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Corneal confocal microscopy: A useful tool for diagnosis of small fiber neuropathy in type 2 diabetes

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ABSTRACT

Aim: To investigate the diagnostic utility of corneal confocal microscopy (CCM) for small fiber neuropathy in type 2 diabetes.

Materials and Methods: There were 186 participants with type 2 diabetes enrolled in this cross-sectional research. Pure small fiber neuropathy and mixed fiber neuropathy were defined using clinical examination, electromyography, and quantitative sensory testing. Demographics and clinical data, corneal confocal microscopy parameters, and other neuropathy measures were compared among the groups. The diagnostic utility of corneal confocal microscopy for small fiber neuropathy was assessed by the receiver operating curve.

Results: Of the 186 patients, 24.7% had a pure small fiber neuropathy and 17.2% of patients were diagnosed with mixed fiber neuropathy. The corneal nerve fiber density (CNFD), corneal nerve fiber branch density (CNBD), and corneal nerve fiber length (CNFL) were significantly lower in subjects with pure small fiber neuropathy compared with those without diabetic peripheral neuropathy (all $P < 0.05$). The receiver operating curve analysis for corneal confocal microscopy diagnosing small fiber neuropathy demonstrated the area under the curve for CNFD of 0.791, CNFL of 0.778, CNBD of 0.710.

Conclusions: Patients with type 2 diabetes with pure small fiber neuropathy showed more corneal nerve loss compared with those without diabetic peripheral neuropathy. It was revealed that corneal confocal microscopy can be a reasonable marker in the diagnosis of small fiber neuropathy in type 2 diabetes.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the challenging and costly complications of diabetes, endangering almost half of patients with diabetes[1]. It can not only cause chronic pain and sensory loss but can also drive the risk of foot ulcers and amputation[2]. The prevailing diagnosis of diabetic peripheral neuropathy is based on symptoms and/or signs of neuropathy and on nerve conduction studies (NCS)[1] reflecting only large fiber function, but previous studies have suggested that the earliest damage to peripheral nerves in diabetes involves small fiber nerves[3–5]. Indeed, small fibers are the earliest to regenerate, as shown in studies of the normalization of hyperglycemia through pancreatic transplantation in type 1 diabetes[6,7].

Small fiber neuropathy (SFN) impairs small fiber nerves, causing sensory and autonomic symptoms, and usually affects daily life[8,9]. In addition to pure small fiber neuropathy that affects small fibers only, mixed fiber neuropathy (MFN) involves both small and large fibers[10]. A follow-up study reported that small fiber neuropathy in type 2 diabetes progressed more rapidly over 5 years compared with type 1 diabetes, while large fiber neuropathy had a minimal progression in both groups[11]. The detection of small fiber neuropathy is essential for timely intervention, further improving the quality of life, reducing mortality and the financial burden[12].

Although the quantification of intraepidermal nerve fiber density (IENFD) is a widely accepted standard for the diagnosis of small fiber neuropathy[13,14], the procedure of skin punch biopsy is invasive and requires professional laboratory assessment. Abnormal quantitative sensory testing (QST) is also able

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to diagnose small fiber neuropathy as recommended[15], but it is subjective and needs the definite cooperation of patients. Thus, it is essential to explore a new method for diagnosing small fiber neuropathy. Recent evidence has established that corneal confocal microscopy (CCM) can distinguish patients with and without diabetic peripheral neuropathy noninvasively and rapidly by quantifying the corneal sub-basal nerve plexus[16–18]. Moreover, several studies showed that corneal confocal microscopy was capable of the detection of small fiber damage in cases with impaired glucose tolerance correlating with skin punch biopsy[19,20]. However, the diagnostic utility of corneal confocal microscopy in small fiber neuropathy remains unclear. Therefore, corneal confocal microscopy was adopted to evaluate its diagnostic utility in small fiber neuropathy and to explore the association with other neurological examinations in type 2 diabetes.

MATERIALS AND METHODS

Participants

Some 186 subjects with type 2 diabetes were recruited from the inpatient department of Nanjing Drum Tower Hospital, China. Type 2 diabetes was diagnosed according to the WHO criteria[21]. Exclusion criteria included a history of keratopathy or wearing contact lenses or refractive surgery, active ocular disease, cerebral infarction, Guillain-Barre syndrome, vitamin B12 or folic acid deficiency, a history of malignancy, liver failure, or renal failure, schizophrenia, infectious or connective tissue disease. This study was approved by the ethics committee of Nanjing Drum Tower Hospital. Written consent forms were obtained from all subjects.

Demographic and laboratory data

The following data of subjects were gathered: age, gender, body mass index (BMI), diabetes duration, waist circumference, smoking and alcohol history, and a history of diabetic retinopathy. All participants were tested for glycated hemoglobin A_{1c} (HbA_{1c}), triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, estimated glomerular filtration rate (eGFR), and the ratio of urinary albumin to creatinine.

Peripheral neuropathy assessment

All enrolled patients were assessed for peripheral neuropathy symptoms through the simplified neuropathy symptom score (NSS) and signs through the neuropathy disability score (NDS)[22]. Cardiovascular autonomic reflex tests (CARTs) were assessed as described previously[23].

Neuroelectrophysiological examination was performed using an electromyogram evoked potentiometer (MEB-9400C; Nihon Kohden, Osaka, Japan) by a skilled technician at a room temperature of 24°C. The patient's skin temperature was maintained at about 31°C. The nerve conduction velocities (NCV) of the bilateral median sensory and motor nerves, bilateral ulnar sensory and motor nerves, bilateral common peroneal motor nerves, bilateral tibial motor nerves, and bilateral sural sensory nerves were measured. If there were three or more abnormal NCVs, the nerve conduction was recognized as abnormal[24].

Quantitative sensory tests were performed on the dorsolateral areas of bilateral feet with a thermode (Pathway, Medoc Ltd, Ramat Yishai, Israel) via the limits method. Abnormal cold thresholds (CT) or warm thresholds (WT) on either side were defined as abnormal thermal thresholds. The normal range of thermal thresholds at different ages was provided by Medoc. Vibration perception thresholds (VPT) of bilateral feet were detected by a vibratory sensory analyzer (VSA-3000, Medoc Ltd). The average CT, WT, and VPT of both feet were used in the analysis.

According to expert opinion recommendations[15], pure small fiber neuropathy was diagnosed according to the following criteria: length-dependent symptoms or signs, normal nerve conduction velocities and abnormal cold and/or warm thresholds at the foot. Mixed fiber neuropathy was defined when small fiber neuropathy was accompanied by abnormal nerve conduction. Patients with normal thermal thresholds and nerve conduction were assigned to the non-DPN group.

CCM examination and image analysis

Corneal confocal microscopy was undertaken by an experienced examiner using the Heidelberg Retina Laser Tomograph Ⅲ (HRT Ⅲ) following the steps described previously[25]. Over 100 images were captured from each patient consecutively. Three images per eye were selected following the criteria of depth, focal position, and contrast. Pixels per image were 384 × 384 dpi. All images were fully automated quantified by specific software (ACCMetrics, Imaging Science, University of Manchester)[26]. Then three morphometric parameters were provided for further analysis: corneal nerve fiber density (CNFD), corneal nerve fiber length (CNFL), and corneal nerve branch density (CNBD).

Statistical analysis

Continuous variables were all expressed by mean ± standard deviation (SD) and dichotomous variables by percentages. For normally distributed data, ANOVA with Bonferroni correction or Pearson correlation was used; otherwise, the Kruskal-Wallis *H* test or Spearman correlation was adopted. The Chi-square test was used for dichotomous variables. Comparisons of neurological examinations among the groups were adjusted for confounding factors. All statistical analyses above were conducted with SPSS22.0 (Chicago, IL, USA). To identify the diagnostic performance of corneal confocal microscopy, the receiver operating curve (ROC) plotted by MedCalc 19.2 software (MedCalc Software Ltd, Ostend, Belgium) was utilized.

RESULTS

Clinical assessment

Of the total 186 subjects enrolled, 46 had a pure small fiber neuropathy (24.7%) and 32 had a mixed fiber neuropathy

Table 1 | Demographics and clinical data in subjects without DPN, with pure small fiber neuropathy, and with mixed fiber neuropathy

	Non-DPN (n = 108)	Pure SFN (n = 46)	MFN (n = 32)	P value	P value		
					Non-DPN vs Pure SFN	Non-DPN vs MFN	Pure SFN vs MFN
Age (years)	52.2 ± 11.5	54.8 ± 10.6	56.9 ± 10.7	0.084	0.546	0.115	1.000
Sex (male) (%)	62.0	71.7	71.9	0.382	0.248	0.308	0.990
Duration of diabetes (years)	7.0 ± 6.7	9.1 ± 6.8	12.7 ± 7.2*	<0.001	0.273	<0.001	0.064
BMI (kg/m^2)	25.5 ± 2.8	25.4 ± 3.3	23.3 ± 3.1*,**	0.001	1.000	0.001	0.007
Waist circumference (cm)	91.4 ± 7.8	92.8 ± 9.5	88.5 ± 9.5	0.088	0.997	0.287	0.086
Smoking history (%)	39.6	50.0	56.7	0.207	0.258	0.101	0.576
Alcohol history (%)	11.6	19.0	13.8	0.539	0.257	1.000	0.796
HbA_{1C} (%)	8.7 ± 2.0	8.5 ± 2.0	10.5 ± 2.5*,**	<0.001	1.000	<0.001	<0.001
eGFR (mL/min/1.73 m^2)	126.7 ± 37.7	121.6 ± 30.7	135.4 ± 59.6	0.361	1.000	0.905	0.466
Triglycerides (mmol/L)	2.1 ± 2.0	1.7 ± 1.2	1.2 ± 0.7*	0.036	0.641	0.036	0.627
Total cholesterol (mmol/L)	4.8 ± 1.1	4.5 ± 0.9	5.1 ± 1.1**	0.045	0.269	0.553	0.043
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.1 ± 0.3	1.4 ± 0.4*,**	0.009	1.000	0.029	0.009
LDL cholesterol (mmol/L)	2.8 ± 1.0	2.6 ± 0.8	3.2 ± 0.9**	0.023	0.753	0.102	0.020
Urinary albumin/creatinine (mg/dL)	31.3 ± 61.1	21.7 ± 29.6	202.8 ± 884.9	0.072	1.000	0.088	0.151
Diabetic retinopathy (%)	16.3	13.6	43.3*,**	0.002	0.677	0.002	0.004

Data are reported as mean ± SD unless otherwise indicated. eGFR, estimated glomerular filtration ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein. *P < 0.05 vs non-DPN group. **P < 0.05 vs pure SFN group.

(17.2%). The demographics and clinical data are listed in Table 1. Patients with mixed fiber neuropathy had a significantly longer duration of diabetes compared with those without diabetic peripheral neuropathy (P < 0.001). Compared with the non-DPN group, patients with mixed fiber neuropathy had a significantly lower BMI, higher HbA_{1C}, and a higher frequency of diabetic retinopathy (P = 0.001, P < 0.001, and P = 0.002). Compared with the small fiber neuropathy group, patients with mixed fiber neuropathy had a significantly lower BMI, higher HbA_{1C}, and a higher frequency of diabetic retinopathy (P = 0.007, P < 0.001, and P = 0.004). Besides, patients with mixed fiber neuropathy had a significantly higher total cholesterol, LDL cholesterol, and HDL cholesterol than those with pure small fiber neuropathy (P = 0.043, P = 0.009, and P = 0.020). There was no significant difference between non-DPN and pure small fiber neuropathy (all P > 0.05; Table 1).

Corneal confocal microscopy

Then the corneal confocal microscopy parameters were compared among the three groups as shown in Table 2. It was found that patients with pure small fiber neuropathy had significantly lower corneal nerve fiber density, corneal nerve branch density, and corneal nerve fiber length compared with those without diabetic peripheral neuropathy (all P < 0.001). Similarly, patients with mixed fiber neuropathy showed significantly lower corneal nerve fiber density, corneal nerve branch density, and corneal nerve fiber length compared with those without diabetic peripheral neuropathy (P < 0.001, P = 0.002, and P < 0.001). Patients with mixed fiber neuropathy had significantly lower corneal nerve fiber length compared with those with pure small fiber neuropathy (P = 0.027; Figure 1 and Table 2).

Peripheral neuropathy assessment

Apart from corneal confocal microscopy, other measures of neuropathy are compared in Table 2. The neuropathy symptom score (NSS) was significantly increased in mixed fiber neuropathy than in non-DPN (P = 0.002). The neuropathy disability score and cardiovascular autonomic reflex tests of mixed fiber neuropathy were both significantly raised compared with those of non-DPN (P < 0.001 and P = 0.008) and pure small fiber neuropathy (P = 0.008 and P = 0.027). The cold threshold of pure small fiber neuropathy and mixed fiber neuropathy was significantly decreased compared with that of non-DPN (both P < 0.001). Moreover, the cold threshold of mixed fiber neuropathy was significantly lower compared with those of pure small fiber neuropathy (P = 0.028). The warm threshold in pure small fiber neuropathy and mixed fiber neuropathy were both significantly higher compared with those in non-DPN (both P < 0.001). Similarly, the vibration perception threshold in pure small fiber neuropathy and mixed fiber neuropathy were both significantly higher compared with those in non-DPN (P = 0.017 and P = 0.001). The nerve conduction velocities of all tested nerves were reduced significantly in mixed fiber neuropathy compared with those in non-DPN and pure small fiber neuropathy (all P < 0.001). Only the tibial motor NCV in pure small fiber neuropathy declined more significantly than that in non-DPN (P = 0.013; Table 2).

Table 2 | Neuropathy measures in the non-DPN group, pure small fiber neuropathy group, and mixed fiber neuropathy group

	Non-DPN (n = 108)	Pure SFN (n = 46)	MFN (n = 32)	P value	P value		
					Non-DPN vs Pure SFN	Non-DPN vs MFN	Pure SFN vs MFN
CNFD (no./mm^2)	29.5 ± 5.0	24.4 ± 4.0*	21.2 ± 4.7*	<0.001	<0.001	<0.001	0.057
CNBD (no./mm^2)	48.4 ± 16.4	36.9 ± 11.8*	33.9 ± 14.8*	<0.001	<0.001	0.002	1.000
CNFL (mm/mm^2)	17.6 ± 2.4	15.3 ± 1.9*	13.6 ± 2.3*,**	<0.001	<0.001	<0.001	0.027
NSS (0–9)	2.8 ± 3.0	3.6 ± 3.3	5.7 ± 3.1*	0.002	0.638	0.002	0.062
NDS (0–10)	0.4 ± 1.0	0.8 ± 1.3	1.9 ± 2.6*,**	<0.001	1.000	<0.001	0.008
CARTs (0–4)	1.9 ± 0.9	1.9 ± 0.9	2.5 ± 0.8*,**	0.009	1.000	0.008	0.027
CT (°C)	28.2 ± 1.3	25.7 ± 3.7*	23.3 ± 5.2*,**	<0.001	<0.001	<0.001	0.028
WT (°C)	37.6 ± 2.4	41.5 ± 3.4*	42.6 ± 3.6*	<0.001	<0.001	<0.001	0.335
VPT (μm)	5.6 ± 4.0	9.1 ± 5.6*	11.3 ± 7.8*	<0.001	0.017	0.001	0.389
Median motor NCV (m/s)	55.9 ± 3.2	55.5 ± 2.9	49.5 ± 4.3*,**	<0.001	1.000	<0.001	<0.001
Ulnar motor NCV (m/s)	52.2 ± 3.7	50.9 ± 3.2	44.3 ± 3.8*,**	<0.001	0.244	<0.001	<0.001
Common peroneal motor NCV (m/s)	45.7 ± 3.4	43.9 ± 2.9	37.6 ± 3.7*,**	<0.001	0.066	<0.001	<0.001
Tibial motor NCV (m/s)	46.3 ± 3.3	44.5 ± 3.2*	38.1 ± 2.9*,**	<0.001	0.013	<0.001	<0.001
Median sensory NCV (m/s)	53.2 ± 4.7	51.7 ± 5.4	44.2 ± 5.7*,**	<0.001	0.571	<0.001	<0.001
Ulnar sensory NCV (m/s)	57.0 ± 3.6	56.2 ± 3.6	50.0 ± 4.9*,**	<0.001	1.000	<0.001	<0.001
Sural sensory NCV (m/s)	47.2 ± 3.2	46.0 ± 3.5	40.2 ± 4.4*,**	<0.001	0.364	<0.001	<0.001

Data are reported as mean ± SD. All comparisons were adjusted for age, sex, BMI, HbA1c, diabetes duration, and blood lipid. CARTs, cardiovascular autonomic reflex tests; CNBD, corneal nerve fiber branch density; CNFD, Corneal nerve fiber density; CNFL, corneal nerve fiber length; CT, cold thresholds; NCV, nerve conduction velocity; NDS, neuropathy deficits score; NSS, neuropathy symptom score; VPT, vibration perception threshold; WT, warm thresholds. *P < 0.05 vs non-DPN group. **P < 0.05 vs pure SFN group.

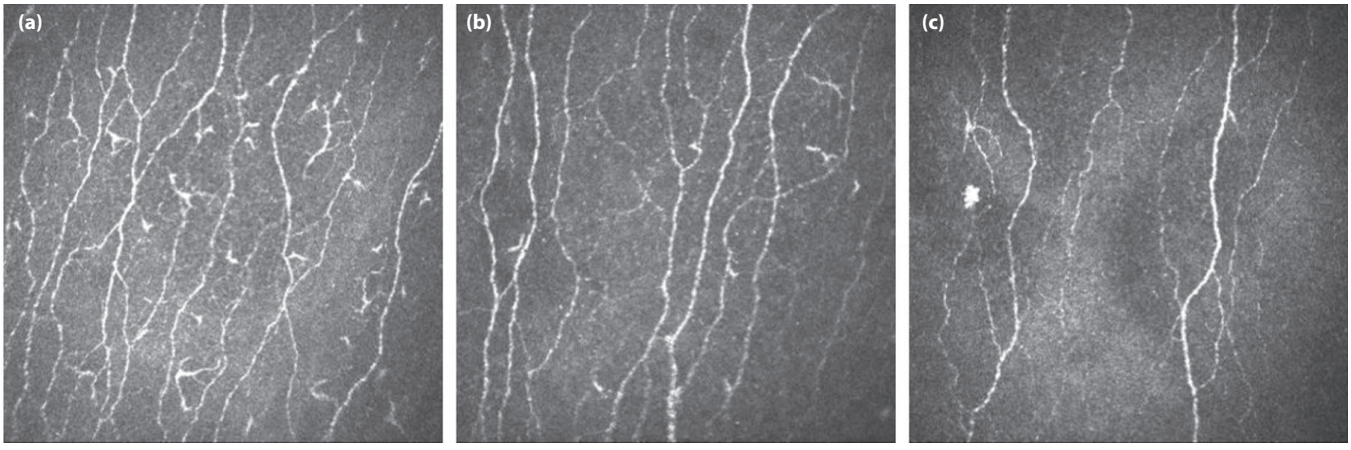

Figure 1 | CCM images of the central cornea in three age-matched male patients. (a) Non-DPN. (b) Pure SFN. (c) MFN. CCM, corneal confocal microscopy; DPN, diabetic peripheral neuropathy; MFN, mixed fiber neuropathy; SFN, small fiber neuropathy.

Association between CNFD, CNBD, CNFL, and other measures of neuropathy

The association between corneal confocal microscopy and other measures of neuropathy was analyzed and is listed in Table 3. The corneal nerve fiber density and corneal nerve fiber length were significantly correlated with neuropathy symptom score, cold thresholds, warm thresholds, and all nerve conduction velocities tested (all P < 0.05). Only the corneal nerve fiber length had a negative correlation with vibration perception threshold (P = 0.022). The corneal nerve branch density was significantly correlated with warm thresholds and sural sensory nerve conduction velocity (P = 0.013 and P = 0.028; Table 3).

Diagnostic utility of CCM for SFN

The ROC curve analysis showed that corneal nerve fiber density had the best performance for the diagnosis of small fiber neuropathy. The area under the curve (AUC) of corneal nerve fiber density was 0.791, the optimal cut-off point was 26.0/

Table 3 | Association between CNFD, CNBD, CNFL, and other measures of neuropathy

	CNFD (no./mm^2)		CNBD (no./mm^2)		CNFL (mm/mm^2)	
	r	*P* value	*r*	*P* value	*r*	*P* value
NSS (0–9)	−0.190	0.038†	−0.159	0.083	−0.203	0.027†
NDS (0–10)	−0.009	0.925	0.038	0.679	−0.073	0.432
CARTs	−0.015	0.871	−0.113	0.220	−0.127	0.169
CT (°C)	0.252	0.006†	0.126	0.173	0.237	0.009†
WT (°C)	−0.334	0.000†	−0.228	0.013†	−0.351	0.000†
VPT (μm)	−0.173	0.057	−0.135	0.142	−0.209	0.022†
Median motor NCV (m/s)	0.251	0.006†	0.023	0.806	0.234	0.011†
Ulnar motor NCV (m/s)	0.296	0.001†	0.064	0.491	0.310	0.001†
Common peroneal motor NCV (m/s)	0.216	0.018†	0.105	0.256	0.288	0.002†
Tibial motor NCV (m/s)	0.353	0.000†	0.104	0.259	0.320	0.000†
Median sensory NCV (m/s)	0.196	0.033†	0.075	0.417	0.219	0.017†
Ulnar sensory NCV (m/s)	0.207	0.024†	0.128	0.166	0.227	0.013†
Sural sensory NCV (m/s)	0.299	0.001†	0.201	0.028†	0.343	0.000†

CARTs, cardiovascular autonomic reflex tests; CNBD, corneal nerve fiber branch density; CNFD, Corneal nerve fiber density; CNFL, corneal nerve fiber length; CT, cold thresholds; NCV, nerve conduction velocity; NDS, neuropathy deficits score; NSS, neuropathy symptom score; VPT, vibration perception threshold; WT, warm thresholds. †Statistically significant after adjustment for age, sex, BMI, HbA1c, and diabetes duration.

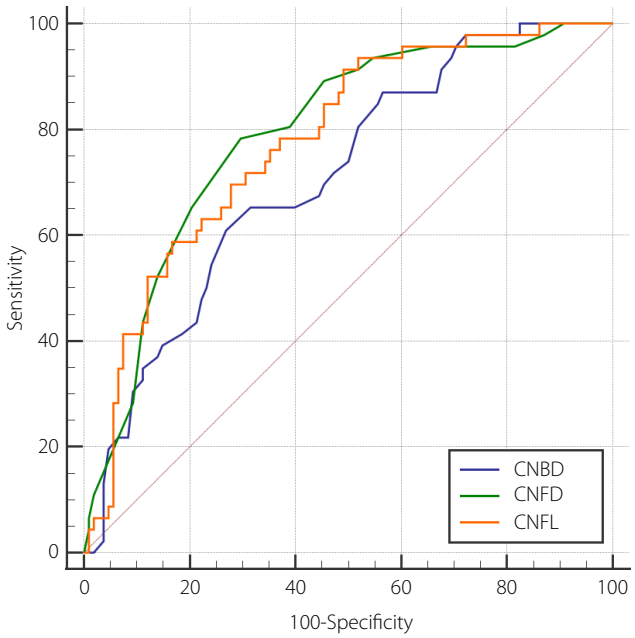

Figure 2 | ROC for pure SFN. CNBD, corneal nerve fiber branch density; CNFD, corneal nerve fiber density; CNFL, corneal nerve fiber length; SFN, small fiber neuropathy; ROC, receiver operating curve.

mm^2, the sensitivity was 78.3%, and the specificity was 70.4%. The AUC of corneal nerve fiber length was 0.778, slightly less than that of corneal nerve fiber density. The optimal cut-off point of corneal nerve fiber length was 17.7 mm/mm^2, the sensitivity was 91.3%, and the specificity was 50.9%. The corneal nerve branch density had a minimum AUC of 0.710. The optimal cut-off point of corneal nerve branch density was 38.5/mm^2, the sensitivity was 60.9%, and the specificity was 73.2% (Figure 2).

DISCUSSION

In the past two decades, corneal confocal microscopy has proven to be a reliable diagnostic tool for diabetic peripheral neuropathy. However, diabetic peripheral neuropathy is diagnosed according to neuropathy symptoms and/or signs and abnormal nerve conduction studies detecting only large fiber function[16–18], very likely overlooking cases of small fiber neuropathy. In the present study, we defined pure small fiber neuropathy and mixed fiber neuropathy in type 2 diabetes and showed more corneal nerve loss in pure small fiber neuropathy compared with non-DPN. Then, we revealed significant correlations between corneal nerve parameters and both large and small fiber function. Moreover, we first reported the diagnostic ability of corneal confocal microscopy in small fiber neuropathy and provided optimal cut-off points.

Following the Toronto criteria[15], we classified 186 participants with type 2 diabetes into non-DPN, pure small fiber neuropathy, and mixed fiber neuropathy. The prevalence of pure small fiber neuropathy in this study was about 24.7%, much higher than that reported in another study conducted in 816 diabetic patients[10]. Different study populations and diagnostic criteria may account for this difference. We then compared the demographics and clinical data among the three groups and found no significant difference between non-DPN and pure small fiber neuropathy, which was in line with the findings from the previous study[10].

When it comes to the neurological examination, we found remarkably reduced corneal nerves in pure small fiber neuropathy compared with non-DPN after adjusting for confounding

factors, indicating that corneal confocal microscopy was a good marker for small fiber impairment. Bucher *et al.*[27] only found decreased corneal nerve fiber density in 14 non-diabetic patients with small fiber neuropathy diagnosed by skin punch biopsy. Different causes of small fiber neuropathy may be the reason for the difference. Besides, corneal nerve fiber length showed a continuous decrease among the three groups, reflecting the initial small fiber involvement and the subsequent progression of large nerve impairment[28]. Interestingly, tibial motor nerve conduction velocity was also declined significantly in pure small fiber neuropathy compared with non-DPN. Although the values of nerve conduction velocity did not exceed the normal range, we assumed that early damage of large fiber may start from the small fiber neuropathy stage, which is in agreement with the viewpoint of Abraham *et al.*[29]

We then analyzed the association between corneal confocal microscopy and other measures of neuropathy. We showed that corneal nerve fiber density and corneal nerve fiber length had significant correlations with thermal thresholds and all the nerve conduction velocities tested in this study, reflecting the impressive relationship between corneal confocal microscopy parameters and both small and large fiber function. Ferdousi *et al.*[30] found corneal nerve fiber density was significantly associated with cold thresholds, vibration perception threshold, nerve conduction velocity of common peroneal motor nerves and sural sensory nerves in type 2 diabetes. Sivaskandarajah *et al.*[31] also found corneal nerve fiber density, corneal nerve branch density, and corneal nerve fiber length had significant correlations with small fiber function in patients with type 1 diabetes.

The technique of skin punch biopsy can diagnose small fiber neuropathy as the Toronto Expert Group recommended, as well as quantitative sensory testing[15]. Although skin punch biopsy is a well-recognized diagnostic standard for small fiber neuropathy, the invasive nature of this method hinders its application in clinical practice. Thus we adopted quantitative sensory testing as an essential condition to define small fiber neuropathy in this study. Truini *et al.*[10] also used thermal thresholds to diagnose small fiber neuropathy in a large sample study of diabetes. Backonja *et al.*[32] showed that cold and warm detection thresholds correlated well with IENFD. Finally, we drew a ROC of corneal confocal microscopy for diagnosing small fiber neuropathy and showed that the corneal nerve fiber density had the highest diagnostic utility for small fiber neuropathy with an AUC of 0.791, sensitivity of 78.3%, and specificity of 70.4%. We found that corneal confocal microscopy, a non-invasive and rapid method, can also be used as a reasonable marker for the diagnosis of small fiber neuropathy with a good performance.

The present study has some limitations. First, this study is a cross-sectional one, so we cannot verify a direct causality between small fiber neuropathy and the loss of corneal nerves. Second, all participants were inpatients, which may lead to selective bias. Third, only patients with type 2 diabetes were included in the study. The diagnostic utility of corneal confocal microscopy for small fiber neuropathy in type 1 diabetes needs further demonstration.

In conclusion, our findings demonstrated that type 2 diabetic patients with pure small fiber neuropathy had significantly fewer corneal nerves than those without diabetic peripheral neuropathy. We also showed corneal nerve parameters had correlations with both large and small-fiber function. Most importantly, we first revealed that corneal confocal microscopy can be a reasonable marker for the diagnosis of small fiber neuropathy. Certainly, prospective studies with large sample sizes are suggested in the future to explore the relationship between small fiber neuropathy and the damage of corneal nerves.

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DISCLOSURE

The authors declare no conflicts of interest.

ETHICS APPROVAL

The study data collections were approved by the Institutional Review Board of Drum Tower Hospital Affiliated to Nanjing University Medical School (approval number: 2017-159-03, approval date: 27-Dec-2018).

CONSENT TO PARTICIPATE

Written informed consent was obtained from all patients.

FUNDING

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DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed in the current study are available from the corresponding authors upon reasonable request.

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