

### Changes in the lamina cribrosa in patient groups differing in severity of diabetic polyneuropathy

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**Background:** To our knowledge, no clinical study has previously been performed to investigate morphometric changes in the lamina cribrosa in diabetes mellitus (DM) patients differing in severity of diabetic polyneuropathy (DPN).

**Purpose:** To identify changes in the lamina cribrosa in patients with DPN differing in severity of the disease.

**Materials and Methods:** A total of 575 patients (1150 eyes) with type 2 diabetes mellitus were included in the prospective analysis of changes in the lamina cribrosa. DPN was diagnosed in 210 (36.5%) patients with DM. In addition to routine eye examination, retinal and optic nerve OCT was performed. Thickness of the cribriform plate and scleral canal area were measured.

**Results:** A relationship was found between the state of the lamina cribrosa and the severity of diabetic polyneuropathy in patients with diabetes mellitus. The mean thicknesses of the lamina cribrosa in DM patients without evidence of DPN, and those with N1A, N1B, N2A, N2B, and N3 stages DPN, were 1.5-fold, 1.9-fold, 2.0-fold, 2.7-fold, 2.8-fold, and 3.0-fold higher than in controls ( $303 \pm 56 \mu\text{m}$ ) ( $p < 0.001$ ).

**Conclusion:** We found that, in patients with DM, lamina cribrosa thickness increased with increase in severity of DPN.

#### Introduction

Early diagnosing neurological complications of diabetes mellitus (DM) is a challenge, and therefore, the search for reliable methods for diagnosing diabetic polyneuropathy (DPN) is still of importance [1, 2]. Diabetic optic neuropathy is a manifestation of a systemic injury to the nervous system, polyneuropathy, in DM [3]. That is, theoretically, the severity of diabetic nerve fiber damage in general may be assessed through changes in the optic nerve and vice versa, and diabetic retinopathy may be regarded as a “model” of systemic DPN [3-6]. The literature is, however, scarce on this issue. We have failed to find any reports on the features of optic nerve damage in patients with different severity of DPN. Findings of some studies are indicative of potential optic nerve damage (i.e., primary damage to ganglion cell axons, and damage secondary to alterations in their blood supply or axoplasmatic current) in the lamina cribrosa with diabetic changes [7].

Changes in the biochemical properties of the lamina cribrosa in diabetes have been established in a recent ex vivo study [7]. It is well known that optic nerve head (ONH) biomechanics depends on the anatomical, chemical

and physical properties of the lamina cribrosa and affect its capacity to provide morphological and functional support for nerve fibers [8-11]. To our knowledge, no clinical study has previously been performed to investigate morphometric changes in the lamina cribrosa in diabetes mellitus patients differing in severity of DPN.

The purpose of this study was to identify changes in the lamina cribrosa in patients with DPN differing in severity of the disease.

#### Materials and Methods

A total of 575 patients (1150 eyes) with type 2 diabetes mellitus (T2DM) were included in the prospective analysis of changes in the lamina cribrosa. Inclusion criteria were no history of glaucoma; Goldmann IOP of 21 mmHg or less; emmetropic, hypermetropic or low myopic eyes; no cataract or mild age-related cataract; and no history of surgery or laser. The patients' age ranged from 44 to 69 years (mean  $\pm$  SD,  $55.9 \pm 7.8$  years). Four hundred and thirteen (71.8%), 93 (16.2%) and 69 (12.0%) had

duration of DM of <5, 5-10 and >10 years, respectively. Three hundred and sixty-five patients with DM (63.5%) were classified as those with no evidence for DPN (N0 stage as per the Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy [12, 13]). DPN was diagnosed in 210 (36.5%) patients with DM. Asymptomatic DPN was observed in 101 (17.5%) patients with DM, including 47 (8.1%) patients with N1A stage and 54 (9.4%) patients with N1B stage. Symptomatic DPN was found in 89 (15.5%) patients with DM, including 46 (8.0%) patients with N2A stage and 43 (7.5%) patients with N2B stage, and disabling DPN (N3 stage) was found in 20 (3.5%) patients with DM. The control group comprised 50 healthy individuals (50 eyes).

All patients underwent a routine eye examination including visual acuity and a dilated fundus examination. In addition, retinal and optic nerve OCT (RTVue-100, Optovue, Fremont, CA) was performed. We used a novel technique for measuring the thickness of the cribriform plate with software programs LC\_Thickness\_programm.m and main\_low\_noise\_filters\_programm.m which is based on (1) the adaptive compensation algorithm for the removal of high-rank noise in deep layers of the optic nerve head and improvement in visualization of the posterior margin of the cribriform plate and (2) B-scan image processing with three digital filters (a Butterworth low-pass filter for inverse image and Daubechies low-pass wavelet filters for original and inverse images) [14]. In addition, SD-OCT-based measurements of the scleral canal area were performed. LC\_cut\_position\_programm.m was used to select the depth dimension, and LC\_diameter\_calculation\_programm.m was used to improve the selected image with basic digital filters and to identify the highest quality image for measurements [14].

Means (M), standard deviations ( $\sigma$ ), standard errors of the mean (SEM) were calculated using Microsoft Excell 2000. In addition, coefficients of variation (Cv), significance (p), 95% confidence intervals (CI) were calculated. Statistical analyses were performed using ANOVA. The level of significance  $p \leq 0.05$  was assumed.

## Results

A correlation was found between the status of the lamina cribrosa and the severity of DPN in patients with DM. The thickness of the lamina cribrosa was found to depend on the severity of DPN. Thus, in DM patients without evidence of DPN, the mean thickness of the lamina cribrosa was  $466 \pm 71 \mu\text{m}$  (range,  $284 \mu\text{m}$  to  $553 \mu\text{m}$ ; 95% CI,  $405 \mu\text{m}$  to  $508 \mu\text{m}$ ), compared to  $583 \pm 73 \mu\text{m}$  (range,  $467 \mu\text{m}$  to  $698 \mu\text{m}$ ; 95% CI,  $523 \mu\text{m}$  to  $649 \mu\text{m}$ ),  $594 \pm 76 \mu\text{m}$  (range,  $478 \mu\text{m}$  to  $705 \mu\text{m}$ ; 95% CI,  $531 \mu\text{m}$  to  $657 \mu\text{m}$ ),  $816 \pm 79 \mu\text{m}$  (range,  $687 \mu\text{m}$  to  $936 \mu\text{m}$ ; 95% CI,  $756 \mu\text{m}$  to  $878 \mu\text{m}$ ),  $846 \pm 75 \mu\text{m}$  (range,  $699 \mu\text{m}$  to  $949 \mu\text{m}$ ; 95% CI,  $784 \mu\text{m}$  to  $903 \mu\text{m}$ ), and  $903 \pm 73 \mu\text{m}$  (range,  $707 \mu\text{m}$  to  $1203 \mu\text{m}$ ; 95% CI,  $837 \mu\text{m}$  to  $979 \mu\text{m}$ ) in those with N1A, N1B, N2A, N2B, and N3 stages DPN, respectively (Table 1). Therefore, the mean thicknesses of the lamina cribrosa in DM patients without evidence of

DPN, and those with N1A, N1B, N2A, N2B, and N3 stages DPN, were 1.5-fold, 1.9-fold, 2.0-fold, 2.7-fold, 2.8-fold, and 3.0-fold higher than in controls ( $303 \pm 56 \mu\text{m}$ ) ( $p < 0.001$ ). The mean thicknesses of the lamina cribrosa was the highest in DM patients with N3 stage DPN, which was 1.9-fold, 1.5-fold, 1.5-fold, and 1.1-fold higher than in DM patients without evidence of DPN, and those with N1A, N1B, and N2A stages DPN, respectively ( $p < 0.001$ ), and was not significantly different from that in DM patients with N2A stage DPN ( $p > 0.05$ ).

No relationship between the scleral canal area and the severity of the disease was found in patients with DPN. Thus, in DM patients without evidence of DPN, the mean scleral canal area was  $2.77 \pm 0.82 \text{ mm}^2$  (range,  $1.71 \text{ mm}^2$  to  $5.53 \text{ mm}^2$ ; 95% CI,  $2.14 \text{ mm}^2$  to  $3.50 \text{ mm}^2$ ), compared to  $2.70 \pm 0.83 \text{ mm}^2$  (range,  $1.52 \text{ mm}^2$  to  $5.50 \text{ mm}^2$ ; 95% CI,  $2.06 \text{ mm}^2$  to  $3.37 \text{ mm}^2$ ),  $2.68 \pm 0.87 \text{ mm}^2$  (range,  $1.45 \text{ mm}^2$  to  $5.53 \text{ mm}^2$ ; 95% CI,  $2.07 \text{ mm}^2$  to  $3.29 \text{ mm}^2$ ),  $2.59 \pm 0.81 \text{ mm}^2$  (range,  $1.27 \text{ mm}^2$  to  $5.34 \text{ mm}^2$ ; 95% CI,  $1.98 \text{ mm}^2$  to  $3.18 \text{ mm}^2$ ),  $2.55 \pm 0.80 \text{ mm}^2$  (range,  $1.39 \text{ mm}^2$  to  $5.21 \text{ mm}^2$ ; 95% CI,  $1.94 \text{ mm}^2$  to  $3.13 \text{ mm}^2$ ), and  $2.52 \pm 0.78 \text{ mm}^2$  (range,  $1.40 \text{ mm}^2$  to  $5.53 \text{ mm}^2$ ; 95% CI,  $2.07 \text{ mm}^2$  to  $2.98 \text{ mm}^2$ ), in those with N1A, N1B, N2A, N2B, and N3 stages DPN, respectively (Table 2). Therefore, in DM patients without evidence of DPN, and in those with N1A, N1B, N2A, N2B, and N3 stages DPN, the mean scleral canal area was not significantly different from that in the control group ( $2.64 \pm 0.77 \text{ mm}^2$ ) ( $p > 0.05$ ).

Given the close contact between the lamina cribrosa and retinal ganglion cell axons, it seems reasonable to assume that the thickness of the lamina cribrosa is associated with the course of diabetic optic neuropathy. We found that, in patients with DM, lamina cribrosa thickness increased with increase in severity of DPN.

## Conclusion

A relationship was found between the state of the lamina cribrosa and the severity of diabetic polyneuropathy in patients with diabetes mellitus, i.e., lamina cribrosa thickness increased with increase in severity of DPN: the mean thicknesses of the lamina cribrosa in DM patients without evidence of DPN, and those with N1A, N1B, N2A, N2B, and N3 stages DPN, were 1.5-fold, 1.9-fold, 2.0-fold, 2.7-fold, 2.8-fold, and 3.0-fold higher than in age-matched controls.

## References

1. Avetisov SE, Chernenkova NA, Surnina ZV. [Clinical features and diagnosis of diabetic polyneuropathy]. Vestn Oftalmol. 2017;133(5):98-102. Russian
2. Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017 Jan; 40(1):136-54.
3. Tsyrenzhapova RB. [Peripheral nervous system injury in carbohydrate metabolism impairments]. [Cand Sc (Med) Thesis Abstract]. Tomsk: Siberian State Medical University; 2015. 129 p. Russian

4. Krasavina MI, Astakhov SY, Shadrachev FE, Dal' NY. [Ophthalmic markers of diabetic polyneuropathy]. *Oftal'mologicheskie vedomosti*. 2016;IX (1):38–46. Russian
5. Shahidi AM, Sampson GP, Pritchard N, Edwards K, Russell A, et al. Exploring retinal and functional markers of diabetic neuropathy. *Clin Exp Optom*. 2010 Sep; 93(5):309-23.
6. Srinivasan S, Dehghani C, Pritchard N, Edwards K, Russell AW, et al. Optical coherence tomography predicts 4-year incident diabetic neuropathy. *Ophthalmic Physiol Opt*. 2017 Jul; 37 (4):451-9.
7. Terai N, Spoerl E, Haustein M, et al. Diabetes mellitus affects biomechanical properties of the optic nerve head in the rat. *Ophthalmic Res*. 2012; 47(4):189-94.
8. Amano S, Kaji Y, Oshika T, et al. Advanced glycation end products in human optic nerve head. *Br J Ophthalmol*. 2001 Jan;85(1):52-5
9. Lee EJ, Kim TW, Kim M, Kim H. Influence of lamina cribrosa thickness and depth on the rate of progressive retinal nerve fiber layer thinning. *Ophthalmology*. 2015; 122:721-9.
10. Sigal IA, Ethier CR. Biomechanics of the optic nerve head. *Exp Eye Res*. 2009; 88(4): 799-807.
11. Spoerl E, Boehm AG, Pillunat LE. The influence of various substances on the biomechanical behavior of lamina cribrosa and peripapillary sclera. *Invest Ophthalmol Vis Sci*. 2005 Apr;46(4):1286-90.
12. Boulton AJ. Diabetic neuropathy: classification, measurement and treatment. *Curr Opin Endocrinol Diabetes Obes*. 2007 Apr; 14 (2):141-5.
13. Boulton AJ, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med*. 1998 Jun; 15 (6):508-14.
14. Bezditko PA, Karliychuk MA, Lukhanin OO, Zavoloka OV. [Peculiarities of spectral coherent tomography using for investigation of the scleral lamina cribrosa thickness and the area of its scleral channel]. *Kharkivska khirurgichna shkola*. 2017;3-4:63-9. Ukrainian

**Table 1.** Thickness of the lamina cribrosa in patient groups differing in severity of diabetic polyneuropathy

| Group                     | Thickness of the lamina cribrosa, $\mu\text{m}$ |             |            |
|---------------------------|---|-------------|------------|
|                           | M $\pm$ SEM                                     | range       | 95% CI     |
| Control, n=100 eyes       | 303 $\pm$ 56                                    | 173 to 435  | 265 to 354 |
| N0 DPN stage, n=730 eyes  | 466 $\pm$ 71* °                                 | 284 to 553  | 405 to 508 |
| N1A DPN stage, n=94 eyes  | 583 $\pm$ 73* °                                 | 467 to 698  | 523 to 649 |
| N1B DPN stage, n=108 eyes | 594 $\pm$ 76* °                                 | 478 to 705  | 531 to 657 |
| N2A DPN stage, n=92 eyes  | 816 $\pm$ 79* °                                 | 687 to 936  | 756 to 878 |
| N2B DPN stage, n=86 eyes  | 846 $\pm$ 75*                                   | 699 to 949  | 784 to 903 |
| N3 DPN stage, n=40 eyes   | 903 $\pm$ 73*                                   | 707 to 1203 | 837 to 979 |

**Notes.** DPN, diabetic polyneuropathy; M, mean; SEM, standard error of mean; CI, confidence interval; \*, statistically significant difference in mean values between the study group and the control group; °, statistically significant difference in mean values between a particular study group and N3 DPN stage group

**Table 2.** Scleral canal area in patient groups differing in severity of diabetic polyneuropathy

| Group                      | Scleral canal area, $\text{mm}^2$ |              |               |
|----------------------------|-----------------------------------|--------------|---------------|
|                            | M $\pm$ SEM                       | range        | 95% CI        |
| Control, n=100 eyes        | 2.64 $\pm$ 0.77                   | 1.74 to 5.43 | 2.13 to 3.35  |
| N0 DPN stage, n=730 eyes   | 2.77 $\pm$ 0.82                   | 1.71 to 5.53 | 2.14 to 3.50  |
| N1A c DPN stage, n=94 eyes | 2.70 $\pm$ 0.83                   | 1.52 to 5.50 | 2.06 to -3.37 |
| N1B DPN stage, n=108 eyes  | 2.68 $\pm$ 0.87                   | 1.45 to 5.53 | 2.07 to 3.29  |
| N2A DPN stage, n=92 eyes   | 2.59 $\pm$ 0.81                   | 1.27 to 5.34 | 1.98 to 3.18  |
| N2B DPN stage, n=86 eyes   | 2.55 $\pm$ 0.80                   | 1.39 to 5.21 | 1.94 to 3.13  |
| N3 DPN stage, n=40 eyes    | 2.52 $\pm$ 0.78                   | 1.40 to 5.33 | 2.07 to 2.98  |