Role of Neuropathy and High Foot Pressures in Diabetic Foot Ulceration

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OBJECTIVE — High plantar foot pressures in association with peripheral neuropathy have been ascertained to be important risk factors for ulceration in the diabetic foot. Most studies investigating these parameters have been limited by their size and the homogeneity of study subjects. The objective of this study was therefore to ascertain the risk of ulceration associated with high foot pressures and peripheral neuropathy in a large and diverse diabetic population.

RESEARCH DESIGN AND METHODS — We studied a cross-sectional group of 251 diabetic patients of Caucasian (group C) (n = 121), black (group B) (n = 36), and Hispanic (group H) (n = 94) racial origins with an overall age of 58.5 ± 12.5 years (range 20–83). There was an equal distribution of men and women across the entire study population. All patients underwent a complete medical history and lower extremity evaluation for neuropathy and foot pressures. Neuropathic parameters were dichotomized (0/1) into two high-risk variables: patients with a vibration perception threshold (VPT) ≥25 V were categorized as HiVPT (n = 132) and those with Semmes-Weinstein monofilament tests ≥5.07 were classified as HiSWF (n = 190). The mean dynamic foot pressures of three footsteps were measured using the F-scan mat system with patients walking without shoes. Maximum plantar pressures were dichotomized into a high-pressure variable (Pmax6) indicating those subjects with pressures ≥6 kg/cm^2 (n = 96). A total of 99 patients had a current or prior history of ulceration at baseline.

RESULTS — Joint mobility was significantly greater in the Hispanic cohort compared with the other groups at the first metatarsal-phalangeal joint (C 67 ± 23°, B 69 ± 23°, H 82 ± 23°, P = 0.000), while the subtalar joint mobility was reduced in the Caucasian group (C 21 ± 8°, B 26 ± 7°, H 27 ± 11°, P = 0.000). Maximum plantar foot pressures were significantly higher in the Caucasian group (C 6.7 ± 2.9 kg/cm^2, B 5.7 ± 2.8 kg/cm^2, H 4.4 ± 1.9 kg/cm^2, P = 0.000). Univariate logistic regression for Pmax6 on the history of ulceration yielded an odds ratio (OR) of 3.9 (P = 0.000). For HiVPT, the OR was 11.7 (P = 0.000), and for HiSWF, the OR was 9.6 (P = 0.000). Controlling for age, diabetes duration, sex, and race (all $P < 0.05$), multivariate logistic regression yielded the following significant associations with ulceration: Pmax6 (OR = 2.1, P = 0.002), HiVPT (OR = 4.4, P = 0.000), and HiSWF (OR = 4.1, P = 0.000).

CONCLUSIONS — We conclude that both high foot pressures (≥6 kg/cm^2) and neuropathy are independently associated with ulceration in a diverse diabetic population, with the latter having the greater magnitude of effect. In black and Hispanic diabetic patients especially, joint mobility and plantar pressures are less predictive of ulceration than in Caucasians.

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Abbreviations: HiSWF, patients with Semmes-Weinstein monofilament test ≥5.07; HiVPT, patients with vibration perception threshold ≥25 V; LJM, limited joint mobility; MPP, maximum peak plantar pressures; MTP, metatarsal-phalangeal; OR, odds ratio; Pmax6, high-pressure variable; STJ, subtalar joint; VPT, vibration perception threshold.

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

Foot ulceration is a significant cause of morbidity in patients with diabetes and can lead to prolonged lengths of hospital stay (1–6). A recent epidemiological review of National Hospital Discharge Survey (NHDS) data indicates an increase in diabetes-related foot ulcer hospitalization rates from 1983 to 1990 and that the average length of hospital stay for such admissions was 59% longer than that for diabetes discharges without them (1). In fact, it has been estimated that ~20% of hospitalizations attributable to diabetes are the result of foot ulcers and infection (7), with an ~15% lifetime risk for foot ulceration in all diabetic individuals (8). Another report further indicates that there is an increased risk of mortality associated with diabetic foot ulcers (9).

Numerous putative risk factors for foot ulceration in diabetes have been ascertained (5,10–14). Among others, peripheral neuropathy, vascular disease, limited joint mobility (LJM), high plantar pressures, and associated extrinsic sources of trauma have all been implicated as significant predisposing factors leading to ulceration in population-based and clinical studies seeking to quantify such relationships (15–25). The value of determining these associations is that such knowledge can be useful in establishing screening programs for patients at risk of developing ulceration or in assigning levels of risk (5,26–29). Risk assessment is also an integral component of prevention-based foot care programs (12,30,31). However, there is no consensus as to which specific testing modality is best suited for screening diabetic patients. Usually several modalities, such as monofilaments, biothesiometry, and/or plantar pressure assessments, are used in conjunction with a brief history and physical examination (27,31–33). Racial differences in LJM, associated foot pressures, and rates of ulceration do exist, however, and these racial characteristics must be considered when assessing levels of risk (34,35). We therefore chose to study the association of neuropathy and plantar foot pressures with ulceration in a geographically diverse population of diabetic patients. Furthermore, we sought to determine and categorize levels of risk associated with patients of Caucasian, black,

Table 1—*Characteristics of the entire study population*

Total	251
Caucasian	121
Black	36
Hispanic	94
Age (years)	58.5 ± 12.5 (20–83)
Sex (M:F)	126:125
BMI	30.1 ± 6.4 (15.4–57.1)
Diabetes type (1:2)	49:202
Diabetes duration (years)	14.3 ± 10.6 (1–54)
VPT (V)	29.3 ± 17.3 (1–51)
Semmes-Weinstein filaments	5.6 ± 1.2 (3.61–7)
MPP (kg/cm^2)	5.7 ± 2.8 (1.86–16.4)

Data are *n* or means ± SD (range).

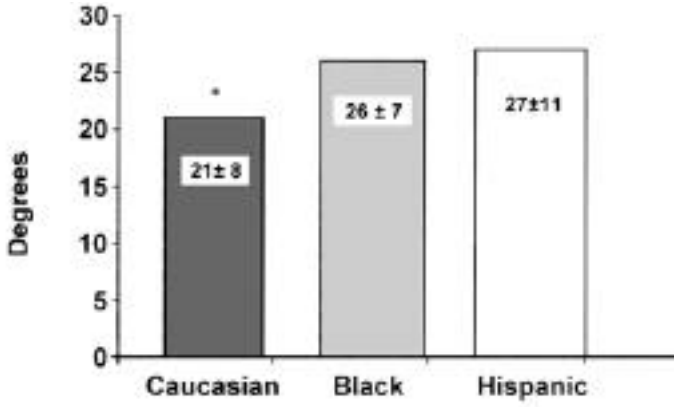

Figure 1—*Subtalar joint range of motion by race (in degrees). A significant reduction was found in Caucasian patients when compared with Hispanic and black participants. *P < 0.003 Caucasian vs. black and Hispanic.*

and Hispanic ethnic origins using multivariate techniques.

RESEARCH DESIGN AND METHODS

We prospectively studied a cross-sectional group of 251 diabetic patients of Caucasian (group C) (*n* = 121), black (group B) (*n* = 36), and Hispanic (group H) (*n* = 94) racial origins with an overall age of 58.5 ± 12.5 years (range 20–83). There was an equal distribution of men and women across the entire study population, but differences did exist in their frequencies in each of the races. The patients were consecutively recruited from diabetic foot centers in Boston, MA, San Antonio, TX, and San Francisco, CA, to provide geographic and racial diversity within our study population. They were enrolled in a longitudinal study to assess risk factors for ulceration that is still ongoing. This report involves the analysis of baseline characteristics of the patients as related to current or prior history of foot ulceration.

All patients underwent a complete medical history and bilateral lower-extremity evaluation including assessments for peripheral pulses, neuropathy, joint mobility, and foot pressures. Peripheral sensory impairment was determined by the inability to sense a 10-g monofilament (Semmes-Weinstein monofilament) at two of three sites on the plantar surface of each foot: great toe, metatarsal head area, and heel. If the great toe had been amputated, an adjacent toe was tested. The vibration perception threshold (VPT) was measured at the great toe (or second toe if the first had been amputated) of each foot using a biothesiometer (Bio-Medical Instruments, Newbury, OH) using established techniques (19,27,33). Neuropathic parameters were dichotomized (0/1) into two high-risk variables: patients with a VPT ≥25 V were categorized as HiVPT, and those with Semmes-Weinstein monofilament tests ≥5.07 were classified as HiSWF. The range of joint motion was measured at the subtalar and first metatarsal joints as previously described (35).

The mean dynamic foot pressures were measured using the F-scan mat system, software version 3.711 (Tekscan, Boston, MA) with patients walking in stockings but without shoes (36). This computerized gait analysis system uses an ultra-thin Tekscan sensor consisting of 960 sensor cells (5 mm^2 each) (37). The sensor is used in a floor mat system designed to measure barefoot or stocking-foot dynamic plantar pressures. We used this system in this study after first calibrating the sensor mat with the patient's own weight (36). Maximum peak plantar pressures (MPP) for the entire foot were obtained without regard for specific location by averaging those obtained for three midgait footsteps and were then dichotomized into a high-pressure variable (Pmax6) indicating those subjects with pressures ≥6 kg/cm^2. This cutoff was chosen because it lies one SD above the mean of healthy subjects (37). In addition, this level provided the greatest risk of ulceration on univariate analysis. The baseline characteristics of the participants are noted in Table 1.

Statistical comparisons were made between patients with and those without a history of current or prior ulcerations using χ^2 tests for categorical variables. For individual continuous variables, comparisons were made using the two-tailed Student's *t* test, if assumptions of normality were achieved, or with Wilcoxon's rank sum test, if nonparametric hypothesis testing was required. One-way analysis of variance was performed to test for differences in continuous covariates across the three racial subpopulations. Univariate and multivariate logistic regression were used in a stepwise fashion to assess variables that were independently significant predictors of ulceration. Significance levels of $\alpha = 0.05$ were used throughout.

RESULTS

Of our patients, 48% were Caucasian, but these accounted for 69% of those who had ulcerated. Hispanics comprised ~38% of the study participants and contributed 21% of ulcers, while 14% were of black ethnicity and contributed only 10% of the ulcers (χ^2 [2 df] = 55.6, $P = 0.000$). This is generally consistent with our findings of significantly less joint mobility in both the subtalar joint (STJ) (C 21 ± 8°, B 26 ± 7°, H 27 ± 11°, $P < 0.001$) (Fig. 1) and first metatarsal-phalangeal (MTP) joints of Caucasians as compared with the other two races (C 67 ± 23°, B 69 ± 23°, H 82 ± 23°, $P < 0.001$). This ostensibly translated into higher MPP, since the Caucasian group demonstrated significantly higher MPP than the other groups (C 6.7 ± 2.9 kg/cm^2, B 5.7 ± 2.8 kg/cm^2, H 4.4 ± 1.9 kg/cm^2, $P < 0.001$) (Fig. 2). Other findings are also contrasted by ethnic group in Table 2.

A total of 99 patients had a current or prior history of ulceration at baseline, 33 of whom presented with active ulcers. All ulcerations were located on the plantar aspect of the foot or on the distal weight-bearing aspect of the digits. There were 132

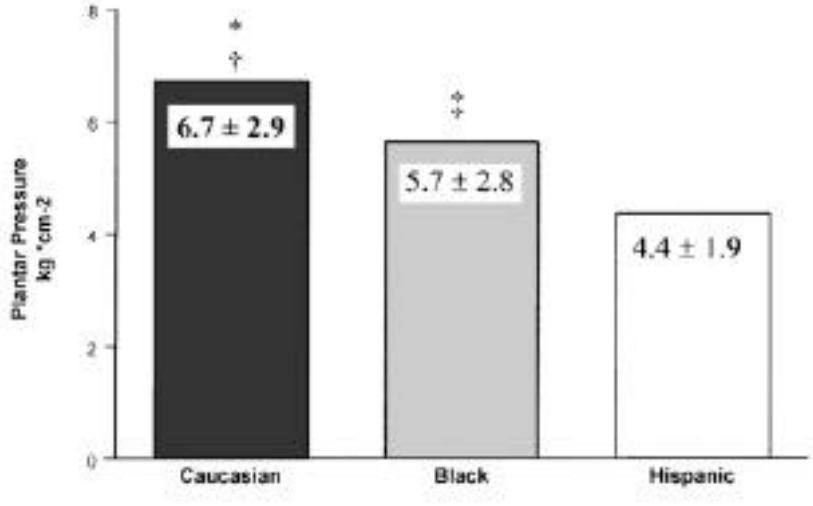

Figure 2—*Mean MPP by race. Caucasian patients had higher pressure when compared with black and Hispanic patients (*P = 0.007 Caucasian vs. black; †P = 0.000 Caucasian vs. Hispanic; ‡P = 0.0001 black vs. Hispanic).*

of the study subjects with VPT ≥25 V (HiVPT); 190 had insensitivity based on Semmes-Weinstein monofilament tests ≥5.07 (HiSWF); and 96 had peak plantar pressures ≥6 kg/cm² (Pmax6). Patients who had ulcerated were very slightly older than those without (60 ± 10.5 vs. 57 ± 13.5 years, $P = 0.05$) and had a longer duration of diabetes (17 ± 9.5 vs. 12 ± 10.8 years, $P = 0.000$). Ulcerated subjects also had a lower BMI than those without ulcers; however, this difference did not reach statistical significance (29.4 ± 5.5 vs. 30.5 ± 6.8 kg/m², $P = 0.130$). Although the total numbers of men and women in our cohort were equivalent, 70% of those subjects with ulceration were male ($P = 0.000$). Pedal pulses were palpable in 86% of the patients, including 77% of those with ulceration ($P = 0.000$). Table 3 further contrasts the findings in ulcerated and nonulcerated patients.

Univariate logistic regression of ulceration on Pmax6 yielded an odds ratio (OR) of 3.9 (95% CI 2.6–5.7, $P = 0.000$). For HiVPT, the OR was 11.7 (95% CI 7.4–18.4, $P = 0.000$), and for HiSWF, the OR was 9.6 (95% CI 5.0–18.5, $P = 0.000$) (Table 4). Controlling for age, diabetes duration, sex, and race (all $P < 0.05$), multivariate logistic regression yielded the following significant predictors of ulceration: Pmax6 (OR = 2.1, 95% CI 1.3–3.4, $P = 0.002$), HiVPT (OR = 4.4, 95% CI 2.6–7.5, $P = 0.000$), and HiSWF (OR = 4.1, 95% CI 1.9–8.9, $P = 0.000$). The presence of pulses was independently protective from ulceration in the univariate analysis (OR = 0.31, 95% CI 0.18–0.52, $P = 0.000$). BMI was also protective in the univariate model, although it barely reached significance (OR = 0.97, 95% CI 0.94–0.99, $P = 0.048$). After adjusting for the other covariates, pulses and BMI were no longer significant and were therefore dropped from the final multivariate model.

When evaluating subjects on the basis of race, several differences became evident in the multivariate analysis. For Caucasians alone, Pmax6 and HiVPT each assumed a higher association with ulceration (eight- and sevenfold, respectively), while HiSWF essentially remained the same (Table 5). In blacks, only HiVPT (OR = 7.2) and HiSWF (OR = 19.8) remained independently associated with ulceration with very wide confidence limits. Pmax6 was very variable in this population and was not a significant predictor for ulceration. In the Hispanic cohort, HiSWF was collinear with the outcome, i.e., all ulcerated patients within this population had insensitivity to the 10-g monofilament. It therefore dropped from the model. Controlling for age, sex, and diabetes duration, only HiVPT remained a significant covariate, yielding almost a sevenfold increased risk of ulceration. As was the case for black participants, Pmax6 had wide variation and did not reach statistical significance.

CONCLUSIONS — In this cross-sectional multicenter study, we have determined the magnitude of association of several different risk factors for foot ulceration in patients with diabetes, 87% of whom had palpable pedal pulses. With a specific focus on plantar foot pressures, joint mobility, and neuropathic parameters attendant with ulceration, we have demonstrated that patients with foot pressures ≥6 kg/cm² were twice as likely to have ulcerated than those without high pressures, even after adjustment for age, sex, diabetes duration, and race. Similarly, indicators for peripheral sensory neuropathy, including VPT ≥25 V and insensitivity to a 10-g monofilament, were each four times as likely to be associated with plantar ulceration.

We have also stratified our findings on the basis of ethnic differences within the study population. Specifically, we have shown that Caucasians have significantly lower STJ and first MTP joint mobility with associated higher foot pressures than our cohorts of both black and Hispanic patients. These differences were also evident from the fact that our Caucasian participants encountered the highest percent frequency of total ulcerations (69%), as compared with their black (10%) and Hispanic (21%) coun-

Table 2—*Examination findings according to race*

	Caucasian	Black	Hispanic	*P* value
n	121	36	94	—
Age (years)	62 ± 10.9	63 ± 13.2	52 ± 11.5	0.000
Sex (M:F)	77:44	8:28	41:53	0.000
BMI	29.4 ± 6.4	30.8 ± 6.9	30.6 ± 6.1	0.072
Diabetes duration (years)	16.9 ± 11.4	13.3 ± 8.7	11.2 ± 9.2	0.000
MPP (kg/cm²)	6.7 ± 2.9	5.7 ± 2.8	4.4 ± 1.9	0.000
STJ mobility (°)	21 ± 8	26 ± 7	27 ± 11	0.000
First MTP joint mobility (°)	67 ± 23	69 ± 23	82 ± 23	0.000
VPT (V)	38 ± 15	20 ± 11	22 ± 16	0.000
Semmes-Weinstein filaments	6.0 ± 1.1	5.2 ± .83	5.3 ± 1.3	0.000
Patients ulcerated	68 (56)	10 (28)	21 (22)	0.000
% frequency of all ulcers	69	10	21	0.000

Data are *n*, means ± SD, or *n* (%).

Table 3—*Clinical findings stratified by ulcer status*

	Ulcerated	Nonulcerated	*P* value
n	99	152	—
Age (years)	60 ± 10.5	57 ± 13.5	0.05
Sex (M:F)	69:30	57:95	0.000
BMI	29.4 ± 5.5	30.5 ± 6.8	0.130
Diabetes duration (years)	17 ± 9.5	12 ± 10.8	0.000
Diabetes type (1:2)	29/70	20/132	0.000
Palpable pulses	74 (77)	139 (91)	0.000
MPP (kg/cm^2)	6.7 ± 3.1	4.9 ± 2.4	0.000
STJ mobility (°)	21 ± 8.9	26 ± 9.5	0.000
First MTP joint mobility (°)	62 ± 23.2	80 ± 21.8	0.000
VPT (V)	41.6 ± 12.8	21.5 ± 15.1	0.000
Semmes-Weinstein filaments	6.4 ± .85	5.1 ± 1.1	0.000
Pmax6	57 (59)	39 (41)	0.000
HiVPT	84 (64)	48 (36)	0.000
HiSWF	93 (49)	97 (51)	0.000

Data are *n*, means ± SD, or *n* (%).

terparts. Furthermore, Caucasians experienced a higher within-group frequency of ulceration than either the black or Hispanic patients (56, 28, and 22%, respectively). As might be anticipated, older age, longer duration of diabetes, and the male sex were also more often associated with the history of ulceration in the entire study population.

High plantar foot pressures have been confirmed as important predisposing risk factors for ulceration, especially in the presence of neuropathy (21,22,24). Veves et al. (21) have reported on a prospective study of diabetic patients in which 17% developed ulcers over a mean period of 30 months. Of these patients, 93% had neuropathy at baseline, and all had abnormally high foot pressures measured by pedobarography. However, no measures of association with ulceration were provided. In a more recent cross-sectional study of male veterans, Stess et al. (22) also reported significant increases in maximal plantar pressures in diabetic patients with a history of neuropathic foot ulcers compared with those without. Again, no levels of risk were attributed to the patients with high foot pressures. In a previous study from the Deaconess-Joslin Foot Center using the same methodology as we report, STJ mobility was found to be significantly reduced in white diabetic patients compared with their black counterparts (35). Concurrently, plantar foot pressures were found to be significantly elevated in the former group. These results are quite similar to ours, except that we have added a Hispanic diabetic group and have reported associated measures of foot ulcer risk for the entire cohort as well as for individual ethnicities. In the black and Hispanic groups, who had significantly lower pressures than the Caucasians, high foot pressures were relatively infrequent and were not found to be significant predictors of ulceration. Considering our cohort as a whole, foot pressures ≥6 kg/cm^2 (Pmax6), were indeed independently associated with ulceration, but to a lesser extent than the neuropathy variables. Presumably, this is because 42% of the ulcerated patients did not have high foot pressures, in contrast with only 16% without high VPT and 6% without high Semmes-Weinstein monofilament measurements (data not shown).

Biothesiometry has successfully been used to screen patients for peripheral neuropathy as well as to predict ulceration in those individuals with diabetes and abnormally high VPTs (12,17,19). A population-based study from the U.K. determined that diabetic patients with present or past history of foot ulceration were more likely to have a higher VPT than those without ulceration (median 28 vs. 17 V) (17). A prospective 4-year study from this same group has validated the utility of this measurement in that those patients with VPT ≥25 V had an eightfold risk of ulceration compared with those with VPT <15 V (19). After adjusting for diabetes duration, a sevenfold risk of ulceration remained. Our study has similarly shown a univariate 12-fold risk of ulceration when comparing those diabetic individuals with or without high VPT. When controlling for several confounders in addition to diabetes duration, a VPT ≥25 V was still strongly associated with the risk of foot ulceration (OR = 4.4).

Cutaneous pressure perception measured by Semmes-Weinstein monofilaments has been widely considered to be an ideal screening instrument for neuropathy and potential for ulceration because of its simplicity, sensitivity, and low cost (12,16,18, 27–29,32). Several cross-sectional studies indicated that foot ulceration and elevated cutaneous pressure perception thresholds were strongly associated and more predictive than biothesiometry (18,28). Magnitudes of association, however, were provided in a case-control study by McNeely et al. (16), who reported an unadjusted sevenfold risk of ulceration in those patients (97% male) with insensitivity to the 5.07 monofilament. Multivariate logistic regression yielded an OR of ~18, although with very wide confi-

Table 4—*Logistic regression results for risk of ulceration*

	OR	95% CI	*P* value
Univariate results			
Age*	1.02	1.00–1.03	0.019
Sex†	0.26	0.18–0.38	0.000
BMI	0.97	0.94–0.99	0.048
Diabetes duration*	1.04	1.02–1.06	0.000
Pulses	0.31	0.18–0.52	0.000
Pmax6	3.9	2.6–5.7	0.000
HiVPT	11.7	7.4–18.4	0.000
HiSWF	9.6	5.02–18.5	0.000
Multivariate results			
Pmax6	2.1	1.32–3.39	0.002
HiVPT	4.4	2.58–7.54	0.000
HiSWF	4.1	1.89–8.87	0.000

Multivariate results are controlled for age, sex, diabetes duration, and race. *OR per year of increase; †reduced risk of ulceration in women relative to men.

Table 5—*Multivariate logistic regression for ulceration by race, controlling for age, sex, and diabetes duration*

	OR	95% CI	*P* value
Caucasian			
Pmax6	7.7	2.07–28.4	0.002
HiVPT	7.4	2.4–22.9	0.001
HiSWF	3.7	1.3–10.3	0.013
Black			
Pmax6	0.53	0.05–5.8	0.608
HiVPT	7.2	1.2–43.7	0.032
HiSWF	19.8	1.1–344.2	0.041
Hispanic			
Pmax6	2.1	0.38–11.5	0.395
HiVPT	6.6	2.3–18.5	0.000
HiSWF*	—	—	—

*HiSWF data were dropped because of collinearity with outcome (all ulcerated patients had HiSWF = 1).

dence limits because of the small sample of cases (n = 46). We also support the role of the 10-g monofilament in the independent prediction of diabetic foot ulcers. However, our study includes a total of 99 ulcerated patients and an equal mix of male and female participants. Failure to perceive the 5.07 monofilament increased the risk of ulceration nearly 10-fold in our univariate analysis, while the adjusted risk was similar to that for high VPT, approximately fourfold. In our Hispanic population, insensitivity to this monofilament invariably was associated with ulceration, making this measurement a useful indicator for such patients at risk for ulceration.

Our study is limited by its cross-sectional design, although we have reported and discussed findings similar to those in other retrospective and prospective observational studies. However, since our measurements of exposures did not temporally precede cases of ulceration, they cannot definitely prove causality and are subject to error or misclassification. Such error is presumed to be random, since all subjects received the same quantitative testing at the time of their enrollment regardless of ulceration status. Although there was some overlap in the centers regarding racial distribution, most of the Hispanics were entered from the San Antonio center; blacks were from the San Francisco site; and the majority of Caucasians were enrolled in the Boston center. This raises the possibility of a center effect in our data. However, since the centers were experienced in clinical studies and investigators had received prior training and were using identical equipment, we do not believe that such an effect is solely the underlying basis for differences found among the races. In fact, the data obtained on pressures is consistent with the trends on lowered foot pressures and higher ranges of motion in blacks already published (35). As mentioned earlier, the patients reported herein are currently part of an ongoing prospective study of risk factors for foot ulceration. Our results of this baseline analysis will therefore be compared and should be validated by the results of the prospective investigation.

In summary, this study has confirmed the association of high foot pressures, high VPT, and insensitivity to the 5.07 monofilament with the development of ulceration in the feet of patients with diabetes. Furthermore, we have demonstrated significant differences in joint mobility, associated foot pressures, and prevalence of ulceration among Caucasian, black, and Hispanic patients. These findings should therefore guide our efforts aimed at detecting diabetic patients at risk of ulceration by incorporating such parameters into our screening programs. Although the two measures of neuropathy have the greater magnitude of effect, foot pressures should still be assessed to detect those neuropathic individuals at risk of ulceration from excessive plantar callus formation or repetitive stress (5).

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