3,4] Retinal nerve fiber layer loss also has been reported in patients with diabetes without diabetic retinopathy but with poorly controlled blood glucose.[5] In this regard, an RNFL defect could be considered another ocular association of diabetes other than DR.

Assessing RNFL loss is crucial because RNFL loss is irreversible and may contribute to diabetic optic nerve dysfunction, such as reduced color sensitivity or impaired color vision.[11,12] Although several studies have indicated the prevalence and patterns of RNFL loss in patients with type 2 diabetes, little information is available on the systemic risk factors for RNFL loss in this population. This cross-sectional study was performed to identify independent factors contributing to the development of RNFL defects in nonglaucomatous patients with type 2 diabetes mellitus without renal impairment.

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Methods

Study Design and Population

In the current study, 96 subjects with type 2 diabetes 40 to 80 years of age who underwent biochemical and ophthalmic examinations were included between February 2013 and February 2014 at St. Vincent's Hospital, Suwon, South Korea. This study was performed according to the tenets of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review and Ethics Boards of The Catholic University, St. Vincent's Hospital.

Patients were excluded if they were mentally ill, pregnant, or unable to conduct self-care activities, or had type 1 diabetes, gestational diabetes, or any severe illness, such as malignancy, severe infection, liver cirrhosis, or heart failure. Additional exclusion criteria were a history of coronary revascularization or ventricular and supraventricular arrhythmias. Patients with type 2 diabetes and impaired renal function (estimated glomerular filtration rate, <60 ml/minute per 1.73 m^2) also were excluded. All eligible patients were required to have no signs of a glaucomatous optic disc (focal or generalized narrowing or disappearance of neuroretinal rim, disc hemorrhage, or cup-to-disc asymmetry >0.2). In addition, they were required to have normal visual field (VF) results on all automated perimetry during the follow-up. A normal VF was defined when the glaucoma hemifield test result was within normal limits and the field did not meet the following criteria for a VF defect: (1) 3 or more adjacent points with $P < 0.05$ on a pattern deviation probability map or (2) 2 or more adjacent points with $P < 0.02$ on a pattern deviation probability map. All patients were required to have best-corrected visual acuity of 20/40 or better, spherical refraction within ±5.0 diopters (D), cylinder correction within ±3.0 D, open angles on gonioscopy, and no history of increased intraocular pressure of more than 21 mmHg or ocular trauma. Subjects with ocular or neurologic diseases other than DR or associated interventions (e.g., panretinal photocoagulation) were excluded.

Ophthalmic and Laboratory Examinations

All participants underwent a comprehensive ophthalmic examination, including a detailed review of medical and ocular histories, best-corrected visual acuity measurement, slit-lamp biomicroscopy, Goldmann applanation tonometry, dilated stereoscopic examination of the optic nerve head and fundus, stereoscopic optic disc photography and red-free RNFL photography (CF-60UD; Canon, Tokyo, Japan), achromatic automated perimetry using the 24-2 Swedish interactive threshold algorithm standard program (Humphrey Visual Field Analyzer; Carl Zeiss-Meditec, Inc, Dublin, CA), and optical coherence tomography scans (Stratus OCT, Carl Zeiss Meditec, Inc) to measure peripapillary RNFL thickness. Peripapillary RNFL thickness was determined 3 times at 256 points around a set diameter (3.4 mm) circle using the fast RNFL program. Only well-focused, well-centered images without eye movement and a signal strength of 7 or more were used. A global average RNFL thickness provided by the software was used for analysis. Diabetic retinopathy was graded by a retinal specialist (D.-H.J.) assigned to each eye according to the modified Airlie House classification system.[13] The patients were assigned to 1 of 4 groups: no evidence of DR, presence of mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, and severe NPDR or proliferative diabetic retinopathy.

Diabetes was diagnosed in subjects with a fasting plasma glucose of 126 mg/dl or more or symptoms of diabetes plus casual plasma glucose concentration of 200 mg/dl or more based on the 1997 and 2003 revisions of the American Diabetes Association guidelines.[14] Diabetes treatment was categorized as using insulin, using an oral agent (sulfonylurea/nonsulfonylurea), or lifestyle modifications alone. Blood samples were collected from all patients after they had fasted for 12 hours, and blood glucose was measured using an automated enzymatic method. Glycated hemoglobin was measured using high-performance liquid chromatography with a reference range of 4.4% to 6.4% (Bio-Rad, Montreal, Canada). Hypertension was defined as systolic blood pressure 140 mmHg or more and diastolic blood pressure of 90 mmHg or more or use of any antihypertensive medications.[15] Standard lipid profiles (total cholesterol, triglycerides, and high-density lipoprotein cholesterol) were measured enzymatically using an automated analyzer (model 736-40; Hitachi, Tokyo, Japan).

Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study equation.[16] The albumin-to-creatinine ratio (ACR) was calculated in first-voided spot urine samples.

The cardiovascular autonomic function test was conducted by one examiner using the Ewing method, which included tests for heart rate variability, such as expiration-to-inspiration ratio, postural change from lying to standing, and responses to the Valsalva maneuver,[17] as described in detail elsewhere.[18] Each of the 3 ratios described above was scored as normal = 0 or abnormal = 1, for a total maximum score of 3. The staging of cardiac autonomic neuropathy (CAN) was confirmed as follows: a score of 0 was defined as normal autonomic function; a score of 1 was defined as early CAN; and a score of 2 or more was defined as definite CAN.[18,19]

Assessment of Retinal Nerve Fiber Layer Defects

Color disc and red-free RNFL photographs were obtained using standard settings on a digital fundus camera (CF-60UD; Canon, Tokyo, Japan) at 60° view. Color disc photographs and red-free RNFL images were evaluated independently in random order and in a blinded manner, without knowledge of the clinical information, by 2 of the authors (J.A.C., and Y.R.P.). Localized RNFL defects were diagnosed as described previously.[20] A decision on

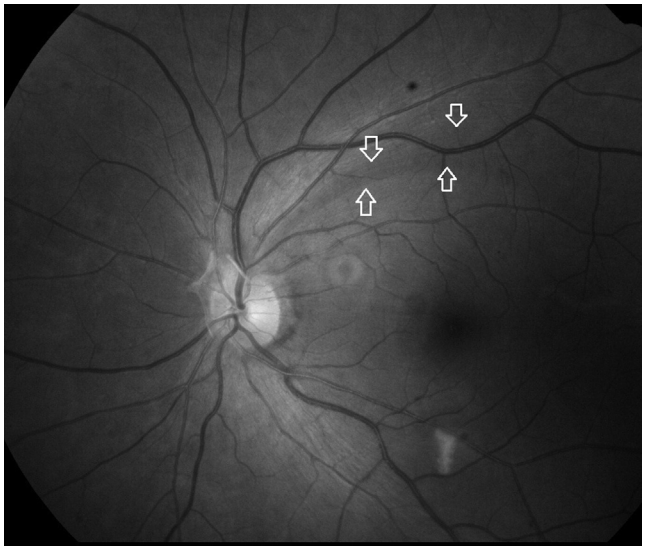

Figure 1. Red-free fundus photograph showing a representative case of retinal nerve fiber layer (RNFL) defect in a 43-year-old man with type 2 diabetes. A narrow RNFL defect is shown at the 1-o'clock position in the red-free photograph (white arrows). A cotton-wool spot is seen on the inferior-temporal side of the retina.

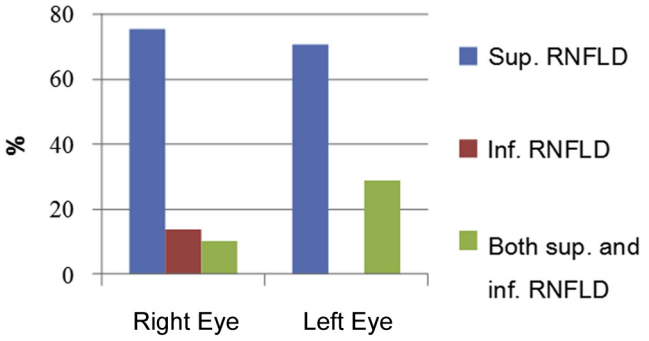

Figure 2. Bar graph showing the location frequency for nonglaucomatous retinal nerve fiber layer defects (RNFLDs) in patients with type 2 diabetes (n = 30). Inf. = inferior; Sup. = superior.

the red-free photographs was made based on consensus between the 2 independent observers. If the 2 observers disagreed, the subject was excluded from further analysis. Based on this information, patients with glaucoma were divided into 2 groups based on the presence (group 1) or absence (group 2) of RNFL defects (Fig 1).

Statistical Analysis

Clinical characteristics were compared between eyes with and without RNFL defects and between eyes with and without DR using Student *t* test. Simple and multiple logistic regression analyses were performed to determine factors related to the RNFL defects. The presence of a RNFL defect in any eye (right or left eye) was the dependent variable, and the independent variables were age, gender, presence of DR, ACR, diabetes duration, current smoking status, use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and use of antiplatelet medication. All analyses were performed using SPSS for Windows version 14.0 (SPSS, Inc, Chicago, IL). A *P* value less than 0.05 was considered significant.

Results

Both observers agreed that 43 patients had RNFL defects and 53 did not, but they disagreed about 9 patients (Cohen's κ coefficient, 0.83). Of the 96 patients enrolled, mean age was 56.0±8.9 years, mean glycated hemoglobin level was 7.6±1.6%, and mean diabetic duration was 8.4±7.4 years, respectively. Forty-three patients (44.8%) had localized RNFL defects. The RNFL defects occurred more frequently on the superior side (75.6% and 71.0% in right and left eyes, respectively) compared with the inferior side (13.8% and 0.0% in right and left eyes, respectively; Fig 2).

A comparison of clinical characteristics between subjects with and without an RNFL defect is shown in Table 1. The percentage of patients with DR was significantly higher in those with an RNFL defect than in those without (60.5% vs. 32.1%, respectively; $P = 0.007$). The CAN grade did not differ between patients with and without an RNFL defect ($P = 0.370$). The ACR was significantly higher in patients with an RNFL defect than in those without (45.3±72.1 μg/mg creatinine vs. 15.4±17.3 μg/mg

Table 1. Comparisons of Characteristics According to the Presence of Retinal Nerve Fiber Layer Defect in Patients with Type 2 Diabetes

Characteristics	Subjects without Retinal Nerve Fiber Layer Defect (n = 53)	Subjects with Retinal Nerve Fiber Layer Defect (n = 43)	*P* Value
Women (%)	38.0	55.8	0.100
Age (yrs)	55.8±10.6	56.2±7.9	0.822
Average RNFL thickness (μm)	98.6±20.3	96.8±13.8	0.636
Diabetes duration (yrs)	8.1±7.2	8.7±6.7	0.677
Hypertension (%)	52.8	32.6	0.213
Presence of DR (%)	32.1	60.5	0.007
Diabetes treatment (%)			
Insulin	5.8	5.0	0.592
Sulfonylurea	60.0	47.6	0.455
Staging of CAN (%)			
Normal	18.0	16.3	0.370
Early	56.0	44.2	
Advancecd	26.0	39.5	
Current smoker (%)	32.0	23.3	0.241
Statin (%)	49.0	55.8	0.327
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (%)	35.3	25.6	0.215
Antiplatelet use (%)	42.3	32.6	0.223
Laboratory findings			
Fasting plasma glucose (mg/dl)	143.7±54.6	127.0±37.1	0.106
HbA1c (%)	7.6±1.4	7.7±1.8	0.779
eGFR (ml/minute per 1.73 m^2)	94.5±19.1	94.6±22.4	0.980
ACR (μg/mg creatinine)	15.4±17.3	45.3±72.1	0.015
Total cholesterol (mg/dl)	170.6±35.9	155.8±40.6	0.071
Triglyceride (mg/dl)	155.6±109.8	128.4±67.6	0.168
LDL (mg/dl)	95.2±25.8	86.0±30.6	0.120
HDL (mg/dl)	42.1±8.1	42.3±7.3	0.907

ACR = urinary albumin-to-creatinine ratio; CAN = cardiac autonomic neuropathy; DR = diabetic retinopathy; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RNFL = retinal nerve fiber layer.

Table 2. Comparisons of Characteristics According to the Presence of Diabetic Retinopathy in Patients with Type 2 Diabetes

Characteristics	Subjects without Diabetic Retinopathy (n = 54)	Subjects with Diabetic Retinopathy (n = 42)	P Value
Women (%)	45.3	46.5	0.534
Age (yrs)	55.8±10.3	56.2±8.3	0.861
Average RNFL thickness (μm)	96.9±19.8	98.8±14.8	0.625
Diabetes duration (yrs)	6.8±5.9	10.4±7.6	0.010
Hypertension (%)	43.4	37.2	0.522
Diabetes treatment (%)			
Insulin	0.0	12.2	0.014
Sulfonylurea	46.2	53.7	0.305
Staging of CAN (%)			
Normal	19.6	14.3	0.300
Early	54.9	45.2	
Definite	25.5	40.5	
Current smoker (%)	27.5	28.6	0.543
Statin (%)	50.0	54.8	0.401
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (%)	34.6	26.2	0.257
Antiplatelet use (%)	30.2	47.6	0.064
Laboratory findings			
Fasting plasma glucose (mg/dl)	136.3±41.9	138.6±51.1	0.813
HbA1c (%)	7.3±1.1	8.1±1.9	0.020
eGFR (ml/minute per 1.73 m^2)	92.2±19.5	97.4±21.8	0.229
ACR (μg/mg creatinine)	16.9±23.9	44.0±71.2	0.030
Total cholesterol (mg/dl)	166.1±36.1	161.3±41.9	0.553
Triglyceride (mg/dl)	151.8±104.7	132.7±77.5	0.336
LDL (mg/dl)	92.2±29.0	86.2±27.5	0.322
HDL (mg/dl)	42.0±16.3	42.4±8.2	0.793

ACR = albumin-to-creatinine ratio; CAN = cardiac autonomic neuropathy; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RNFL = retinal nerve fiber layer.

creatinine, respectively; $P = 0.015$). No significant differences were observed between the 2 groups for the other variables, such as medication use, diabetes duration, estimated glomerular filtration rate, or average RNFL thickness.

The ACR was significantly higher in patients with DR than in those without (44.0±71.2 μg/mg creatinine vs. 16.9±23.9 μg/mg creatinine, respectively; $P = 0.030$; Table 2). Diabetes duration also was longer in patients with DR than in those without (10.4±7.6 years vs. 6.8±5.9 years; $P = 0.010$). The glycated hemoglobin level was significantly higher in patients with DR than in those without (8.1±1.9% vs. 7.3±1.1%; $P = 0.020$). Use of insulin was more frequent in patients with DR than in those without ($P = 0.014$).

The logistic regression analyses results are shown in Table 3. The ACR level ($P = 0.021$) was associated significantly with the presence of an RNFL defect in the univariate logistic regression analysis, which was maintained after controlling for age, gender, ACR, presence of DR, diabetes duration, current smoking status, and statin, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, and antiplatelet use.

Discussion

This present study investigated factors contributing to the presence of RNFL defects in patients with type 2 diabetes without renal impairment. The results indicated that approximately 45% of diabetic eyes are accompanied by RNFL defects (Table 1). We showed that an increase in albuminuria tended to increase the risk for nerve fiber layer loss in patients with type 2 diabetes (Table 2). After controlling for other confounding factors, albuminuria was the only factor related to the presence of a RNFL defect (Table 3). We are unaware of previous studies determining the effects of systemic risk factors on RNFL loss in patients with diabetes.

Microalbuminuria is an important prognostic marker for kidney disease in patients with diabetes or hypertension.[21–23] It is also a well-known marker of vascular endothelial dysfunction,[24,25] which indicates impaired ability of the endothelium to maintain vascular homeostasis

Table 3. Association between Urinary Albumin-to-Creatinine Ratio and Prevalence of the Retinal Nerve Fiber Layer Defect in Nonglaucomatous Type 2 Diabetic Population

	Model 1	Model 2	Model 3
ACR			
Exp (B)	1.019	1.022	1.018
95% confidence interval	1.003–1.036	1.005–1.039	1.001–1.035
P value	0.021	0.012	0.036

ACR = albumin-to-creatinine ratio; Exp (B) = exponentiation of the B coefficient.
Mutltivariate logistic regression models were adjusted as follows: model 1, unadjusted; model 2, age and gender; model 3, model 2 plus presence of diabetic retinopathy, diabetes duration, smoking, use of statin, antiplatelet, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

properly, and could be an important determinant of altered vascular reactivity.[26] Endothelial dysfunction, which is strongly related to autoregulation, is particularly important for retinal circulation because the retinal blood supply is controlled mainly by vascular autoregulation, rather than by autonomic control. Thus, we found increased albuminuria in patients with DR, but no differences in autonomic function test results were noted (Table 2). It seems that diabetic optic neuropathy is partly associated with endothelial dysfunction by decreasing blood supply to the optic nerve head, considering that the superficial portion of the optic nerve head displays microvascular morphologic features similar to those of the retinal circulation.[27] In this regard, diabetic optic neuropathy seems to be caused by vascular insufficiency of the optic nerve head, as well as a manifestation of diabetic neuropathy.

We adjusted for the presence of DR to assess the association between urinary albumin excretion and nerve fiber layer loss because microalbuminuria is an important risk factor for DR[28] and also because DR is also associated with endothelial dysfunction in patients with type 2 diabetes.[18] As expected, the incidence of DR was significantly higher in patients with an RNFL defect than without (Table 2). However, increased albuminuria remained an independent risk factor for nerve fiber layer loss after adjusting for DR (Table 3). Consistent with our results, Özdek et al[5] reported that RNFL thickness on the superior side tends to decrease in patients with diabetes and poor glucose control as well as with DR severity. Our results suggest that vascular insufficiency may play a role in optic nerve head damage, regardless of DR.

In this study, we excluded eyes with a glaucomatous optic disc because an RNFL defect is also a characteristic feature of glaucoma. Consistent with previous studies,[3–5] we found that RNFL defects occurred predominantly in the optic disc on the superior side (Fig 1). The locations of the RNFL defects in patients with diabetes seemed to be clearly different from those resulting from glaucomatous RNFL damage, which occurs predominantly in the inferior temporal retina.[29] The lamina cribrosa is the principal region for death of ganglion cells in patients with glaucoma, and the main pathogenic features of glaucoma are deformation and compression of the lamina cribrosa and large pores associated with a decrease in connective tissue.[30,31] In particular, the inferior temporal lamina cribrosa has larger single pore sizes and the least amount of supporting connective tissue,[32,33] which may be associated with greater susceptibility to damaging nerve fibers passing through these regions. A vascular insufficient optic nerve head and structurally normal lamina cribrosa may result in RNFL loss in the optic disc on the superior side because of gravitational influence. In contrast, a glaucomatous optic nerve head with a regional lamina deformation may result in RNFL loss in the optic disc on the structurally susceptible side.

Despite the regional differences between the 2 diseases, co-occurrence of glaucoma and diabetes is quite common. Patients with type 2 diabetes often have elevated intraocular pressure, and many reports suggest that diabetes may be a risk factor for glaucoma.[34–36] Therefore, a cautious clinical examination is required in patients with diabetes and an RNFL defect.

Our study had several limitations. We used red-free fundus photography to detect RNFL defects, which is superior to color fundus photography. Subjects with diffuse atrophy or ambiguous results were excluded from our analyses, which may have affected the study results. We excluded patients with VF defects to avoid confounding the results of RNFL loss caused by glaucoma. This may have excluded patients with VF defects caused by diabetes-associated RNFL loss and could have affected the final results. Because this was a cross-sectional study, a causal relationship cannot be concluded; therefore, our results should be interpreted with caution. Finally, ACR is known to have high intraindividual variation, particularly in patients with intermittent microalbuminuria.[37] A highly variable ACR may have biased the results, because only a single measurement in each patient was considered.

In conclusion, we demonstrated that albuminuria was an independent risk factor for nerve fiber layer loss in patients with type 2 diabetes without renal impairment. Careful examination of the optic disc may be necessary, particularly in patients with type 2 diabetes exhibiting albuminuria. Further studies are necessary to determine the mechanism underlying the pathogenesis of diabetic nerve fiber layer loss.

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Abbreviations and Acronyms:
ACR = albumin-to-creatinine ratio; **CAN** = cardiac autonomic neuropathy; **D** = diopter; **RNFL** = retinal nerve fiber layer; **VF** = visual field.

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