Cutaneous sensory function in diabetes mellitus

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SUMMARY That disorders of cutaneous sensation are common in diabetes mellitus can be substantiated by quantitative cutaneous sensory testing. Cutaneous sensory disturbances are not clearly related to clinical factors such as the type, treatment, or duration of diabetes, or ocular complications. Diabetics can be distinguished from nondiabetics on quantitative examination of skin sensation. Juvenile diabetics appear to have fewer cutaneous abnormalities than adults who develop the disease, but the juvenile diabetic is not spared. Disorders of cutaneous sensation may represent a fundamental abnormality of the nervous system in diabetes mellitus. While altered peripheral sensory mechanisms are likely, abnormality of central sensory processing is not excluded by the results of this study.

The origin, prevalence, and nature of sensory disturbances in patients with diabetes mellitus are unclear. Early investigators suggested that objective involvement of the nervous system resulting in sensory disturbance occurred in a small proportion of diabetics (Murphy and Moxon, 1931; Joslin and Root, 1939; Buschmann *et al.*, 1958; Michon *et al.*, 1961). More recently, others who considered the same problem claim that disturbances of sensation are pervasive (Collens *et al.*, 1959; Mulder *et al.*, 1961; Chochinov *et al.*, 1972). The longitudinal course and consequences of sensory deficits are also unclear, but even minimal cutaneous sensory disorders in the diabetic may produce serious disability. Sensation-defective skin in the fingertips, for example, has been shown to hinder the diabetic blind in learning Braille (Heinrichs and Moorhouse, 1969). The common reason cited for cutaneous sensory defects is diabetic neuropathy, a heterogeneous condition (Collens *et al.*, 1946; Heinrichs and Moorhouse, 1969; Chochinov *et al.*, 1972), the prevalence and causes of which are matters of current investigation (Raff and Asbury, 1968; Gabbay, 1973; Winegrad and Greene, 1976). The state of understanding concerning neuropathy and sensory disturbances in diabetics has been summarised by Bruyn and Garland (1968): "The prevalence may vary between zero and one hundred per cent. . . . The subject is

one of total confusion. . . . A maximal and therefore truly ridiculous divergence of results."

Formidable problems are encountered if we attempt to relate sensory disorders in diabetics to abnormalities of the peripheral sensory mechanism. Even after disorders of the brain and spinal cord have been excluded on clinical grounds, the positive establishment of neuropathy as the cause for cutaneous sensory disturbances is difficult. As Goodman (1966) has stated: "The neuropathies of diabetics can be characterised by subjective symptoms . . . in contrast to rather meager objective neurologic findings." A diabetic individual can be the victim of an uncomfortable disorder of the peripheral nerves at such a time that clinical examination and commonly employed electrophysiological studies lack diagnostic clarity. When critical quantitative methods of testing are employed, sensory disturbances in diabetic patients can be both identified and made objective. Indeed, those studies in which sensory defects and neuropathy are established at the highest prevalence are those that use refined methodology. While clinical forms of peripheral nerve disease can be substantiated by suitable testing, it is far from clear whether sensory disturbances in the diabetic can always be attributed to peripheral nerve disease. Biochemical and physiological disturbances at the central encoding level must also be considered, along with receptor and peripheral sensory abnormalities which are discrete, highly selective, and neuropathic in a non-traditional sense.

Method

Our studies were started to improve delineation of the prevalence of cutaneous sensory disturbances in diabetics. Fifty diabetic patients were studied by a method of quantitative cutaneous sensory testing devised by Conomy and Barnes (1975, 1976). The method is analogous to the von Bekesy technique of audiometry. The patient signals sensation by pressing a lever in response to perception of non-noxious, incremental, electrical stimulation of the skin. Pressing the bar reduces the stimulus until it is no longer perceived. The testing paradigm is nonverbal, free from bias, and quantified in terms of precise characteristics of both the stimulus and the response. Although the exact identity of the receptive structures which are activated by this stimulus is unknown, since normal thresholds are uniformly low (1–3 mA), they must be restricted to the group of low threshold cutaneous receptors. The methodology has been used by our group in the study of cutaneous sensation in normal adults and children as well as in patients with a wide variety of peripheral and central nervous system diseases and chronic pain syndromes (Conomy and Barnes, 1976; Conomy *et al.*, 1977; Cruse *et al.*, 1977).

During the test a stimulator operated by the subject provides pulsed constant current stimulation of the skin through 9 mm silver disc electrodes (Grass Corporation) spaced approximately 20 mm apart. A permanent computer-generated record of stimulus and nonverbal response is produced and subjected to statistical analysis (Figure). This analysis includes determination of mean sensory threshold, limits of stimulus intensity during detection, perceptual duration, cycle rate, and perceptual persistence indices. Skin resistance is constantly monitored. Each individual serves as his or her own control. Test sites in this study included the shoulder (C5 dermatome), the forearm (T1 dermatome), the C6 dermatome in the hand, and points in the L3, L5, and S2 dermatomes in the legs and feet. Each stimulus was a 200 millisecond train of rectangular pulses at 20 Hz and 200 microseconds pulse duration. Trains were repeated once per second, with increments of 0.1 milliamperes every two seconds. For a minimum of two minutes at each site, the patient signalled perception intermittently by pressing a lever.

Fifty diabetic patients were chosen for this study and taken sequentially from volunteers in the diabetes outpatient department and the hospital wards of The Cleveland Clinic Foundation. Test subjects included 23 males and 27

Figure Segment of a stimulus-response record: stimulus voltage at top, and current at bottom of figure, with time increasing from left to right. Stimulus intensity increases 0.1 mA every two seconds until subject responds by pressing a lever which reduces stimulus intensity. Statistical analysis includes Ymax, current peaks at which subject first responds to indicate perception (arrows above trace); Ymin, current troughs at which response and perception cease (arrows below trace); PD, the average length in seconds of each detection response (time between vertical lines); and Ybar, the average current presented during a sample of detection behaviour.

females, ranging in age from 10 to 80 years (mean 55 years). Those with known or probable illnesses of the brain or spinal cord were excluded. Duration of diabetes ranged from newly detected

to over four decades, and all forms of therapy (insulin, oral hypoglycaemic drugs, diet, and combinations of these) were used among the test group. We subdivided the diabetic patients into two groups on the basis of age of onset of the disorder. Those individuals in whom diabetes was diagnosed before the age of 31 years were classified as juvenile onset diabetics, according to the definition used by Deckert *et al.* (1978) and Milner (1978).

For purposes of comparison, a nondiabetic, neurologically normal group of 20 individuals, 10 men and 10 women, ranging in age from 35 to 76 years (mean 54 years), served as control subjects. We initially subdivided the control subjects into a young group (age less than 50 years, $n=8$) and an older group (age 50 years and over, $n=12$) to see whether different norms should be used for patients in these two age groups. However, no significant differences (t test, $P<0.05$) were found between the means of the two groups for any of our test parameters. Thus the analysis of the diabetic data compares the sensory measurements for each of the diabetic patients with the 95% confidence intervals computed from the entire control group of 20 individuals.

Results and discussion

When we compared the quantitative sensory findings in the group of 50 diabetics with the 95% confidence intervals for normal control subjects, the following findings emerged. When all test sites were considered, 66% of diabetics showed elevations of the mean threshold (Table 1, column 2).

Table 1 *Cutaneous perception parameters: percentages of diabetics showing diminished sensory function at each site*

Site	Site total abnormal	Ymax elevated	Ymin elevated	$\bar{Y}$ elevated	PD prolonged	CR reduced
T1	70	70	62	66	70	83
C5	61	69	57	60	54	63
C6	62	64	55	60	55	74
L3	59	52	41	50	65	89
S2	61	67	60	60	59	59
L5	65	73	65	67	50	71
Group total ab- normal	63	66	57	61	59	75

Ymax=stimulus maxima where perception and response are initiated.
Ymin=stimulus minima where perception and response cease.
 $\bar{Y}$ =average level of stimulation presented during detection behaviour sample.
PD=average duration of perception for each response.
CR=average number of stimulus detection-disappearance cycles per minute.

The distribution of threshold abnormalities showed a proximal-to-distal gradient occurring on the leg, with only 52% abnormally high thresholds on the thigh (L3), increasing to 73% abnormal on the foot (L5). However, no such pattern was seen in the three arm sites; threshold abnormalities at C5, T1, and C6 dermatomes were nearly uniform. In addition, 59% of the diabetics showed prolonged duration of perception (Table 1). This temporal alteration occurred in the face of raised, low, or normal thresholds, suggesting the possibility of a distinct perceptual abnormality in the diabetic state which is separable from altered threshold function. In this condition perception persists unusually long, occasionally in the absence of stimulation. Cycle rates (subject-controlled cycling frequencies per unit time) were abnormally slow at 75% of the test sites examined in the diabetic group. As with threshold related functions, there was a high prevalence of slowed cycle rates at proximal as well as distal sites.

When the results of quantitative sensory testing for individual diabetic patients were compared with the 95% confidence intervals for nondiabetic control subjects, the prevalence of abnormalities was apparent. In terms of stimulus current at onset of signalled perception, only four diabetics (8%) fell into the normal range at all sites. One of these was a juvenile onset diabetic. When perceptual duration was examined among patients, seven fell into the normal ranges for all sites, two of these being juvenile diabetics. It is, therefore, clear that while not all diabetics are found to have abnormal cutaneous sensory function when examined by this quantitative method, the majority of them show significant abnormalities. Juvenile diabetics, comprising 16% of the test group, accounted for 50% of the normal findings. This suggests that age or some other nuance of the juvenile diabetic state allows sensation to be relatively spared.

The comparison of the results of testing the diabetic group with the 95% confidence intervals for normal individuals yielded the following conclusions:

1. When the results for all test sites in diabetic patients were compared with nondiabetics, diabetics who were normal at all six sites were rarely found.
2. When diabetics were considered as a group, more than half the mean threshold values were elevated for all test sites.
3. In the patient with clinically and electro-diagnostically proven neuropathy, sensation thresholds at proximal sites are often elevated, and thresholds in the hand may be raised before

those in the feet. This suggests that the classic concept of distal to proximal gradients of severity of sensory disturbances in diabetics, particularly those with early neuropathy, needs to be challenged. Sensory defects in diabetics can be identified in all portions of the limbs.

A very clear demonstration of differences in skin sensation between diabetic and nondiabetic individuals is provided by a comparison of the 95% confidence intervals established from each group for Ymax, which signifies the perceived onset of a skin stimulus. For each of the six test sites there was a clear separation between diabetic and nondiabetic groups with no overlap (Table 2). P values for differences at each site were all highly significant. When considered as a group with respect to perceptual threshold, diabetics were clearly differentiated from age-matched, nondiabetic control subjects.

Other questions to be considered are whether there is a relationship between cutaneous detection threshold and any of the other perceptual parameters we measured, and are the abnormalities in threshold function an expression of variation in some other sensory parameter? To answer these questions we computed the correlation coefficients and plotted linear regression for both normal control subjects and diabetics at each stimulus site for four pairs of parameters: Ymax versus Y, Ymax versus YSD, Ymax versus PD, and Ymax versus CR (Table 3). From the table values it is immediately apparent that the detection peaks (Ymax) are almost perfectly correlated with the mean threshold (Y), since the correlations range from 0.976 to 0.998. Thus either index can be used to represent perceptual threshold. The remainder of the table is striking in the lack of correlation it displays. We can conclude that there is no relationship between either perceptual duration (PD) or cycle rate (CR) and detection thresholds. The highest correlations for these groups are ± 0.21 , with most close to zero. On the

Table 3 Diabetic patients versus control subjects: correlations between perceptual parameters at the six test sites

Site	Ymax versus $\bar{Y}$	Ymax versus YSD	Ymax versus PD	Ymax versus CR
D	0.988*	0.149	-0.021	0.014
T1				
N	0.990*	0.331	0.091	-0.199
D	0.976*	0.405*	0.097	-0.154
C5				
N	0.992*	0.108	-0.066	0.113
D	0.992*	0.391*	-0.016	-0.133
C6				
N	0.996	0.395	-0.209	-0.194
D	0.993*	0.118	0.186	-0.001
L3				
N	0.997*	0.433*	-0.031	0.069
D	0.997*	0.077	-0.121	-0.007
S2				
N	0.991*	0.081	-0.180	-0.124
D	0.998*	0.088	-0.006	0.060
L5				
N	0.996*	-0.045	-0.140	-0.129

D=diabetic group.
N=normal control group
*=P<0.05.
YSD=standard deviation of mean sensory threshold ($\bar{Y}$).
Other symbols as in Table 1.

other hand, there does seem to be an association between threshold and its variability at some sites which becomes significant in three cases (C5 and C6 dermatomes in diabetics, L3 dermatome in normal subjects). However, in no cases did both diabetics and control subjects demonstrate increased variability related to threshold elevation, while at L5 dermatome, the site of the most severe threshold increases in diabetics, there was no correlation with variability. In general, the various perceptual abnormalities which we have observed are usually independent. A diabetic with elevated perceptual thresholds at some sites may also have increased threshold variability, but is not likely to have increased perceptual duration or low cycle rates at the same site. The elevation of perceptual threshold is the prominent disturbance in the diabetic group. While disturbances in perceptual duration are commonly encountered, they are independent of threshold abnormalities.

The final phase of this study included an analysis of clinical factors in the diabetic state as they relate to cutaneous sensory disturbances. We chose three cutaneous sites which represented the least to greatest sensory change: C5, T1, and L5 dermatomes. Using the mean and standard error of Ymax from the control group, we constructed three ranges of perceptual threshold at each site for the diabetic group. Those diabetics whose thresholds were less than four standard errors above the mean of the controls were considered

Table 2 Ninety-five per cent confidence intervals for Ymax: diabetic patients and non-diabetic control subjects

Site	Ymax(mA) Control subjects	Ymax(mA) Diabetic patients	P value (t test)
T1	0.83-1.24	1.59- 2.18	< 0.001
C5	0.97-1.40	1.56- 2.19	< 0.01
C6	1.42-2.20	2.36- 3.72	< 0.05
L3	0.91-1.63	1.81- 2.80	< 0.02
S2	1.34-2.05	2.87- 5.38	< 0.02
L5	3.08-4.19	6.89-11.29	< 0.01

Ymax designates the electrical current strength delivered to the skin at the time that sensation is perceived as signalled by operation of a response lever.

the least affected group. Patients with values between four and six standard errors above the mean were considered moderately affected. Those with values more than six standard errors above the mean formed the group with the greatest cutaneous deficit. We then subdivided each of the above groups according to their status on each of five clinical variables. Chi-squared values were computed to test for association between the clinical indices and severity of cutaneous sensory deficit (Table 4).

The first parameter separated 24 obese from 19 nonobese patients (Food and Nutrition Board, National Research Council, 1974). The obese group weighed an average of 18.5 ± 2.5 kg above their ideal weight. There was no relationship between obesity and sensory threshold at any of the three sites tested. Since obesity was not associated with the degree of threshold elevation, body weight could not predict severity of sensory alteration in diabetics. The second index we evaluated was presence or absence of retinopathy. Twenty patients had some evidence of retinopathy while 23 had none. There was no significant relationship at any site in diabetics between retinal damage and skin sensation thresholds. Thus presence of retinal damage cannot be used as an index of degree of cutaneous sensory abnormality in these patients. Next we compared juvenile diabetics (insulin-dependent diabetics with onset before the age of 31 years, $n=8$) with adult onset patients ($n=36$). Only at L5 dermatome was there a significant association: adult onset diabetics were more likely to have elevated thresholds in the feet. We also evaluated age at the time of testing in relation to perceptual threshold. We divided the diabetic group into young patients (age less than 20 years), middle-aged (aged 21 to 50 years), and an elderly group (aged more than 51 years). Only the foot (L5) threshold was significantly elevated with increasing age. However, since the elderly

group was entirely composed of maturity onset diabetics, it was not possible to determine which factor was actually responsible for the elevated thresholds in the foot found in this group. The last parameter was blood glucose level as determined in a fasting sample. Blood glucose levels (millimoles of glucose per litre of peripheral blood) were divided as follows: 5.5, 5.5–8.5, 8.5–11.0 and >11.0 . There was no association between fasting blood glucose level and cutaneous sensory threshold for any site. This finding agrees with the data of Chochinov *et al.* (1972), who found no relationship between blood glucose levels and impairment of flicker fusion, or electric taste thresholds.

This assessment of clinical data is striking in the absence of any relationship between these variables and the elevation of perceptual threshold in the diabetic. Although past reports suggest the contributions or interactions of these factors in states of diabetic sensory disorders (Martin, 1953; Sullivan, 1958; Colby, 1965), our data fail to confirm these assumptions. Our clinical-perceptual correlative studies rather suggest the following:

1. Neither the age of onset of diabetes nor the age at the time of quantitative sensory testing can be used to predict the presence or absence of a cutaneous sensory abnormality. There are older diabetics who, by our methods, are found to be normal, and diabetic children who are found to be abnormal.
2. The type and duration of diabetic treatment cannot always be used as a predictor of the presence of cutaneous sensory abnormality, since defective skin sensation can be demonstrated in newly discovered diabetics as well as in those treated by diet, drugs, or insulin, alone or in combination for various periods of time.
3. Sensory abnormality appears in the slender as well as in the obese diabetic and in the face of either normal or abnormal postprandial blood glucose levels.
4. Symptomatic diabetic nephropathy, evidenced by proteinuria and hypertension with impaired renal function and present in 6% of the patients in this series, and diabetic retinopathy, detectable in 25% of the series, were similarly not correlated with the presence of a cutaneous sensory abnormality in a clear way.

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Table 4 Relationship of clinical factors to severity of cutaneous perceptual threshold elevation: χ^2 values

Clinical factor	Test site		
	T1	C5	L5
Obese versus nonobese	0.04	0.40	4.82
Retinopathy versus no retinopathy	0.15	3.91	1.68
Juvenile versus maturity onset	0.02	2.51	*11.10
Age at time of QST	1.40	2.56	*10.30
			0.025 < P < 0.05
Blood glucose level	9.33	6.99	3.09

* = P < 0.05

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