

Corneal Sensitivity Is Reduced and Relates to the Severity of Neuropathy in Patients With Diabetes

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The focus in relation to the consequences of nerve damage in diabetes has been the loss of sensation in the feet predisposing to the development of foot ulceration and lower extremity amputation (1). However, the cornea is 300–600 times more sensitive than skin (2). In addition to serving a protective function, corneal nerves regulate corneal epithelial integrity, proliferation, and wound healing (3). In diabetic patients, corneal sensitivity is reduced (4), due to a loss of corneal nerve fibers (5), which leads to corneal keratopathy (6,7) and a susceptibility to injury, with recurrent erosions and ulcers (8). Thus, these changes are analogous to the diabetic foot, but because the cornea is not exposed to high pressures, ulceration infrequently occurs. Corneal sensation is mediated via myelinated A- δ and C-nerve fibers (9,10), which can be evaluated using the Cochet-Bonnet aesthesiometer (C-BA) (2) or the noncontact corneal aesthesiometer (NCCA) (11), respectively. In diabetic patients, the C-BA has been used to show a reduction in corneal sensitivity in some (12) but not other (13) studies. Furthermore, loss of corneal sensation has been related to the severity of retinopathy (12) and neuropathy (14).

We have assessed corneal sensitivity in a large group of diabetic patients using both C-BA and NCCA to assess concordance between the two methods and also to define whether C-nerve fibers are the

earliest to undergo damage (15). Using corneal confocal microscopy, we have previously shown that corneal nerve fiber damage is directly related to the severity of somatic neuropathy (16,17). Thus, detecting loss of corneal sensation may well be a logical screening tool for neuropathy, and hence we have assessed the relationship between loss of corneal sensitivity and the severity of diabetic neuropathy.

RESEARCH DESIGN AND METHODS

After local research ethics committee (Greater Manchester Health Authority) approval and written informed consent, 147 diabetic patients and 18 age-matched control subjects underwent assessment of the neuropathy deficit score (NDS) (18,19) and were stratified into the following groups: no neuropathy (NDS 0–2), mild neuropathy (NDS 3–5), moderate neuropathy (NDS 6–8), and severe neuropathy (NDS 9–10). A C-BA (model II; Luneau Ophthalmologie, Chartres, France) was used to measure the corneal touch threshold 2 mm superior to the six o'clock limbal position to avoid a reflex blink (20). The filament length was decreased in steps of 0.5 cm until the subject felt the stimulus, which was repeated four to six times. The corneal sensation threshold corresponds to the filament length (mm), giving a positive response to 50% of the presentations (21). The NCCA (Caledonian University, Glasgow, U.K., 1996) uses a puff of air on

the center of the cornea, lasting 0.9 s, to exert a force expressed in millibars, which quantifies corneal sensitivity using established methodology (4,11,21). Data are presented as means \pm SD and analyzed using one-way ANOVA and Scheffe Post hoc test to study differences between groups and the Pearson test for correlation between variables.

RESULTS— 147 diabetic patients with no, mild, moderate, and severe neuropathy were compared with 18 control subjects (Table 1). Age, type of diabetes, and A1C did not differ significantly between groups, and diabetes duration increased with neuropathic severity ($r = 0.40$, $P < 0.0001$). Corneal sensitivity assessed using the C-BA was significantly reduced in diabetic patients compared with control subjects (31.4 ± 19.4 mm vs. 52.3 ± 9.7 mm, respectively; $P < 0.0001$). It was not reduced in diabetic patients without neuropathy ($P = 0.32$) but demonstrated a significant reduction in mild ($P = 0.01$), moderate ($P < 0.0001$), and severe ($P < 0.0001$) neuropathy (Table 1). Corneal sensitivity assessed using NCCA was significantly reduced in diabetic patients compared with control subjects (1.4 ± 0.9 mbar vs. 0.7 ± 0.1 mbar; $P < 0.0001$). It was not significantly reduced in patients without ($P = 0.31$) or with mild ($P = 0.13$) neuropathy but was significantly reduced in those with moderate ($P < 0.0001$) and severe ($P = 0.02$) neuropathy (Table 1). C-BA correlated significantly with NCCA ($r = -0.42$, $P < 0.0001$). Age correlated with C-BA ($r = -0.22$, $P = 0.018$) but not NCCA ($r = 0.13$, $P = 0.14$). Duration of diabetes correlated with NCCA ($r = 0.28$, $P = 0.002$) and C-BA ($r = -0.30$, $P = 0.001$). There was a significant correlation between neuropathic severity assessed using NDS with NCCA ($r = 0.35$, $P < 0.0001$) and C-BA ($r = -0.62$, $P < 0.0001$).

CONCLUSIONS— Diabetic patients may develop epithelial defects and corneal erosions (4,5,15–17,22,23) secondary to loss of corneal sensitivity (4,5,23,24). Increasing age and duration

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Abbreviations: C-BA, Cochet-Bonnet aesthesiometer; NCCA, noncontact corneal aesthesiometer; NDA, neuropathy deficit score.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Clinical details and corneal sensitivity using C-BA and NCCA in control subjects and diabetic patients with increasing neuropathic severity in accordance with NDS, with statistical difference compared with control subjects

	Control subjects	No neuropathy	Mild neuropathy	Moderate neuropathy	Severe neuropathy
n	18	51	49	27	20
Age (years)	56 ± 17	56 ± 11	58 ± 12	61 ± 10	60 ± 9
Type 1/type 2 diabetes	—	5/46	14/35	6/21	3/17
Diabetes duration (years)	0	11 ± 10	16 ± 12	19 ± 10	19 ± 12
A1C (%)	<6.5	8.1 ± 1.5	7.9 ± 1.33	8.4 ± 1.45	8.3 ± 1.32
NDS (0–10)	0	1.3 ± 0.9	3.9 ± 0.7	7.1 ± 0.9	9.8 ± 0.4
C-BA (mm)	52.28 ± 9.74	41.49 ± 17.16	34.09 ± 16.32*	16.06 ± 14.61†	11.36 ± 11.42‡
NCCA (mbar)	0.73 ± 0.14	1.15 ± 0.43	1.29 ± 0.61	1.68 ± 0.75‡	2.35 ± 1.76§

Data are means ± SD unless otherwise indicated. * $P < 0.01$; † $P < 0.0001$; ‡ $P < 0.00001$; § $P < 0.02$. mbar, millibar.

of diabetes may lead to loss of corneal sensation (25). We have shown that increasing age is related to loss of corneal sensation, confirming some (4,25) but not other (26) studies. We also demonstrate a significant association between the duration of diabetes and loss of corneal sensitivity using both NCCA and C-BA, which is in contrast with a previous study using NCCA (4). C-BA demonstrated considerable variability in corneal sensitivity, consistent with quantitative sensory testing in general (27). We also demonstrate a correlation between C-BA and NCCA, which has not been reported in previous studies (4,21). Although the development and progression of retinopathy, nephropathy, and neuropathy are closely associated (28), loss of corneal sensitivity has been related to the severity of retinopathy in one (12) but not other (14,24) studies. In the present study, we did not quantify retinopathy or nephropathy and therefore could not assess for any association with loss of corneal sensitivity. However, one would expect loss of corneal sensation to be most strongly associated with neuropathy. Indeed, we (15–17) and others (5,14) have previously demonstrated that corneal nerve fiber abnormalities are related to the severity of neuropathy. Accordingly, we show that corneal sensation is reduced in diabetic patients and progresses with the severity of neuropathy, suggesting that corneal nerve fiber damage accompanies somatic nerve fiber damage. In conclusion, loss of corneal sensation is easily quantifiable, occurs in diabetic patients with mild to moderate somatic neuropathy, and progresses with the severity of neuropathy. These findings have important clinical implications regarding the development of corneal abnormalities in diabetic patients and also raise the possi-

bility that corneal sensation could be used to screen for diabetic neuropathy.

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