Specific Assessments of Warm and Cool Sensitivities in Adult Diabetic Patients

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We have specifically examined warm and cool sensitivities in 60 diabetic and 43 nondiabetic individuals. Diabetic patients tended to have less warm and cool sensitivity than the control subjects ($P < .001$ for age <50 yr and $P < .05$ for age ≥50 yr). Both patients asymptomatic for neuropathy and patients with symptoms had impairment of warm and cool sensitivity ($P < .05$ for comparisons with control subjects). These differences persisted ($P < .05$) in covariance analyses with age included as a covariate. There was a nonlinear association between warm sensitivity and hemoglobin A_{1c}. Warm-sensitivity values in the lowest and middle tertiles of the hemoglobin A_{1c} distribution were similar; however, warm-sensitivity values of patients in the highest tertile were markedly increased ($P < .05$ for the comparison of the highest tertile with the lowest and middle tertiles combined). There tended to be more warm insensitivity than cool insensitivity among the diabetic patients, and this difference increased with worsening glycemia. These data indicate that both warm and cool sensations are markedly impaired in asymptomatic adult diabetic patients. They also suggest that warm sensitivity is more impaired than cool sensitivity, and that this is the result of a stronger association between warm sensitivity and metabolic factors. *Diabetes Care* 11:481–83, 1988

Diabetes mellitus can have a marked effect on thermal sensitivity, yet little is known about its specific effects on warm and cool sensitivities. Neurophysiologic studies have shown that specific receptors respond to either warm or cool stimuli. "Warm" sensation is conveyed by C-fibers, while "cool" sensation is conveyed by C- and Aδ-fibers of cutaneous nerves (1). We have examined warm and cool sensitivities in diabetic patients unselected for peripheral neuropathy to determine the extent to which these sensory modalities are affected by diabetes. In addition, we have studied the associations between warm and cool sensitivities and glycosylated hemoglobin.

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MATERIALS AND METHODS

Subjects. Warm and cool sensitivities were studied in 60 diabetic patients, 46 (77%) of whom had non-insulin-dependent diabetes mellitus. Forty-three nondiabetic control subjects were also studied. Forty-one (68%) of the diabetic patients and 27 (63%) of the control subjects were female. Patients who attended medical clinics at Jackson Memorial Hospital were invited to participate without the investigators' knowledge of whether diabetic neuropathy was present. Control subjects were all screened with 2-h glucose tolerance tests. Subjects with histories of alcoholism were excluded. Mean ± SD ages were 55 ± 10 yr for diabetic and 40 ± 11 yr for nondiabetic subjects. Among the diabetic patients, average hemoglobin A_{1c} (HbA_{1c}) values were 8.1 ± 2.0% and the average duration of diabetes was 9.8 ± 7.0 yr. Three patients were not tested for HbA_{1c}. All subjects signed an informed consent approved by the Medical Sciences Subcommittee for the Protection of Human Subjects at the University of Miami.

Procedures. Thermal sensitivity was measured with the Thermal Sensitivity Tester (Sensortek, Clifton, NJ). This instrument assesses the ability of patients to discriminate differences in temperature on a centigrade scale (2). Warm and cool sensitivities were assessed on each subject by

testing the ability to discriminate temperatures warmer and cooler than 25°C. For measurements of warm sensitivity, one plate was set at 25°C while the other plate was set at a higher temperature. The 25°C plate and the warmer plate were changed according to a standard algorithm. The right hallux was placed on each of the two plates for not more than 2 s, and the subject was asked which plate was warmer. The subject was first asked to discriminate large temperature differences. If there was an incorrect response, the subject was tested again at the same level and the difference was not lowered until there were two correct responses in a row. With a correct response the temperature difference between the two plates was lowered by 10% decrements until a difference of 1.0°C was reached. At that point the difference was gradually lowered by 0.1°C for the remainder of the test. For temperature differences <1.0°C, it was necessary for subjects to respond correctly twice in a row at the same level before the temperature difference was reduced. The test was concluded after a total of five incorrect responses. Warm sensitivity was determined by averaging the levels of the five incorrect responses and the levels of the last five correct responses after excluding the highest and lowest values. Cool sensitivity was measured in the same manner with one plate set at 25°C and the other plate set at a cooler temperature. Subjects were asked which plate was cooler. The absolute temperature differences from 25°C and the algorithm were exactly the same as those for warm-sensitivity testing. The sequence of warm testing and cool testing was alternated for both the diabetic and nondiabetic subjects.

To assess sensory symptoms, subjects were asked whether they had numbness (hypesthesia) and such sensations as pins and needles or pain (paresthesia) in the lower extremities. HbA_{1c} was measured by ion-exchange chromatography.

TABLE 1
Warm- and cool-sensitivity values of nondiabetic and diabetic subjects

		Sensitivity (°C)	
	n	Warm	Cool
Age <50 yr			
Nondiabetic	31	0.55 ± 0.06	0.45 ± 0.04
Diabetic	12	3.48 ± 1.08	1.46 ± 0.36
*P**		<.001	<.001
Age ≥50 yr			
Nondiabetic	12	1.04 ± 0.23	0.89 ± 0.19
Diabetic	48	2.43 ± 0.39	1.83 ± 0.25
*P**		.026	.032
All ages			
Nondiabetic	43	0.68 ± 0.08	0.57 ± 0.07
Diabetic	60	2.64 ± 0.38	1.76 ± 0.21
*P**		<.001	<.001

Values are means ± SE.
*Based on log transformations.

TABLE 2
Warm- and cool-sensitivity values of nondiabetic and diabetic subjects according to neuropathic symptom status

		Diabetic subjects	
Sensitivity (°C)	Nondiabetic subjects (*n* = 43)	Asymptomatic (*n* = 15)	Symptomatic (*n* = 45)
Warm	0.68 ± 0.08	1.99 ± 0.48*	2.85 ± 0.48*
Cool	0.57 ± 0.07	1.61 ± 0.35*	1.81 ± 0.26*

Values are means ± SE.
*$P < .001$ for comparison with nondiabetic subjects. *P* values are based on log transformations.

Data analysis. Paired *t* tests and *t* tests for the comparison of independent means were utilized to assess differences. Because there was skewness in the distributions for warm and cool sensitivities, comparisons between them were performed after log transformations. However, actual values are displayed in the tables. The difference between warm- and cool-sensitivity values was obtained by subtracting the level of cool sensitivity from that of warm sensitivity in each subject. Analyses of covariance were utilized to allow for potential confounding. *P* values are two-sided. Calculations were performed with the Systat statistical package (Systat, Evanston, IL).

RESULTS

Table 1 shows warm- and cool-sensitivity values of the nondiabetic and diabetic subjects. Because there was a difference in age between the groups, values are displayed according to age categories. There were statistically significant differences for warm and cool sensitivities between patients and control subjects in both younger and older individuals. Among the younger subjects (<50 yr), 50% of the patients had warm-sensitivity values and 42% had cool-sensitivity values greater than the highest control values (1.4°C for warm and 1.0°C for cool). Among the older subjects (≥50 yr), 33% of the patients had warm-sensitivity values and 25% had cool-sensitivity values greater than the highest control values (2.3°C for warm and 2.1°C for cool).

Warm-sensitivity values were significantly higher than cool-sensitivity values among the patients (mean difference ± SE: 0.88 ± 0.30°C, $P < .01$). This trend was also apparent among the control subjects, although the difference was much smaller (0.11 ± 0.05°C, $P < .05$).

Warm- and cool-sensitivity values are shown according to neuropathic symptom status in Table 2. Both asymptomatic and symptomatic patients had significantly higher warm- and cool-sensitivity values than those of the nondiabetic subjects ($P < .001$ for all comparisons). When analyses of covariance were performed with age included as a covariate, all differences re-

TABLE 3
Warm- and cool-sensitivity values of diabetic patients according to hemoglobin A_{1c} tertiles

	Hemoglobin A_{1c} Tertile		
Sensitivity (°C)	Lowest	Middle	Highest
Warm	1.97 ± 0.46	1.75 ± 0.33	4.45 ± 0.94*†
Cool	1.70 ± 0.38	1.61 ± 0.32	2.15 ± 0.45

Values are means ± SE. n = 19 for each tertile.
*P = .037 for comparison with middle tertile.
†P = .026 for comparison with lowest and middle tertiles combined.
P values are based on log transformations.

mained statistically significant ($P < .05$). There was a tendency for the symptomatic patients to have more warm insensitivity than the asymptomatic patients; however, the difference was not significant.

Age and diabetes duration were not associated with either warm or cool sensitivity in the patients. There was a nonlinear association between warm sensitivity and HbA_{1c}, which is evident in Table 3. When patients were categorized according to HbA_{1c} tertiles, warm-sensitivity values of the lowest and middle tertiles were similar. However, there was a marked increase in values of the highest tertile. Warm-sensitivity values were significantly higher in this tertile than those in the other two tertiles combined ($P < .05$). There was little association between cool sensitivity and HbA_{1c}. The difference between warm- and cool-sensitivity values (warm − cool) was much greater in the highest tertile than the difference in the other two tertiles combined (2.30 ± 0.73 vs. 0.22 ± 0.24°C, $P < .01$).

DISCUSSION

The data in this report indicate that both warm and cool sensitivities are markedly impaired in diabetic patients. Even patients asymptomatic for neuropathy tended to have abnormal warm and cool sensitivities. Although the diabetic patients were older than the nondiabetic control subjects, these differences persisted with allowances for potential confounding by age.

Patients in the highest tertile for HbA_{1c} values had much more warm-sensitivity impairment than those in the other tertiles. In contrast, there was little association between cool sensitivity and HbA_{1c}. The basis for the stronger relation of warm sensitivity to glycemia is not easily explained; however, warm and cool sensations are conveyed by different nerve fibers. Most warm receptors have unmyelinated axons with conduction velocities between 0.3 and 1.3 m/sec. Myelinated fibers conducting between 2.2 and 9.5 m/sec have also been shown to emanate from warm receptors. Cool receptors have unmyelinated fibers with conduction velocities of 0.6 to 1.5 m/sec and thinly myelinated fibers with conduction velocities of ~14 m/sec (1).

The diabetic patients had higher warm values than cool values. Because the nondiabetic subjects also had higher warm values, the difference in the diabetic patients could have been a function of the baseline temperature (25°C) that was chosen. However, the greater difference in the diabetic patients suggests that diabetes is associated with more warm insensitivity than cool insensitivity. The difference between warm and cool sensitivity was greatest in patients with the highest levels of HbA_{1c}. Thus, the greater impairment of warm sensitivity in diabetic patients may be the result of a stronger association of warm sensitivity with metabolic factors.

Both warm and cool sensitivities of the asymptomatic patients were significantly different from those of the control subjects. This is consistent with our previous findings of vibratory- and thermal-sensitivity abnormalities in asymptomatic diabetic patients (3,4). Thus, it appears that quantitative sensory testing can detect sensory impairment before certain patients are aware of a problem.

The quantitation of sensory function has already been useful in both clinical trials and epidemiologic studies (3–7). Because warm and cool sensitivities are abnormal subclinically and warm sensitivity appears to be related to glycemia, the specific examinations of these sensory modalities should yield additional information in future investigations.

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