Plantar Fascia Thickness, a Measure of Tissue Glycation, Predicts the Development of Complications in Adolescents With Type 1 Diabetes

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OBJECTIVE — Direct measurement of collagen glycation requires skin biopsy, which is invasive. We hypothesized that measurement of plantar fascia thickness (PFT) by ultrasound is an alternative index of tissue glycation and a marker of microvascular disease.

RESEARCH DESIGN AND METHODS — This was a prospective longitudinal study of microvascular complications in 344 adolescents with type 1 diabetes, whose PFT was assessed by ultrasound at baseline. Retinopathy was assessed by seven-field fundal photography, albumin excretion rate (AER) measured from three consecutive timed overnight urine specimens, autonomic neuropathy by pupillometry and cardiovascular tests, and peripheral neuropathy by vibration and thermal thresholds. Longitudinal analysis was performed using generalized estimating equations with baseline PFT, duration, and A1C as explanatory variables.

RESULTS — At first assessment, median (interquartile range) age was 15.1 (13.5–17.2) years and diabetes duration was 8.5 (6.0–11.5) years. Median follow up was 3.2 (2.1–4.5) years with a median of 4 (2–13) complications assessments per patient. In multivariate analysis, baseline PFT (abnormal in 132 subjects, 38%) predicted subsequent development of retinopathy (odds ratio 2.4 [95% CI 1.1–5.0]), elevated AER (2.24 [1.05–5.11]), peripheral neuropathy (2.3 [1.2–4.41]), and autonomic neuropathy (4.94 [2.46–9.91]). Limited joint mobility was present in only 4%.

CONCLUSIONS — PFT is a significant predictor of the subsequent development of complications in type 1 diabetes, suggesting that glycation and oxidation of collagen in soft tissues may be independent risk factors for microvascular complications.

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The potential mediators of vascular damage and chronic complications in diabetes are the interrelated processes of lipoprotein abnormalities, protein glycation, oxidation, and endothelial dysfunction. Nonenzymatic reactions between reducing sugars and several precursors such as collagen, plasma proteins, lipoproteins, cell membranes, and intracellular proteins lead to the formation of multiple compounds collectively named advanced glycation end products (AGEs) (1).

In patients with diabetes, hyperglycemia-mediated synthesis of new collagen (2) and accumulation of glycation products (3) accelerate age-related changes to the skin, connective tissue, and joints, including decreased elasticity, increased collagen cross-linking, and loss of enzymatic digestibility of the extracellular matrix (4). The rate of protein turnover is also a significant determinant of AGE accumulation, being increased in tissues with slow collagen turnover such as skin and cartilage. AGE residues in skin collagen are associated with severity of hyperglycemia as well as the presence of long-term complications (3,5). Limited joint mobility of the interphalangeal joints in the hands is also associated with increased risk of retinopathy and nephropathy (6,7).

Because AGEs are compounds coupled to tissue proteins, their accurate measurement requires sophisticated and expensive techniques that limit their use in the clinical setting. In particular, measurement of collagen glycation obtained by skin biopsy is invasive and not applicable in routine clinical care. Limited joint mobility in the hands has been previously described as an index of tissue glycation, but its prevalence has fallen significantly in the past two decades (8). Ultrasound has recently been used to detect thickening of the plantar aponeurosis, a tissue rich in collagen and susceptible to nonenzymatic glycation, in adults with type 1 and type 2 diabetes (9,10). We have previously demonstrated that increased plantar fascia thickness (PFT) was present in one-third of adolescents with type 1 diabetes compared with nondiabetic control subjects, whereas limited passive extension of the interphalangeal joints of the hands was present in 13% (11).

We hypothesized that abnormal PFT, as an index of tissue glycation, is an early marker for the future development of microvascular complications in young patients with type 1 diabetes. In this longitudinal study of adolescents followed for up to 13 years, we investigated the relationship between the thickness of plantar fascia at baseline, glycemic control, and subsequent development of retinopathy, microalbuminuria, and neuropathy.

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Abbreviations: AER, albumin excretion rate; AGE, advanced glycation end product; PFT, plantar fascia thickness.

RESEARCH DESIGN AND METHODS

— This was a prospective longitudinal study of adolescents and young adults performed at the Children's Hospital at Westmead (Sydney, Australia) from 1997 to 2006. PFT was measured at baseline in participants who all had type 1 diabetes with duration >5 years. Informed consent was obtained from all participants, and the study was approved by the hospital's ethics committee.

Plantar facia ultrasound

PFT was assessed by ultrasound (ACUSON 128 gray scale imager; Siemens, Mountain View, CA). For the aponeurosis measurements, the transducer was placed longitudinally over the center of the arch at least 3 cm from the calcaneus insertion of the plantar aponeurosis, as described previously (11). Abnormal PFT was defined as plantar aponeurosis thickness >2 SD above the mean of nondiabetic control subjects (>1.7 mm). The 57 healthy control subjects (47% men) assessed at baseline had a median age of 15.6 (interquartile range 13.8–16.4) years and were not related to patients with diabetes (11). All measurements were performed by the same podiatrist (A.D.), who was blinded to patients' complication status. The intraclass correlation coefficient for aponeurosis measurement was 0.89 (good reliability).

Complications assessment

Retinopathy was assessed by seven-field fundal photography using a Topcon Fundus camera (TRC 50-VT; Tokyo Optical Co., Tokyo, Japan) after dilatation of the pupils with cyclopentolate 1% and phenylephrine 2.5%. Nonsimultaneous photographic pairs were taken of seven standardized fields in each eye and then were viewed with a Donaldson Stereoviewer, which provided a three-dimensional representation of the fundus and enabled microaneurysms to be more easily distinguished from hemorrhages and artifacts. From September 2004 the IMAGEnet 2000 Lite system was used to digitalize images. The photographs were graded by the same ophthalmologist (S.H.) according to the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification of diabetic retinopathy as described previously (12,13) .

Albumin excretion rate (AER) was determined from three consecutive timed overnight urine specimens. Microalbuminuria was defined as AER ≥20 and <200 μg/min in two of three samples and early elevation of AER as mean AER >5 μg/min.

Cardiovascular autonomic nerve function was assessed by three tests of heart variation (maximum-minimum heart rate during deep breathing, Valsalva, and lying-standing change). Reference ranges for cardiovascular tests were from nondiabetic control subjects (14). These tests were only performed in 124 patients until 2001. Pupillary autonomic function was assessed by measuring the pupil size before and 3 s after a light stimulus was delivered, using an infrared pupillometer (Pupilscan; Fairvill Medical Optics). Pupillary abnormalities were defined as <5th percentile for nondiabetic control subjects (15). Small resting pupil diameter, defined as <5.3 mm, was also used as an outcome because we have previously shown that this cutoff predicts subsequent development of retinopathy and microalbuminuria (13).

Peripheral nerve function was assessed by thermal threshold testing for hot and cold at the left foot (Thermal Threshold Tester; Medelec, Old Woking, Surrey, U.K.) and vibration threshold at the left medial malleolus and left great toe (Biothesiometer; Biomedical Instrument, Newbury, OH). Peripheral nerve abnormalities were defined as <95% of the normal range in a nondiabetic adolescent control group (14). Limited joint mobility was assessed by active extension of the interphalangeal joint ("the prayer sign") and confirmed by passive extension (16,17).

Glycemic control was assessed by measurement of A1C using the Bio-Rad Diamat analyzer (Bio-Rad, Hercules, CA). The nondiabetic range for A1C is 4–6%. Systolic and diastolic blood pressure percentiles and BMI SD scores (*z* scores) were determined using age- and sex-related reference standards (18,19).

Statistical analysis

Descriptive statistics are reported as mean ± SD and median (interquartile range). Clinical characteristics and complication rates at baseline were compared between patients with normal and abnormal PFT using the χ^2 test for categorical variables, Student's *t* test for normally distributed continuous data, and Mann-Whitney *U* test for skewed data. Cross-sectional analysis of baseline factors associated with PFT (as a continuous variable, measured in millimeters) was also performed using multiple linear regression.

Longitudinal analysis of predictors of complications (retinopathy, early elevation of AER, microalbuminuria, and neuropathy) was performed using generalized estimating equations. Baseline PFT and variables at subsequent visits (age, duration, BMI *z* score, small pupil size, and A1C) were used as explanatory variables, with results expressed as odds ratios (ORs) and 95% CI. Clinically relevant interaction terms were examined in the models but were not significant, and models were assessed for goodness of fit. Analyses were performed using Stata (version 10, Stata, College Station, TX).

RESULTS

Baseline

At first assessment ($n = 344$, 45% male), median age was 15.1 (interquartile range 13.5–17.2) years and diabetes duration was 8.5 (6.0–11.5) years. There was no difference in the prevalence of microvascular complications or blood pressure at baseline, although an abnormal pupillary test and, in particular, small pupil diameter (markers of autonomic dysfunction) were more frequent in the abnormal PFT group (Table 1). In cross-sectional regression analysis, increased PFT was associated with higher BMI *z* score ($\beta = 0.06$ [95% CI 0.0–0.09], $P = 0.001$), male sex (0.11 [0.07–0.16], $P < 0.001$), longer diabetes duration (0.008 [0.001–0.015], $P = 0.03$), and an abnormal pupillary test (0.06 [0.01–0.11], $P = 0.04$).

Longitudinal follow-up

Follow-up data were available for 344 patients. The median time between first and last assessments was 3.2 (interquartile range 2.1–4.5) years and the median number of assessments per patient was 4 (2–13). At last visit, median diabetes duration was 11.9 (9.5–14.8) years, age was 18.2 (16.6–20.7) years, and A1C was 8.4 (7.6–8.4)%. Retinopathy was present in 42%, AER >5 μg/min in 59%, microalbuminuria in 3%, abnormal pupillary test in 68%, small pupil size in 22%, abnormal peripheral nerve test in 27%, abnormal cardiovascular autonomic nerve test in 16% (available in only 45 patients), and limited joint mobility in 4%.

PFT at baseline was a significant predictor of subsequent development of retinopathy, early elevation of AER (>5 μg/

Table 1—*Characteristics of patients at baseline stratified by plantar fascia thickness*

	Normal plantar fascia thickness (<1.7 mm)	Abnormal plantar fascia thickness (>1.7 mm)	*P* value
n	212	132	
Age (years)	15.1 (13.3–17.0)	15.0 (13.7–17.3)	0.64
Male sex (%)	80 (38)	74 (56)	0.001
Diabetes duration (years)	9.1 ± 3.2	9.5 (4.3)	0.28
BMI *z* score	0.79 ± 0.77	0.61 (0.76)	0.04
Systolic blood pressure percentiles	70 (53–85)	73 (49–85)	0.96
Diastolic blood pressure percentiles	74 (50–83)	72 (48–85)	0.94
Random blood glucose (mmol/l)	10.9 (6.7–15.5)	11.2 (8.2–14.2)	0.91
A1C (%)	8.4 ± 1.5	8.6 (1.1)	0.65
Retinopathy	62 (31)	39 (31)	0.94
Mean AER (μg/min)	4.9 (3.3–7.5)	4.9 (3.6–7.7)	0.56
Early elevation of AER (>5 μg/min)	104 (49)	69 (52)	0.57
Microalbuminuria	11 (6)	3 (3)	0.26
Cardiovascular test abnormality	15 (12)	13 (15)	0.45
Small resting pupil diameter*	23 (11)	25 (19)	0.04
Any pupillary abnormality	69 (54)	58 (70)	0.02
Peripheral nerve abnormality	55 (27)	38 (30)	0.57
Limited joint mobility	6 (3)	5 (4)	0.75

Data are means ± SD, median (interquartile range), or *n* (% within each group of PFT). *Abnormal resting pupil diameter <5.3 mm.

min), and nerve abnormalities (Table 2). A1C was also a significant predictor for all outcomes with the exception of small resting pupil size, whereas diabetes duration was significant for retinopathy, early elevation of AER, and small resting pupil size. The relationship between PFT and the risk of retinopathy, stratified by quintiles of A1C, is shown in Fig. 1. Among patients with normal plantar fascia measurements at baseline, the frequency of retinopathy increased with higher A1C levels ($\chi^2 = 23.0$, degrees of freedom = 4, $P < 0.001$), whereas for those with abnormal plantar fascia, the prevalence of retinopathy was similar across the quintiles of A1C ($\chi^2 = 2.7$, $P = 0.6$).

CONCLUSIONS — Thickening of plantar fascia is an early marker for the subsequent development of retinopathy, early elevation of AER, and neuropathy in adolescents with type 1 diabetes after a median duration of 12 years. The effect of PFT measured by ultrasound remained significant after adjusting for A1C and other variables (including diabetes duration, sex, and BMI). These findings suggest that glycation and oxidation of collagen in soft tissues may be independent risk factors for microvascular complications.

Previous studies assessing PFT in diabetes have been cross-sectional and predominantly examined foot biomechanics (10,20). This is the first longitudinal study to demonstrate that baseline PFT is an independent predictor of microvascular complications and thus is a novel measure of tissue glycation. Skin AGE levels measured by biopsy, an alternative index of tissue glycation, were associated with microvascular complications in cross-sectional and longitudinal analysis of adults with type 1 diabetes, after adjustment for A1C (3,21). Limited joint mobility, another proposed marker of tissue glycation, has been associated with microvascular disease in adolescents (6,16,17); however, the prevalence of this abnormality was low in our cohort. This finding is in keeping with recent data from the U.K. (8) and suggests that

Table 2—*Predictors of microvascular complications in longitudinal analysis using generalized estimating equations*

Outcome/risk factor	Odds ratio (95% CI)	*P* value
Retinopathy		
Plantar fascia thickness	2.37 (1.12–5.02)	0.03
Female sex	1.52 (1.06–2.17)	0.02
A1C	1.29 (1.14–1.46)	<0.001
Diabetes duration	1.24 (1.18–1.31)	<0.001
AER >5 μg/min		
Plantar fascia thickness	2.24 (1.05–5.11)	0.02
A1C	1.31 (1.16–1.47)	<0.001
Diabetes duration	1.04 (1.00–1.08)	0.05
Small resting pupil diameter (<5.3 mm)		
Plantar fascia thickness	4.94 (2.46–9.91)	<0.001
Diabetes duration	1.08 (1.04–1.11)	<0.001
Peripheral nerve abnormality (>95th percentile)		
Plantar fascia thickness	2.30 (1.20–4.41)	0.01
A1C	1.13 (1.00–1.27)	0.04
Female sex	0.69 (0.48–0.99)	0.04
Cardiac autonomic nerve abnormality (<5th percentile)		
Plantar fascia thickness	4.93 (1.32–18.31)	0.02
A1C	1.59 (1.22–2.08)	0.001

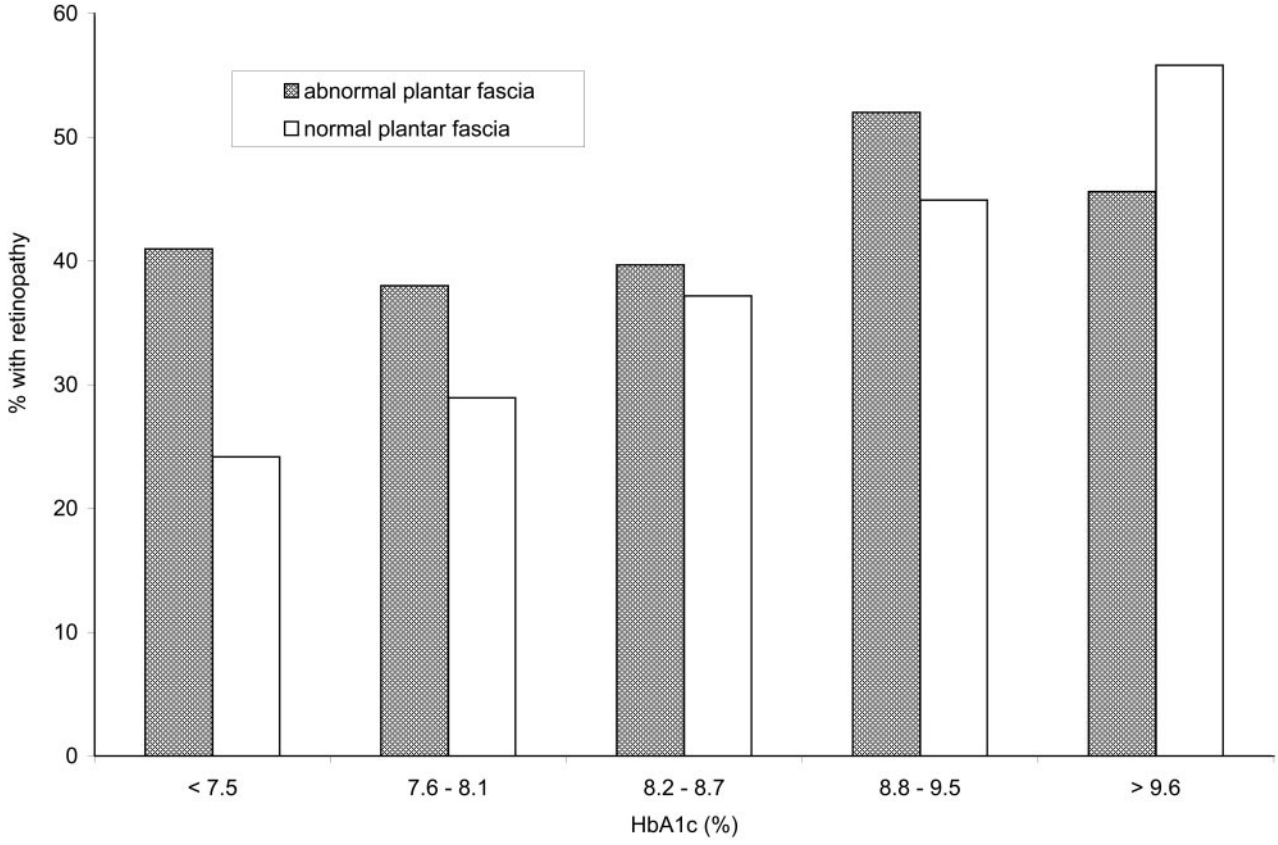

Figure 1—*Frequency of subsequent development of retinopathy across quintiles of A1C according to plantar fascia status at baseline (normal versus abnormal). For those with normal plantar fascia* (n = *212), the frequency of retinopathy was greater with increasing A1C* ($\chi^2 = 23.0$, $P < 0.001$), *but for those with abnormal plantar fascia* (n = *132), there was no effect of A1C* ($\chi^2 = 2.7$, $P = 0.6$).

PFT is a more sensitive measure of tissue glycation.

In the present study, the association of abnormal PFT at baseline with subsequent retinopathy was particularly evident in the group with lower A1C levels, whereas the prevalence of retinopathy was similar in patients with normal and abnormal PFT at higher levels of A1C. It may be that in the absence of hyperglycemia, transforming growth factor-β and other profibrotic cytokines are the major stimulants of collagen production, whereas multiple mechanisms (including endothelial dysfunction, apoptosis, and collagen glycation) contribute to vascular damage in the hyperglycemic environment. An alternative explanation is that factors that predispose to enhanced oxidative damage to collagen, such as genetic susceptibility, are important in the pathogenesis of vascular complications independently of glycation. Increased rates of the oxidized amino acid methionine sulfoxide, a direct product of collagen oxidation that does not require correction for glycemia, have been reported in complications-prone diabetic subjects compared with those resistant to complications (22). Another explanation is that transient elevation of glucose in patients with lower A1C levels is sufficient to increase concentrations of glycation products (23); thus, PFT may be a more sensitive index of prior glycemic status.

PFT was associated with early elevation of AER >5 μg/min but not microalbuminuria. This result is likely to be due to the low prevalence of microalbuminuria in this cohort (4%) and in other recent reports (12,13). Early elevation of AER precedes the development of microalbuminuria (24); therefore, a possible interpretation of our findings is that augmented collagen deposition within the extracellular matrix of the glomeruli parallels collagen glycation in connective tissues including the plantar aponeurosis.

PFT also predicted abnormal peripheral nerve abnormalities. Previously we have not found an association between PFT and foot pressure (11); however, a likely explanation is that patients were only examined at baseline and at a relatively early time point in the disease. In adults with type 1 and type 2 diabetes, PFT was associated with increased foot pressure, suggesting that PFT contributes to the development of neuropathy (10). In contrast, an inverse association between PFT and pressure was found in neuropathic patients with diabetes (mean age 61 years) (20), but it may be that longstanding increased pressure in the diabetic foot led to secondary thinning of the plantar fascia.

This study helps us understand other parallel mechanisms involved in the pathogenesis of complications. At baseline, the patients with abnormal PFT had the same rates of retinopathy, microalbuminuria, and peripheral nerve abnormalities as those with normal PFT, and the groups did not differ by blood pressure or A1C. However, more subjects in the abnormal plantar fascia group manifested autonomic dysfunction assessed by pupillometry, even after adjustments for duration, sex, and BMI *z* score. These findings could be due to both nerves and collagen responding in the same way to hyperglycemia. Of all the autonomic tests, pupillary diameter is the only mea-

sure of sympathetic nervous system defects and is potentially the most sensitive method for detecting subclinical autonomic neuropathy (15). Abnormal pupillary size was associated with subclinical signs of autonomic neuropathy (blood pressure variation) and intermittent microalbuminuria in cross-sectional analysis of adolescents with type 1 diabetes (25), suggesting that it predated persistent microalbuminuria. In our recent longitudinal study, small pupil size predicted the development of microalbuminuria and retinopathy after a 12-year follow-up period (13). Therefore, autonomic dysfunction and PFT may be the first evidence of vascular complications in young patients with type 1 diabetes.

Higher BMI *z* score was associated with abnormal PFT at baseline, in keeping with findings of Abouaesha et al. (20) in adults with diabetes. However, it is unclear whether higher BMI is causative in its relationship with PFT, as BMI *z* score was not a predictor of complications in longitudinal analysis. Obesity and insulin resistance may contribute to PFT via secretion of cytokines and adiponectin in adipose tissue, increasing oxidative stress, inflammation, and endothelial dysfunction, thereby contributing to diabetes complications.

This study was limited by the lack of direct evidence (using biopsy) of soft tissue glycation in parallel to the plantar fascia ultrasound. However, as a tissue rich in collagen, the plantar aponeurosis is susceptible to damage from chronic hyperglycemia and oxidative stress. Furthermore, thickening of the plantar fascia (9,11) has been has been reported in subjects with diabetes compared with control subjects, even in the absence of complications. Other noninvasive measures of tissue collagen glycation such as skin autofluorescence are markers for accumulation of glycation and oxidative stress-derived AGEs (26). Skin autofluorescence was associated with cardiac mortality and with the severity of peripheral and autonomic neuropathy in adults with diabetes (26). A potential limitation of this technique in other populations, however, is the interference of skin pigmentation with autofluorescence.

In summary, this study shows that assessment of PFT using ultrasound is a noninvasive measure of early damage to collagen and a novel predictor of the future development of microvascular complications in patients with type 1 diabetes. In this group, PFT was more sensitive than limited joint mobility measured in the hands.

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