Prediction of Diabetic Foot Ulcer Occurrence Using Commonly Available Clinical Information

The Seattle Diabetic Foot Study

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OBJECTIVE — The ability of readily available clinical information to predict the occurrence of diabetic foot ulcer has not been extensively studied. We conducted a prospective study of the individual and combined effects of commonly available clinical information in the prediction of diabetic foot ulcer occurrence.

RESEARCH DESIGN AND METHODS — We followed 1,285 diabetic veterans without foot ulcer for this outcome with annual clinical evaluations and quarterly mailed questionnaires to identify foot problems. At baseline we assessed age; race; weight; current smoking; diabetes duration and treatment; HbA_{1c} (A1C); visual acuity; history of laser photocoagulation treatment, foot ulcer, and amputation; foot shape; claudication; foot insensitivity to the 10-g monofilament; foot callus; pedal edema; hallux limitus; tinea pedis; and onychomycosis. Cox proportional hazards modeling was used with backwards stepwise elimination to develop a prediction model for the first foot ulcer occurrence after the baseline examination.

RESULTS — At baseline, subjects were 62.4 years of age on average and 98% male. Mean follow-up duration was 3.38 years, during which time 216 foot ulcers occurred, for an incidence of 5.0/100 person-years. Significant predictors ($P \leq 0.05$) of foot ulcer in the final model (hazard ratio, 95% CI) included A1C (1.10, 1.06–1.15), impaired vision (1.48, 1.00–2.18), prior foot ulcer (2.18, 1.61–2.95), prior amputation (2.57, 1.60–4.12), monofilament insensitivity (2.03, 1.50–2.76), tinea pedis (0.73, 0.54–0.98), and onychomycosis (1.58, 1.16–2.16). Area under the receiver operating characteristic curve was 0.81 at 1 year and 0.76 at 5 years.

CONCLUSIONS — Readily available clinical information has substantial predictive power for the development of diabetic foot ulcer and may help in accurately targeting persons at high risk of this outcome for preventive interventions.

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Diabetic foot ulcer and amputation continue to cause considerable morbidity among persons with diabetes (1). Foot ulcer has been recognized as an important antecedent of lower extremity amputation in multiple studies (2,3). Progress has occurred in understanding the pathogenesis of these complications (4), and methods to assist in the prediction of these outcomes have also been developed using various modalities, including lower limb sensory testing (5), thermography (6), and assessment of peak plantar pressure (7). Some of these modalities are unavailable to the vast majority of primary care clinical practitioners who provide much of the preventive and acute care of persons with diabetes. Also, the use of multiple risk indicators in combination to assist in the future prediction of diabetes complications has not been thoroughly explored and reported in a manner that permits assessment of prediction accuracy.

Given the need for a prediction model of diabetic foot ulcer that utilizes multiple risk indicators that would be available in all clinical encounters that take place between patients and primary care or nonfoot specialist providers, we examined this issue using prospective data from the Seattle Diabetic Foot Study. We have previously reported results from this study that emphasized physiologic measurements, many of which are not widely available, with the intention of establishing potential etiologic mechanisms for foot ulcer development. The aim of this article, though, is to provide patient-level (as opposed to limb-level) estimates of foot ulcer risk with commonly available clinical and laboratory information.

RESEARCH DESIGN AND METHODS

— All ambulatory general internal medicine clinic patients at a Veterans Affairs Medical Center with diabetes were eligible for enrollment. The study received prior approval from the University of Washington Human Subjects Office, and informed consent was obtained from all subjects for their participation in this research. Exclusion criteria included a current foot ulcer, bilateral foot amputations, wheelchair use or inability to walk, illness too severe to participate, or psychiatric illness that prevented informed consent. Subjects with clinically apparent diabetes were identified by review of hospital computerized pharmacy data for receipt of insulin, oral hypoglycemic medication or blood or urine glucose test strips, review of laboratory data, and review of medical record problem lists for the diagnosis of diabetes. The diagnosis was then confirmed by communication with clinical providers or medical record review.

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Abbreviations: ROC, receiver operating characteristic.

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—*Baseline subject characteristics by ulcer development during follow-up*

	No incident ulcer	Incident ulcer	HR (95% CI)	*P* value
n	1,069	216		
Age (years)*	62.4 ± 10.8	62.3 ± 9.2	1.00 (0.99–1.01)*	0.983
Male sex (%)	98	98	0.84 (0.31–2.24)	0.699
Race (%)				
White	77	83	Referent category	
Black	16	13	0.76 (0.51 to 1.12)	0.17
Other	7	4	0.66 (0.34–1.29)	0.23
Weight (lb)	213.2 ± 48.7	215.7 ± 45.5	1.00 (1.00–1.00)	0.19
Diabetes duration (years)	10.0 ± 9.3	12.6 ± 10.0	1.02 (1.01–1.04)	<0.001
Diabetes treatment (%)				
Diet	11	7	Referent category	
Insulin	38	60	2.73 (1.60–4.66)	<0.001
Oral medication	51	33	1.29 (0.74–2.25)	0.37
A1C (%)	9.5 ± 3.0	11.8 ± 3.4	1.13 (1.09–1.17)	<0.001
Claudication				
None	72	60	Referent category	
<1 block	14	21	1.74 (1.23–2.45)	0.002
≥1 block	14	19	1.30 (0.91–1.85)	0.15
Monofilament insensitivity (%)	33	60	3.10 (2.36–4.07)	<0.001
History of foot ulcer (%)	20	51	2.94 (2.26–3.84)	<0.001
History of amputation (%)	3	14	5.21 (3.53–7.69)	<0.001
Abnormal foot shape (%)	40	50	1.93 (1.07–3.48)	0.001
Callus present (%)	29	40	0.99 (0.76–1.30)	0.95
Hallux limitus (%)	36	29	1.10 (0.82–1.48)	0.52
Edema (%)	29	40	1.45 (1.11–1.91)	0.007
Tinea pedis (%)	35	37	0.91 (0.68–1.22)	0.53
Onychomycosis (%)	52	67	1.75 (1.31–2.32)	<0.001
Poor vision (%)	11	18	2.15 (1.52–3.05)	<0.001
Laser photocoagulation (%)	14	24	2.12 (1.55–2.90)	<0.001
Current smoking (%)	24	19	0.88 (0.62–1.23)	0.46

Data are mean ±SD or % unless otherwise indicated. *HRs are shown for a 1-unit increase in continuous variables.

Baseline data collection

Subjects were interviewed to collect data on demographics; diabetes type, duration, and treatments; smoking; self-care behaviors; neuropathic symptoms; presence of intermittent claudication, and past history of foot or leg ulcer and amputation. A physical examination with emphasis on the lower limbs was performed by research nurse practitioners, who assessed the presence of the following: abnormal foot shape (high arch or dropped foot), hammer/claw toe, Charcot deformity, hallux limitus, pedal edema, callus, tinea pedis, and onychomycosis. Visual acuity was assessed with a Snellen chart and was defined as poor if worse than 20/40 in both eyes. Weight in kilograms was measured with a balance beam scale. Persons whose diabetes developed after age 30 years or who were treated with diet or oral hypoglycemic agents were considered to have type 2 diabetes. Sensory testing was performed at nine locations on each foot using the Semmes-Weinstein monofilament. Inability to perceive the 5.07 monofilament at one or more sites on a foot was considered to represent peripheral sensory neuropathy in that foot. A random blood sample was drawn for measurement of serum A1C (Isolab, Akron, OH). To examine correlations with readily available clinical information, we assessed autonomic function by measuring cardiovascular reflexes, including heart rate variability and systolic blood pressure response to standing from a supine position as described previously (5,8).

Follow-up data collection

Foot ulcer was defined as a full-thickness skin defect that required >14 days for healing. Subjects were reexamined at 12- to 18-month intervals (mean interval = 13 months) to assess whether the outcome had occurred. Also, subjects were contacted quarterly by mail and were encouraged to call study staff or drop by the research clinic if they suspected that they had a foot ulcer. Subjects who did not return mailed questionnaires were contacted whenever possible in person at their next scheduled clinic visit at this medical center. To assure capture of incident foot ulcers that were not detected by the above means, study staff publicized the project throughout the medical center and emphasized the need for clinical providers to notify them of all incident ulcers seen in ambulatory, urgent care, and surgical specialty clinics and other clinical settings. Fluorescent orange labels were affixed to the medical record problem list, reminding providers to check their patients' feet. As an incentive for this reporting, study staff offered to expedite triage of patients with foot lesions, thereby reducing provider workload.

Statistical analysis

The outcome was defined as the first ulcer occurrence on either foot after the baseline examination. Follow-up on both limbs was terminated after the first ulcer occurrence. Limb-specific measurements (e.g., sensory neuropathy) were not analyzed in relation to ulcer occurrence on the same foot, but instead were used to predict ulcer occurrence on either foot. Limb-specific findings were defined as present if these occurred on either (or both) feet for a given subject. Therefore these results will apply to prediction of foot ulcer on the subject level as opposed to the foot level. We have previously reported results of this study using a limb-specific analysis of clinical and physiological measurements (5).

We estimated hazard ratios (HRs) in univariate Cox proportional hazards models with 95% CIs and level of statistical significance (9). Continuous variables were entered into these analyses as linear terms. To develop the optimal multivariable prediction model, we used a backwards selection algorithm beginning with a model that contained all of the variables shown in Table 1; a variable was ultimately retained in the final model if its *P* value was ≤0.05. To assess the classification accuracy of the final model, we estimate the area under the receiver operating characteristic (ROC) curve for the model using a special method developed for censored survival data (10). An

Table 2—*Final multivariable model predicting the occurrence of foot ulcer*

Characteristic	HR (95% CI)	*P* value
A1C*	1.10 (1.06–1.15)	<0.001
Vision poorer than 20/40	1.48 (1.00–2.18)	0.05
History of foot ulcer	2.18 (1.61–2.95)	<0.001
History of amputation	2.57 (1.60–4.12)	<0.001
Monofilament insensitivity	2.03 (1.50–2.76)	<0.001
Tinea pedis	0.73 (0.54–0.98)	0.035
Onychomycosis	1.58 (1.16–2.16)	0.004

*HR shown for a 1% increase in A1C level.

area under the ROC curve of 0.5 indicates that the test has no ability to discriminate between persons who do and do not develop foot ulcers, whereas values between 0.5 and the maximum value of 1 indicate that the test has utility in distinguishing between persons who do and do not develop foot ulcer. Because classification accuracy using this method is specified at a given time point, ROC curves and their areas were estimated for time intervals of 1 year and 5 years from the start of follow-up. All statistical analyses were performed using S-Plus version 6.0, release 1.0 for Linux 2.2.12 (Mathsoft, Cambridge, MA) or Stata SE 8 (Statacorp, College Station, TX).

RESULTS — Of the eligible subjects whom we recruited for this study, 83.5% agreed to participate. Of the 1,285 subjects included in this study, 216 developed foot ulcer over the course of follow-up, 210 subjects died before developing a foot ulcer, and 277 subjects were lost-to-follow-up, withdrew, or were terminated from the study because of severe illness. Thus, 78.4% of subjects remained in the study until the development of foot ulcer, death, or the time of this analysis. The mean follow-up interval was 3.38 years, with 75% of subjects followed for up to 4.95 years. Subjects were mainly male Caucasians with type 2 diabetes (94.9%), an average age of about 62 years, and mean diabetes duration of >10 years (Table 1).

Subjects who did and did not develop ulcers over the follow-up period differed by several baseline characteristics (Table 1). The following features were related to a higher risk of foot ulcer in univariate analysis: longer diabetes duration, treatment with insulin, higher A1C, claudication with less than one block of walking, sensory neuropathy, history of foot ulcer or amputation, abnormal foot shape, foot edema, onychomycosis, poor vision, and a history of laser photocoagulation therapy. Too few subjects with Charcot foot ($n = 18$) were available to test with adequate power the association between this deformity and foot ulcer risk. Six of these subjects had bilateral Charcot deformity, and eight developed an ulcer during follow-up.

The backwards stepwise selection algorithm that considered all variables shown in Table 1 yielded seven independent and statistically significant factors in the final Cox regression model of foot ulcer prediction (Table 2). The following factors that were significant in univariate analysis were no longer statistically significant in the multivariable model and were therefore removed from it: longer diabetes duration, treatment with insulin, claudication with less than one block of walking, abnormal foot shape, foot edema, and a history of laser photocoagulation therapy. Although tinea pedis was unrelated to foot ulcer occurrence in a univariate model, after adjustment for the covariates shown in Table 2, its presence was related to a significant reduction in risk of foot ulcer. Of note, the presence of tinea pedis was associated with a significantly greater mean heart rate variability (7.33 vs. 6.80 bpm, $P = 0.0201$) and a smaller but not significant orthostatic blood pressure drop (6.40 vs. 7.19 mmHg, $P = 0.140$). Variance inflation factors for the final model ranged from 1.02 to 1.11, thereby indicating that the presence of multicollinearity was unlikely.

The prediction accuracy of the final multivariable model was evaluated using area under the ROC curve (Fig. 1). The prediction model displayed good short- and medium-term classification accuracy

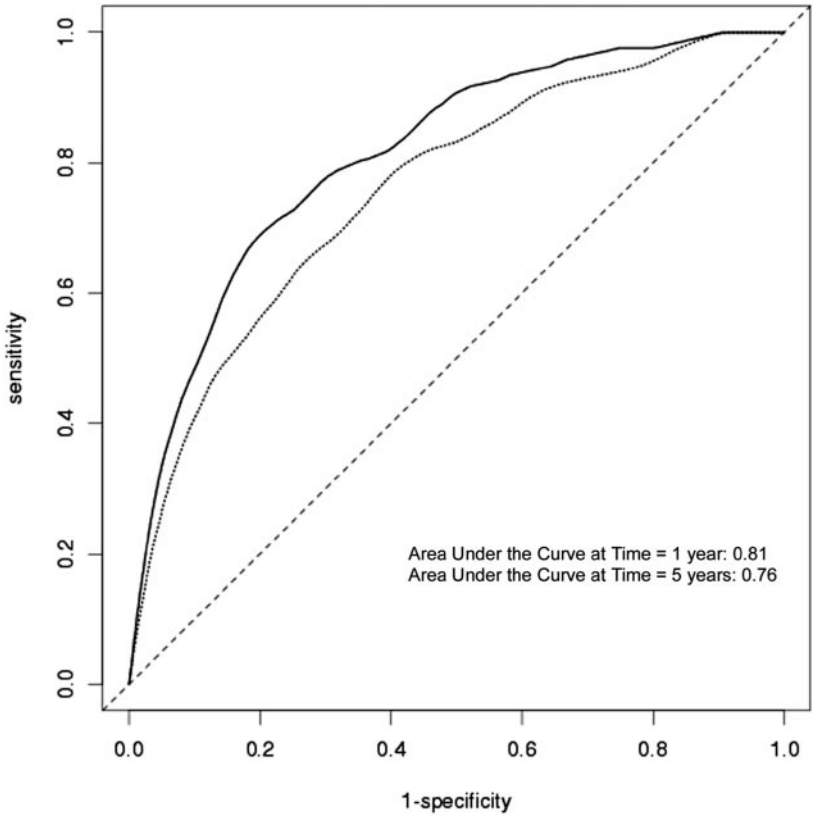

Figure 1—*Prediction model ROC curve for time until foot ulcer. The ROC curve for the final multivariable Cox proportional hazards model is shown. The ROC curve was generated using a model specifically developed for failure time data (10). Area under the ROC curve varies according to the time interval since baseline and is shown for 1- and 5-year follow-up intervals.*

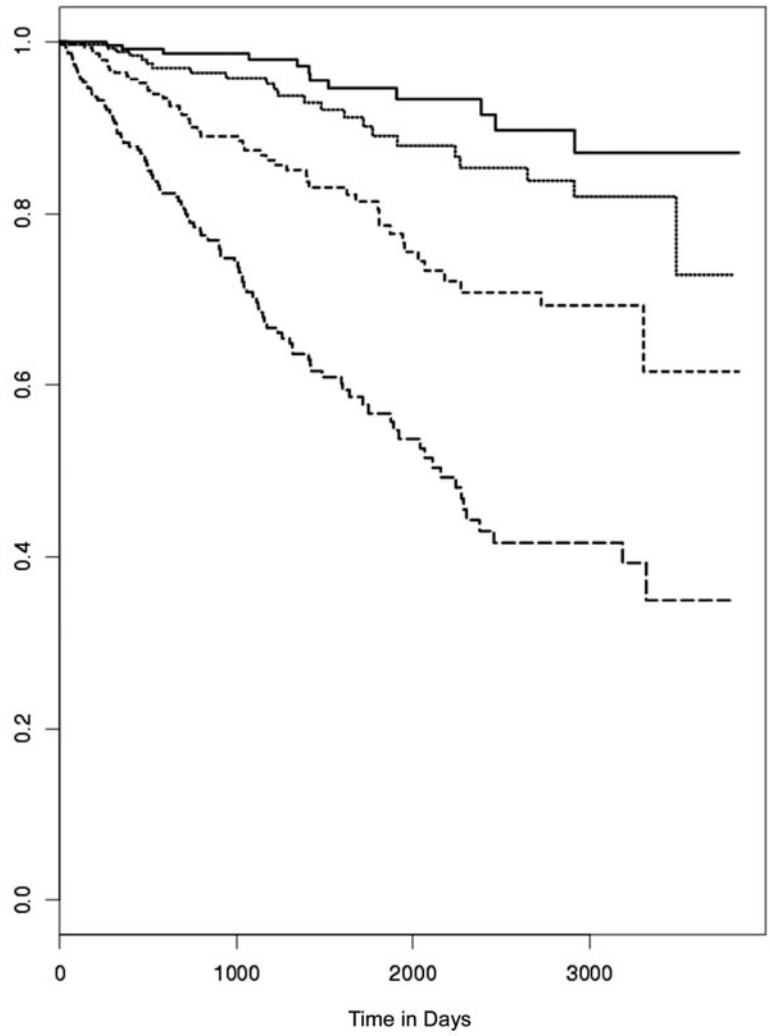

Figure 2—*Probability of ulcer-free survival by quartile of risk score. Kaplan-Meier survival curves are shown for the probability of ulcer-free survival (y-axis) in relation to quartile of score based on the multivariable model shown in Table 2. The x-axis displays follow-up time since baseline in days. The risk score quartiles can be identified as follows: solid dark line, lowest (0.61–1.47); solid gray line, second lowest (1.48–1.99); shorter broken line segments, second highest (2.00–2.61); and longer broken line segments, highest (2.62–5.07).*

regarding the development of foot ulcer over 1 and 5 years of follow-up, with areas under the ROC curves of 0.81 and 0.76, respectively. In addition, a risk score was assigned to each subject as a linear function of the coefficients of the final Cox regression model and individual values of the variables shown (Table 2), and these scores were divided into quartiles. The probability of remaining ulcer-free was lowest in the highest risk score quartile and highest in the lowest risk score quartile (Fig. 2). Subjects in the lowest ulcer-free survival category experienced a >60% probability of developing a diabetic foot ulcer during follow-up. The score was obtained from the following equation: score = A1C × 0.0975 + 0.7101 (neuropathy present) + 0.3888 (poor vision) − 0.3206 (tinea pedis present) + 0.4579 (onychomycosis present) + 0.7784 (past history of foot ulcer) + 0.943 (past history of lower limb amputation). A score of ≥2.62 places a subject in the highest risk quartile. For example, from the above equation, a subject with neuropathy, a past history of foot ulcer, onychomycosis, and a A1C of 10% would place in the top quartile by virtue of a score of 2.92. An acceptable A1C of 7.0% would reduce the score to 2.63, but the subject would still remain in the highest quartile of risk.

CONCLUSIONS — We found that commonly available clinical information has the ability to predict the development of diabetic foot ulcer over 1- and 5-year periods of time with a high degree of accuracy. The area under the ROC curve can be interpreted as the probability that a randomly selected ulcer case has a higher prediction model score than a randomly selected paired noncase. Thus, the model produced a higher score, corresponding to a higher likelihood of ulcer among 81% of all case and noncase pairs at 1 year of follow-up. The prediction model developed from the regression analysis showed excellent ability to classify subjects into different strata of risk in relation to a calculated risk score (Fig. 2). To facilitate calculation of this risk score, the authors have made available a downloadable spreadsheet for its calculation from http://www.eric.seattle.med.va.gov/downloads.

Inspection of the ROC curve in Fig. 1 also provides estimates of model sensitivity and specificity and demonstrates that the model provides a more accurate prediction of foot ulcer risk than data available from selected predictors taken individually. At 1 year, at a specificity of 80% corresponding to a false-positive rate of 20%, model sensitivity is ~65%, at a sensitivity of 80%, model specificity is ~60%, and at a sensitivity of 60%, model specificity is ~86%. Estimates of sensitivity and specificity for the prediction of diabetic foot ulcer for individual predictors of interest are available from Table 1. For example, 60% of persons who developed diabetic foot ulcer were insensate to the 10-g monofilament at baseline, compared with 33% of persons who did not experience this outcome, corresponding to a sensitivity of 60% and a specificity of 67%. The prediction model at 1 year therefore is more accurate than the monofilament because it has a higher specificity at the same value for sensitivity. The same is true for past history of foot ulcer, which exhibits a sensitivity of 51% and a specificity of 80% (Table 1). At this level of sensitivity, the prediction model at 1 year can be seen from Fig. 1 to yield a higher specificity of ~90%. To our knowledge, ROC interpretation of prospective data in the prediction of diabetic foot ulcer is not available in the literature.

A decline in the accuracy of prediction occurred over time, but this is not surprising given that during follow-up other events might have developed that changed foot ulcer risk that were not detected at the baseline evaluation. For example, A1C might have deteriorated in

some subjects, or neuropathy might have developed in other subjects who were free of this complication at baseline. Also, it is possible that the independent variables in the foot ulcer prediction model also predicted a higher risk of death, thereby depleting the cohort of persons at highest risk for diabetic foot complications. We have previously demonstrated this to be true among persons who developed a diabetic foot ulcer and subsequently experienced a higher risk of death than persons who did not develop foot complications (11).

Most independent predictors of diabetic foot ulcer have been previously identified by our group and others, but there were some surprising findings. Although A1C level is related to other diabetes complications, it has not to our knowledge been independently associated with a higher risk of foot ulcer in existing prospective research. In our previous limb-specific analysis, we did not find a significant independent association between A1C level and risk of diabetic foot ulcer (5). The discrepancy between the current and previous analyses in this same population may arise from adjustment for additional confounding factors in the previous limb-specific analysis that were related to a higher risk of foot ulcer and higher level of A1C. Also, the current analysis includes additional follow-up and more study subjects, thereby providing greater power to detect statistically significant differences. The association between poor vision and higher risk ulcer risk may be due to impaired ability for self-care as a result of this disability and/or a correlation between poor vision and the presence of diabetic retinopathy, a complication that has been associated with diabetic foot ulcer (12). A history of foot ulcer and amputation reflects the presence of underlying pathologic conditions not otherwise captured by the measurements made in this study and have been shown previously to be related to a higher risk of recurrent ulcers and amputations (13). Also, amputation may produce changes in gait and/or foot shape that increase the subsequent risk for foot ulcer (14). Sensory neuropathy has consistently been demonstrated to be associated with a higher risk of foot ulcer in prospective research as measured using the monofilament or other modalities (15–18). Tinea pedis was associated with a lower risk of foot ulcer. No prior information is available on this association. Tinea pedis is thought to be due in part to sweating, warmth, and use of occlusive footwear, and therefore its presence may be a clinical marker for intact autonomic function, which has been associated with a lower risk of diabetic foot ulcer (5,19). Our finding of significantly higher mean heart rate variability in persons with tinea pedis argues in favor of this association. Subjects with tinea pedis also had a lower drop in orthostatic blood pressure, which is associated with better autonomic function, although this difference did not achieve statistical significance. Autonomic neuropathy may result in anhidrosis, which, when present, may decrease the risk of developing tinea pedis (20). The mechanism or chain of association linking onychomycosis to diabetic foot ulcer is speculative but may be due to the association between this infection and the presence of diabetic neuropathy (21).

This study has several potential limitations that have been described previously (5). Bias could have resulted if loss to follow-up was associated with both ulcer risk and baseline risk factors. This effect is probably minimized due to the high proportion (78.4%) of study subjects who were followed until occurrence of ulcer, death, or the conclusion of the study. Incomplete ascertainment of ulcer was unlikely owing to the frequency and intensity of follow-up contacts and evaluations of study subjects. This study was conducted in a mainly elderly, male population with type 2 diabetes. It remains to be determined whether its results would apply to women, younger subjects, or persons with type 1 diabetes, and if this prediction model is used in these populations this limitation must be kept in mind.

We conclude that information that is readily available to all clinicians may assist with the prediction of the development of foot ulcer among persons with diabetes. A risk score can be easily generated using the information provided in conjunction with a spreadsheet program or even a calculator. Alternately, the results of the study may be considered in a less quantitative manner, as absence of all five factors that we identified in association with an increased risk of foot ulcer (history of ulcer or amputation, onychomycosis, sensory neuropathy, and poor vision) would indicate that the subject is in one of the lower quartiles of risk, assuming that the A1C level is not extremely elevated (>15%). These results may prove helpful in guiding clinicians and health care planners with regard to allocation of resources to persons who might benefit most from interventions to prevent the occurrence of diabetic foot ulcer.

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