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ORIGINAL ARTICLE

Plantar Fascia Thickness is Longitudinally Associated with Retinopathy and Renal Dysfunction: A Prospective Study from Adolescence to Adulthood

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Abstract

Aim:

The aim was to study the longitudinal relationship between plantar fascia thickness (PFT) as a measure of tissue glycation and microvascular (MV) complications in young persons with type 1 diabetes (T1DM).

Methods:

We conducted a prospective longitudinal cohort study of 152 (69 male) adolescents with T1DM who underwent repeated MV complications assessments and ultrasound measurements of PFT from baseline (1997–2002) until 2008. Retinopathy was assessed by 7-field stereoscopic fundal photography and nephropathy by albumin excretion rate (AER) from three timed overnight urine specimens. Longitudinal analysis was performed using generalized estimating equations (GEE).

Results:

Median (interquartile range) age at baseline was 15.1 (13.4–16.8) years, and median follow-up was 8.3 (7.0–9.5) years, with 4 (3–6) visits per patient. Glycemic control improved from baseline to final visit [glycated hemoglobin (HbA1c) 8.5% to 8.0%, respectively; $p = .004$]. Prevalence of retinopathy increased from 20% to 51% ($p < .001$) and early elevation of AER (>7.5 μg/min) increased from 26% to 29% ($p = .2$). A greater increase in PFT (mm/year) was associated with retinopathy at the final assessment (ΔPFT 1st vs. 2nd–4th quartiles, $\chi^2 = 9.87$, $p = .02$). In multivariate GEE, greater PFT was longitudinally associated with retinopathy [odds ratio (OR) 4.6, 95% confidence interval (CI) 2.0–10.3] and early renal dysfunction (OR 3.2, CI 1.3–8.0) after adjusting for gender, blood pressure standard deviation scores, HbA1c, and total cholesterol.

continued →

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Abbreviations: (AER) albumin excretion rate, (AGE) advanced glycation end product, (BMI) body mass index, (DBP) diastolic blood pressure, (DCCT) Diabetes Control and Complications Trial, (GEE) generalized estimating equations, (HbA1c) glycated hemoglobin, (MA) microalbuminuria, (MV) microvascular, (OR) odds ratio, (ORPS) Oxford Regional Prospective Study, (PFT) plantar fascia thickness, (RAGE) advanced glycation end product receptors, (SBP) systolic blood pressure, (SD) standard deviation, (SDS) standard deviation scores, (T1DM) type 1 diabetes mellitus

Keywords: advanced glycation end products, diabetes complications, metabolic memory, nephropathy, retinopathy, tissue glycation

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Abstract cont.

Conclusions:

In young people with T1DM, PFT was longitudinally associated with retinopathy and early renal dysfunction, highlighting the importance of early glycemic control and supporting the role of metabolic memory in MV complications. Measurement of PFT by ultrasound offers a noninvasive estimate of glycemic burden and tissue glycation.

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Introduction

Advanced glycation end products (AGEs) are implicated in the development of chronic diabetes complications.[1] Accumulation of AGEs in long-lived proteins such as collagen contributes to matrix expansion and decreased elasticity in tissues, a process exaggerated in diabetes.[2,3] Advanced glycation end product residues from skin collagen homogenates are associated with the severity of hyperglycemia and long-term microvascular (MV) complications.[4] Still, AGE heterogeneity makes their biochemical quantification challenging, costly, and time-consuming. Furthermore, skin biopsies are invasive and impractical, particularly in the pediatric setting. A single commercially available assay to adequately quantify AGEs remains elusive.[5]

Assessment of the plantar fascia with ultrasound is a well-established method in foot care. Plantar fascia thickness (PFT) increases with age and is greater in males than females.[6,7] Diabetes has been associated with greater plantar fascia thickening,[8] an effect likely due to collagen glycation. The long half-life of collagen in tendons and ligaments makes PFT, assessed by ultrasound, a relevant surrogate measure of tissue glycation and metabolic burden. Greater PFT has been associated with diabetic neuropathy and decreased first metatarsal mobility in adults.[9,10] We have demonstrated that PFT measurements at baseline predicted subsequent development of MV complications in adolescents with type 1 diabetes (T1DM) independent of glycated hemoglobin (HbA1c) levels,[11] and a cross-sectional Egyptian study supported these findings.[12] However, the longitudinal, contemporaneous relationship between PFT and MV complications has not been examined.

We hypothesize that temporal trends in PFT also predict incident diabetes MV complications, in particular that the greatest increase in PFT is associated with retinopathy and early renal dysfunction (AER >7.5 μg/min). In the present study, we examine the longitudinal relationship between PFT and MV complications in a cohort of 152 young adults with repeated PFT measures over a 10-year period.

Methods

This was a prospective longitudinal study of 152 (69 male) young persons with T1DM who underwent repeated MV complications assessments and ultrasound measurements of PFT at the Children's Hospital at Westmead, Sydney, Australia. The study was approved by the Hospital's Ethics Committee, and written informed consent was obtained from all participants.

Participants who attended the complications clinic between 1997 and 2002 (baseline)[8,11] and had PFT measured were eligible for inclusion in the longitudinal study. Complications assessments and PFT measurements were performed every 1 to 2 years from baseline during adolescence until transition to adult care. Between 2007 and 2008, invitation letters were sent to 546 patients who were seen at baseline for a follow-up (final) visit. Of these, 331 could not be contacted, 34 declined, 27 agreed but did not attend, and 2 had died. Thus, there were 152 (69 male) participants who returned for a final visit between 2008 and 2009. Glycated hemoglobin was higher in nonparticipants (8.9 ± 1.4% vs 8.6 ± 1.5%, $p = .003$) compared with participants, but no other significant differences in clinical characteristics were observed at baseline. The cohort had attended a total of 698 clinical visits from baseline to final visit [median 4 (3–6) visits per patient].

Measurement of Plantar Fascia Thickness

Plantar fascia thickness was assessed by ultrasound as previously described.[11] Briefly, participants rested prone on an examination table with feet overhanging the edge and toes pointing down. A linear array high-resolution transducer was used to measure the plantar fascia. The transducer was placed longitudinally over the center of the arch at least 3 cm from the calcaneal insertion of the aponeurosis. This particular site was chosen for its high reproducibility. For each patient, seven measurements each of the left and right PFT were performed, and the mean PFT was calculated for each foot. The higher of the two means (i.e., thickest fascia) was used for analysis. All participants were free of symptoms (i.e., heel pain) or sonographic evidence of plantar fasciitis. All measurements prior to the final assessment were performed by a single examiner, using ultrasound (ACUSON 128 gray-scale imager, Siemens, Mountain View, CA). Final PFT measurement was performed by a second examiner, masked to patients' complications status, using the LOGIQ e Compact Ultrasound (GE Medical System, Jiangsu, China), as described earlier. In the changeover of ultrasound machines, seven individuals had the fascia measured (left and right foot, 14 measurements)\using both ACUSON and LOGIQ e ultrasound machines. The intraclass correlation coefficient between machines was 0.98, indicating good reproducibility.

Rate of change in PFT in mm/year (ΔPFT) was estimated by calculating the difference between final and baseline PFTs divided by the number of years of follow-up.

Diabetes Complications Assessment

Retinopathy was detected using 7-field fundal stereoscopic photography with a Topcon Fundus camera (TRC 50-VT, Tokyo Optical Co., Tokyo) after dilation of the pupils (cyclopentolate 1% and phenylephrine 2.5%). Nonsimultaneous photographic pairs taken of seven standardized fields in each eye were viewed with a Donaldson stereo viewer. This provides a three-dimensional representation of the fundus and enables microaneurysms to be distinguished from hemorrhages and artifacts. From September 2004, the IMAGEnet 2000 Lite system was used to digitize images. One experienced pediatric ophthalmologist graded all photographs according to the Early Treatment Diabetic Retinopathy Study adaptation of the modified Airlie House classification of diabetic retinopathy, as previously described.[11] Retinopathy was defined as the presence of at least one microaneurysm or one hemorrhage (grade 21).

Albumin excretion rate was obtained from three consecutive timed overnight urine specimens. Although microalbuminuria (MA) (AER >20 μg/min) is a well-established predictor of progression to overt nephropathy, it is uncommon in young adolescents with T1DM early in the course of disease. Lower thresholds for early renal dysfunction (AER >7.5 μg/min) have been clearly demonstrated as predictors of MA.[13–15] We defined early renal dysfunction as mean AER >7.5 μg/min, as this is above the 95th percentile of normal AER described in adolescents, and MA as AER ≥20, and <200 μg/min in two out of three samples, as previously described.[14]

Glycemic control was assessed by measurement of HbA1c using the Bio-Rad Diamat Analyzer (Bio-Rad, Hercules, CA) from 1995 and 2001 with changeover to Variant analyzer (Bio-Rad, Hercules, CA) for the remainder of the study period. A cross-validation analysis found no significant differences or systematic bias between methods in the estimation HbA1c ($R^2 = 0.99$).

Clinical Measurements

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by auscultation with a conventional mercury sphygmomanometer device, using appropriate cuff sizes. Blood pressure was measured after 5 min of rest in the seated position. Anthropometric data included height measured to the nearest centimeter, weight to the nearest 100 g, and body mass index (BMI) was calculated. Standard deviation scores (SDS) for BMI and blood pressure were determined using age and gender-related reference standards.[16,17]

Statistical Analysis

Descriptive statistics are reported as mean ± standard deviation (SD) for normally-distributed variables, and median [interquartile range] for skewed distributions. Clinical characteristics and complications rates were compared between baseline and final visits using χ^2 tests for categorical variables, including ΔPFT quartiles, Student's *t*-test for normally distributed continuous data, and Mann-Whitney U-test for skewed data.

Longitudinal analysis of complications (retinopathy and early renal dysfunction) was performed using generalized estimating equations (GEE). Generalized estimating equations extend generalized linear models to allow for analysis of repeated measurements or other correlated within-subject observations. Explanatory variables included in univariate models were: PFT, diabetes duration, sex, visit HbA1c, mean HbA1c, BMI SDS, SBP SDS, DBP SDS, and total cholesterol (mmol/liter). We built multivariate GEE models by incorporating variables significantly

associated with complications in univariate analysis in a stepwise fashion and examined relevant interactions. Plantar fascia thickness and diabetes duration could not be included in the same multivariate models due to co-linearity and significant interaction terms. Adjustments were made for total diabetes duration by including a term of diabetes duration at the final visit ("final duration"). For similar reasons, we adjusted for age by adding the variable, "age at baseline."

The variable "mean HbA1c" was created as a measure of cumulative glycemic burden by calculating the average of all visits' HbA1c levels available through follow-up; the average number of HbA1c measurements was 4.6. Results were expressed as odds ratio (OR) and 95% confidence interval (CI). Analyses were performed using PASW version 18.0 (SPSS Inc, Chicago, IL).

Results

Baseline clinical characteristics of participants (n = 152) and nonparticipants (n = 394) are shown in **Table 1**. Glycemic control improved from adolescence to adulthood (HbA1c 8.5 ± 1.4% to 8.0 ± 1.4%, $p < .001$). Females had higher cumulative mean HbA1c than males (8.6 ± 1.2% vs 8.1 ± 0.8%, $p = .01$), with higher HbA1c at baseline (8.7 ± 1.5% vs 8.3 ± 1.2%, $p = .05$) and final (8.2 ± 1.6% vs 7.8 ± 1.1%, $p = .08$) visits. The use of multiple daily injection therapy increased throughout the study period (32% to 65%; $p < .001$), with a corresponding decrease in total daily insulin dose per kilogram of body weight (1.13 units/kg/day to 0.88 units/kg/day; $p < .001$). Plantar fascia thickness was greater in males than females and increased with age and diabetes duration (baseline: 1.66 ± 0.23 mm vs 1.54 ± 0.20 mm; $p = .001$, final: 1.93 ± 0.29 mm vs 1.81 ± 0.22 mm; $p = .005$).

Diabetes Complications

Retinopathy

During a mean follow-up of 8.3 (1.5) years, 67% (102/150) of participants had at least one episode of retinopathy. The point prevalence of retinopathy increased from 20% at baseline to 51% at the final visit. There were 72 incident retinopathy cases, of which 53 (74%) persisted at the final visit. Participants with persistent retinopathy at the last

Table 1.
Baseline Characteristics for all Patients and by ΔPFT Quartiles

	Nonparticipants	Participants	*p*	ΔPFT Q1	ΔPFT Q2	ΔPFT Q3	ΔPFT Q4	*p*
ΔPFT (mm/year)	—	—	—	<0.010	0.010–0.035	0.036–0.056	>0.056	—
Number (% male)	394 (49)	152 (45)	.4	36 (42)	35 (46)	37 (51)	44 (41)	.8
PFT (mm)	1.61 (0.25)	1.60 (0.22)	.7	1.76	1.61	1.54	1.49	<.001
Age (years)	15.0 (13.0–16.8)	15.1 (13.4–16.8)	.3	14.3	14.5	15.4	15.1	.007
Diabetes duration (years)	6.4 (3.8–9.8)	6.6 (4.4–11.0)	.2	6.3	5.8	8.4	6.9	.4
HbA1c (%)	8.9 (1.4)	8.5 (1.4)	.003	8.3	8.7	8.5	8.5	.7
SBP (mm Hg)	117 (11)	116 (11)	.2	112 (12)	114 (11)	120 (10)	116 (11)	.018
SBP SDS	0.63 (0.86)	0.52 (0.83)	.2	0.30	0.44	0.69	0.56	.3
DBP (mm Hg)	69 (8)	69 (8)	.5	68 (8)	67 (7)	70 (8)	69 (9)	.3
DBP SDS	0.58 (0.76)	0.57 (0.70)	.9	0.51	0.45	0.57	0.65	.7
BMI (kg/m^2)	22.9 (4.0)	22.4 (3.3)	.2	21.9 (3.2)	22.0 (2.8)	22.7 (3.8)	22.5 (3.3)	.7
BMI SDS	0.70 (0.78)	0.61 (0.69)	.3	0.61	0.62	0.51	0.61	.7
Log AER	0.71 (0.32)	0.74 (0.36)	.3	0.72	0.80	0.79	0.67	.4
Retinopathy *n* (%)	97/377 (26)	31/145 (21)	.3	7/33 (21)	4/35 (11)	14/37 (38)	6/40 (15)	.03
AER >7.5 μg/min	83/357 (23)	35/138 (25)	.6	9/33 (27)	11/32 (34)	8/34 (24)	7/39 (18)	.5
AER >20 μg/min	19/357 (5)	9/138 (7)	.6	0/33	3/33	3/34	3/39	.4
MA	13/356 (4)	7/137 (5)	.5	0/32	3/32	1/34	3/39	.3

Q, quartile.

visit had greater rate of increase in PFT (ΔPFT 1st vs 2nd–4th quartiles, $\chi^2 = 9.87$, $p = .02$) (**Figure 1**).

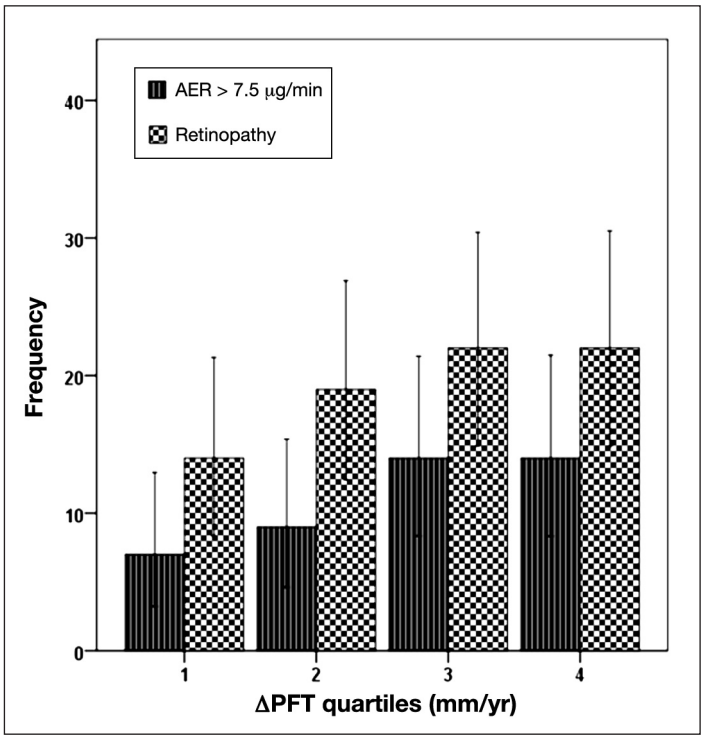

Figure 1. Frequency of retinopathy and early renal dysfunction (AER > 7.5 μg/min) at the final visit by ΔPFT quartiles. Retinopathy persisting at the final visit was significantly more frequent in those above the 1st ΔPFT quartile ($\chi^2 = 9.87$, $p = .02$). Renal dysfunction followed a similar trend but did not reach significance ($\chi^2 = 2.4$, $p = .05$). The error bars represent 95% CI.

Renal Dysfunction

The prevalence of early renal dysfunction (defined as AER >7.5 μg/min) increased slightly but not statistically significantly from 26% (38/149) at baseline to 29% (44/131) at the final visit ($p = .2$). At least one episode of early renal dysfunction was observed in 80/150 (58%) of participants during follow-up. Of those with AER >7.5 μg/min at baseline, 15/38 (40%) met the definition of MA during follow-up compared with 5% (6/111) of those with AER ≤7.5 μg/min at baseline ($p < .001$). Microalbuminuria was observed in 21/150 (14%) participants during follow-up, yielding a cumulative prevalence of 10% and 16% at 10 and 15 years of diabetes duration, respectively.

Longitudinal Analysis

There were 698 clinical visits with a median of 4 (3–6) visits per patient available for longitudinal analysis. In univariate GEE analysis, retinopathy was associated with greater PFT, longer diabetes duration, female sex, higher cumulative HbA1c (with lower ambient HbA1c), and greater BMI SDS (**Table 2**). Plantar fascia thickness predicted retinopathy, both incident and at any other time point, after adjusting for age at diagnosis, mean HbA1c, sex, and final diabetes duration (**Table 2**).

In univariate analysis, early renal dysfunction was associated with greater PFT, mean HbA1c, lower BMI SDS, and DBP SDS. These statistically significant associations persisted in multivariate analysis (**Table 3**).

Table 2.
Generalized Estimating Equation Models for Retinopathy

	Univariate models				Multivariate models			
	Incident retinopathy *n* = 120 OR (95% CI)	*p*	Any retinopathy *n* = 150 OR (95% CI)	*p*	Incident retinopathy *n* = 120 OR (95% CI)	*p*	Any retinopathy *n* = 150 OR (95% CI)	*p*
PFT (mm)	5.36 (2.04–14.12)	.001	5.33 (2.50-11.38)	<.0001	5.3 (2.1–13.0)	.005	4.6 (2.–10.3)	<.001
Sex (female)	2.0 (1.2–3.3)	.004	1.3 (0.8–2.2)	.2	2.0 (1.2–3.4)	.008	—	—
Age at final visit (years)	1.16 (1.07–1.26)	<.001	1.20 (1.11–1.29)	<.001	—	—	—	—
Final duration (years)	1.15 (1.08–1.24)	<.001	1.21 (1.15–1.27)	<.001	1.14 (1.07–1.22)	<.001	1.21 (1.14–1.27)	<.001
HbA1c (%)	0.72 (0.57–0.90)	.004	0.81 (0.70–0.94)	.007	—	—	—	—
Mean HbA1c (%)	1.39 (1.19–1.63)	<.001	1.35 (1.07–1.69)	.005	1.52 (1.24–1.88)	<.001	1.4 (1.2–1.7)	<.001
Total cholesterol (mmol/liter)	1.2 (0.9–1.5)	.2	1.20 (0.97–1.49)	.09	—	—	—	—
BMI SDS	1.37 (0.97–1.94)	.07	1.49 (1.09–2.03)	.01	—	—	1.42 (1.04–1.94)	.03
SBP SDS	1.10 (0.88–1.37)	.4	1.09 (0.92–1.29)	.3	—	—	—	—
DBP SDS	1.11 (0.85–1.44)	.5	1.14 (0.93–1.40)	.2	—	—	—	—
Multiple daily injections	1.87 (1.17–2.99)	.009	1.71 (1.18-2.49)	.005	—	—	—	—

Table 3.
Generalized Estimating Equation Models for Early Renal Dysfunction (AER >7.5 μg/min)

	Univariate models				Multivariate models			
	Incident renal dysfunction n = 111 OR (95% CI)	p	Any renal dysfunction n = 150 OR (95% CI)	p	Incident renal dysfunction n = 111 OR (95% CI)	p	Any renal dysfunction n = 150 OR (95% CI)	p
PFT (mm)	6.5 (2.3–18.1)	<.001	2.73 (1.17–6.35)	.02	4.9 (1.6–15.2)	.02	3.22 (1.29–8.01)	.02
Sex (female)	1.03 (0.55–1.92)	.9	0.85 (0.51–1.41)	.5	—	—	—	—
Age at final visit (years)	1.00 (0.92–1.09)	1.0	0.72 (0.95–1.07)	.7	—	—	—	—
Final duration (years)	1.06 (0.98–1.14)	.9	1.04 (0.98–1.10)	.2	1.09 (1.00–1.19)	.02	--	--
HbA1c (%)	1.26 (1.00–1.59)	.052	1.21 (1.05–1.40)	.009	—	—	1.21 (1.05–1.40)	.01
Mean HbA1c (%)	1.48 (1.02–2.14)	.04	1.27 (0.96–1.67)	.1	1.51 (1.11–2.06)	.008	—	—
Total cholesterol (mmol/liter)	0.86 (0.59–1.25)	.4	0.87 (0.63–1.19)	.4	—	—	—	—
BMI SDS	0.95 (0.55–1.67)	.9	0.69 (0.49–0.97)	.03	—	—	0.70 (0.49–1.00)	.05
SBP SDS	0.70 (0.54–0.93)	.01	0.83 (0.69–0.99)	.04	—	—	—	—
DBP SDS	0.77 (0.58–1.01)	.07	0.78 (0.64–0.94)	.01	0.60 (0.40–0.91)	.02	0.77 (0.62–0.94)	0.01
Multiple daily injections	0.34 (0.18-0.64)	.001	0.55 (0.39-0.78)	0.001	—	—	—	—

Discussion

In this prospective longitudinal study of 152 adolescents and young adults with T1DM, both PFT and rate of increase in PFT (mm/year) were associated with the development of MV complications during 10 years of follow-up.

Despite a significant improvement in glycemic control from puberty to early adulthood, retinopathy prevalence increased more than twofold (20% to 51%, $p < .001$) throughout the study period. These findings support metabolic memory for retinopathy, as observed in the Diabetes Control and Complications Trial (DCCT),[18] and underscore the importance and difficulties in maintaining tight glycemic control during early puberty and the period of growth and development.[19] There was a nonsignificant increase in prevalence of renal dysfunction between baseline and final visits in keeping with the apparent disparity observed between prevalence of retinopathy and nephropathy. However, renal anatomical changes can occur in the absence of renal functional abnormalities in patients with T1DM.[20]

Longitudinal GEE analysis demonstrated that retinopathy was associated with greater PFT, higher mean HbA1c, female gender, longer diabetes duration, and greater BMI SDS. Early renal dysfunction (AER >7.5 μg/min) was associated with greater PFT, higher mean HbA1c, longer diabetes duration, lower BMI SDS, and DBP SDS.

In longitudinal analysis, mean HbA1c, a surrogate marker of chronic glycemic exposure, was positively associated with retinopathy, whereas HbA1c at each individual visit had an inverse association. Although the inverse association appears a paradox, we speculate this may be explained by the significant improvement in glycemic control from baseline to final visits. Further, mean HbA1c, but not "visit HbA1c," was a significant predictor of incident renal dysfunction in both univariate and multivariate GEE models.

We also analyzed HbA1c SD as a surrogate marker of glycemic variability (results not shown), and unlike other studies,[6] we found no association between HbA1c SD and complications. Although this is likely due to the small numbers in the present study, it suggests that PFT may better reflect the additive effect of early glycemic control and glycoxidative stress from glycemic variability.

Changes in plantar fascia collagen are likely to reflect widespread systemic glycation and AGE formation, which may parallel changes in the vasculature. The compounding effects of chronic hyperglycemia,[21] glycemic variability,[6] and oxidative stress associated with T1DM are not comprehensively quantified by single assay measures such as HbA1c. Abnormal glycation of proteins, lipids, and other moieties, resulting in delayed clearance and exaggerated accumulation of AGEs, may be better assessed through tissue biopsy measures, as used in the

DCCT study.[4] The impractical nature of these, however, emphasizes the role of PFT as a useful, noninvasive measure of chronic glycation and metabolic burden, especially in those with early vascular complications.

Our longitudinal PFT findings are in agreement with skin biopsy AGE levels in the DCCT and their predictive value for MV complications.[4] In adults with type 2 diabetes, skin autofluorescence predicted nephropathy but did not predict retinopathy.[22] However, skin autofluorescence only detects fluorescent products, whereas PFT is a physical measure to which both fluorescent and nonfluorescent AGEs may contribute. A distinct advantage of PFT is that it uses readily available, easily reproducible, and noninvasive technology in the clinical setting.

The significant reduction in HbA1c with a parallel increase rather than decrease in PFT suggests that early glycation and formation of AGEs may irreversibly change collagen structure, reflecting the differences in half-lives of hemoglobin and skin collagen. Furthermore, these findings are consistent with "the shape of the metabolic memory of HbA1c" proposed by Lind and colleagues,[18] who demonstrated that HbA1c values from 5–10 years earlier contribute the greatest risk to progression of present retinopathy rather than concurrent visit HbA1c. The enduring effects of glycation on collagen, both in tendons and the microvasculature, have been demonstrated in animal models.[2,23] The role of the AGE receptor (RAGE), through the activation of nuclear factor-κB in oxidative stress and its association with diabetes complications, has been explored.[24] Daily glycemic variability may play a significant role in oxidative stress, both acutely and longer-term, which may further increase AGE production.[25] The production of AGEs, activation of RAGE, and irreversible cellular changes appear to perpetuate the cycle of oxidative stress and further production of AGEs independent of HbA1c.[26,27]

We speculate that glycemic variability, along with metabolic memory (which may be AGE- or epigenetic-mediated, or both), may be an explanation for the role of PFT as an independent predictor of complications.

Our data support the cutoff value of AER >7.5 μg/min as a measure of early renal dysfunction and an early risk marker for subsequent development of MA.[13–15] Young people with early renal dysfunction (AER >7.5 μg/min) at baseline were more likely to progress to an episode of MA (40% vs 5%, $p < .001$) throughout the study period. The cumulative prevalence of MA throughout the study period was 10% and 17% at 10 and 15 years diabetes duration, respectively. This contrasts with the findings from the population-based Oxford Regional Prospective Study (ORPS), which reported a cumulative prevalence of 26% and 51% of MA after 10 and 19 years duration, respectively.[28] However, participants from the ORPS had higher HbA1c and longer diabetes duration than our cohort. Our cohort was clinic-based, and participants had lower HbA1c than nonparticipants, thus selection bias may also contribute to the differences between the two studies. On the other hand, this selection bias towards patients with better glycemic control supports the robustness of PFT as a potential predictor of MV complications, since an association was found even in those with presumably lower levels of tissue glycation. Ideally, direct tissue evidence of glycation and AGE levels from plantar fascia biopsies would be available for correlation with PFT, however, this was not feasible.

The strengths of this study include the prospective longitudinal study design, repeated PFT measures, and the use of all available data points using GEE modeling. Other studies of PFT were cross-sectional in design or used a single baseline PFT measure as a predictor of MV complications; here we present repeated measures in the same individual over time. Another strength of this study is the use of the same laboratory throughout the study to quantify HbA1c, total cholesterol, and AER. Study weaknesses include the loss to follow-up, which usually related to discharge from pediatric clinical care. Study results may be influenced by the changes in ultrasound equipment and operator for the final assessment; however, these were validated and had a very reliable interobserver correlation coefficient.

In conclusion, PFT is longitudinally associated with the development of early MV complications in young people with T1DM. These findings support the concept of metabolic memory. Studies correlating PFT with other noninvasive measures of tissue glycation, such as skin autofluorescence and vascular function, will provide further insight into the pathophysiology and clinical relevance of tissue glycation in diabetes complications.

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