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, $\geq$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$\pm$72.1 µg/mg vs. 15.4$\pm$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.

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
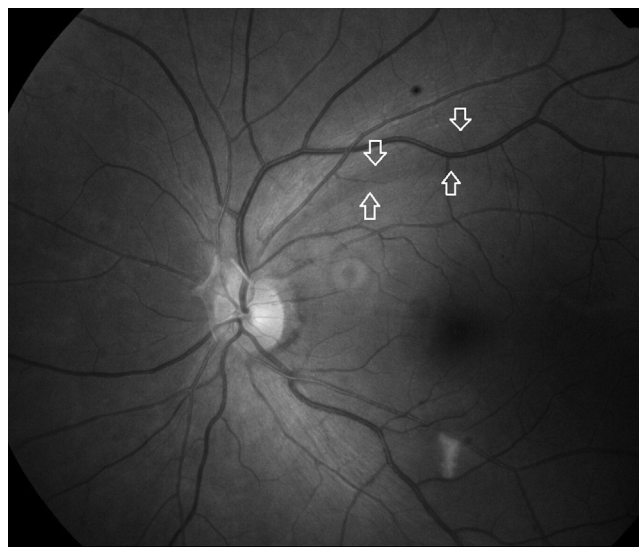

Figure 1. Red-free fundus photograph showing a representative case of retinal nerve fiber layer (RNFL) defect in a 43-year-old man with type 2 diabetes. A narrow RNFL defect is shown at the 1-o'clock position in the red-free photograph (white arrows). A cotton-wool spot is seen on the inferior-temporal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