Association Between p.Leu54Met Polymorphism at the Paraoxonase-1 Gene and Plantar Fascia Thickness in Young Subjects With Type 1 Diabetes

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OBJECTIVE — In type 1 diabetes, plantar fascia, a collagen-rich tissue, is susceptible to glycation and oxidation. Paraoxonase-1 (PON1) is an HDL-bound antioxidant enzyme. PON1 polymorphisms have been associated with susceptibility to macro- and microvascular complications. We investigated the relationship between plantar fascia thickness (PFT) and PON1 gene variants, p.Leu54Met, p.Gln192Arg, and c.-107C>T, in type 1 diabetes.

RESEARCH DESIGN AND METHODS — This was a cross-sectional study of 331 adolescents with type 1 diabetes (162 male and 169 female). PFT was assessed by ultrasound, PON1 was assessed by genotyping with PCR and restriction fragment–length polymorphism, and serum PON1 activity was assessed by rates of hydrolysis of paraoxon and phenylacetate.

RESULTS — Median (interquartile range) age was 15.4 (13.5–17.3) years, and diabetes duration was 7.6 (4.9–10.6) years. The distribution of p.Leu54Met genotypes was LL 135 (40.8%), ML 149 (45%), and MM 47 (14.2%). PFT was abnormal (>1.7 mm) in 159 adolescents (48%). In multivariate analysis, predictors of abnormal PFT were ML/LL versus MM p.Leu54Met polymorphism (odds ratio 3.84 [95% CI 1.49–9.82], $P = 0.005$); BMI (percentile) (1.02 [1.01–1.03], $P = 0.007$); systolic blood pressure (percentile) (1.01 [1.00–1.02], $P = 0.03$); and male sex (3.29 [1.98–5.46], $P < 0.001$).

CONCLUSIONS — Thickening of the plantar aponeurosis occurs predominantly in overweight and male adolescents with type 1 diabetes. The MM genotype at PON1 p.Leu54Met is associated with a reduced risk of abnormal PFT.

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Paraoxonase-1 (PON1) is a calcium-dependent HDL-associated enzyme that protects LDLs from oxidation. In type 1 diabetic patients, the serum paraoxonase concentration is lower and HDL is a less efficient antioxidant than in healthy individuals (1). Oxidized LDL is implicated in the pathogenesis of atherosclerosis, diabetic retinopathy, and nephropathy (2). Variations in lipoprotein-related enzymes and genotypes may also promote diabetic microvascular damage (3).

Soft-tissue thickening is associated with chronic hyperglycemia and is hypothesized to be due to collagen glycation (4). With use of ultrasound techniques to measure plantar aponeurosis, a collagen-rich tissue, researchers demonstrated previously that people with diabetes have increased plantar fascia thickness (PFT) (5). Recently, this group reported that increased PFT predicted the development of microvascular complications in adolescents with type 1 diabetes and proposed abnormal PFT as a putative marker of soft-tissue glycation (6).

The PON gene cluster maps to chromosome 7q21-22 and influences gene expression and serum activity. There is an established link between PON1 and macrovascular disease (7) and emerging evidence linking PON1 to microvascular complications (8,9). In this study we investigated whether the variants c.-107C>T at the promoter region and p.Leu54Met and p.Gln192Arg at the coding regions of PON1 are associated with PFT in type 1 diabetes.

RESEARCH AND METHODS —
The cohort consisted of 331 Caucasian adolescents and young adults (162 male and 169 female) with a median (interquartile range) age of 15.4 (13.5–17.3) years and type 1 diabetes duration of 7.6 (4.9–10.6) years, who presented for routine complications assessment at the Children's Hospital at Westmead (Sydney, Australia) between 1998 and 2004. The study was approved by the hospital's ethics committee, and written informed consent was obtained.

PFT measurement
A single investigator (A.D.) measured PFT using ultrasound (Acuson 128 gray scale imager; Acuson, Mountain View, CA). For aponeurosis measurements, a linear-array, 7-MHz high-resolution transducer was placed longitudinally over the center of the arch at least 3 cm from the calcaneal insertion. To assess test-retest variability, four individuals were assessed 10 times in the same session. The assessor was masked to the measurements until they were completed and stored. The intraclass coefficient was 0.89. Abnormal PFT

Table 1—*Clinical characteristics of young subjects with type 1 diabetes with and without abnormal PFT*

	Normal PFT	Abnormal PFT	Total	*P* value
n	172	159	331	
Age (years)	15.7 (13.5–17.3)	15.1 (13.5–17.3)	15.4 (13.5–17.3)	0.46
Sex (male/female)	62/110	100/59	172/159	<0.001
Diabetes duration (years)	7.6 (5.0–10.3)	7.9 (4.3–11.0)	7.6 (4.9–10.6)	0.77
A1C (%)	8.6 ± 1.3	8.5 ± 1.1	8.6 ± 1.3	0.69
Total cholesterol (mmol/l)	4.3 (3.9–5.0)	4.3 (3.8–4.8)	4.3 (3.8–4.9)	0.42
SBP (percentile)	54 (27–82)	71 (38–85)	59 (32–82)	0.004
DBP (percentile)	73 (48–83)	73 (48–87)	73 (48–84)	0.49
BMI (percentile)	74 (56–87)	78 (63–91)	76 (61–88)	0.02
PON1 activity*				
Paraoxon (units/ml)	39.6 (28.3–79.3)	45.4 (28.1–85.4)	41.4 (28.4–79.9)	0.41
Phenylacetate (units/ml)	64.9 (44.6–81.6)	70.6 (56.7–80.4)	66.7 (52.8–80.5)	0.26

Data are means ± SD or median (interquartile range). *PON1 activity was measured in 144 subjects.

(>1.7 mm) was defined as 2 SDs above the mean measurement of 57 age-matched unrelated nondiabetic control subjects (27 male, median age 15.6 years) (5).

PON1 genotyping
DNA was extracted from peripheral white blood cells collected in lithium-heparin tubes using a modified salting out protocol. Polymorphisms were analyzed by PCR-restriction fragment–length polymorphism using a slightly modified version of the procedure described by Humbert et al. (10). DNA (100 ng) was denatured (94°C, 12 min) and then amplified for 35 cycles using PCR primers. Each cycle consisted of denaturation (94°C, 30 s), annealing (55°C, 30 s), and extension (72°C, 30 s) with a final extension of 5 min. For p.Leu54Met genotyping, the 171-bp PCR product was digested (37°C, 2 h) with *Hsp*92II (Promega, Madison, WI), and products were separated by PAGE (10%) and stained by ethidium bromide. The leucine allele corresponded to the presence of a nondigested fragment of 171 bp; the methionine allele corresponded to two digestion fragments of 127 and 44 bp.

For p.Gln192Arg genotyping, the 99-bp PCR product was digested with *Dpn*II, and products were separated by PAGE (10%). The arginine allele corresponded to the presence of three digestion fragments (40, 31, and 28 bp); the glutamine allele corresponded to two digestion fragments of 59 and 40 bp.

For c.-107C>T genotyping, the 240-bp PCR product was digested with *Bsr*BI, and products were separated by PAGE (10%). The TT genotype corresponded to a nondigested 240-bp fragment, the CC genotype corresponded to two digestion fragments of 212 and 28 bp, and the CT genotype corresponded to three digestion fragments of 240, 212, and 28 bp.

PON1 activity
In a representative subgroup of subjects (*n* = 144), PON1 activity of lithium-heparin plasma was measured by the rates of hydrolysis of paraoxon and phenylacetate as described previously (9).

Other variables
A1C was measured by a Bio-Rad Diamat analyzer (nondiabetic range of 4–6%; Bio-Rad Laboratories, Hercules, CA). Nonfasting plasma cholesterol was measured by Cobas Mira. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI percentiles were determined using age- and sex-related reference standards.

Statistical analysis
Descriptive statistics are reported as means ± SD or median (interquartile range) for skewed distributions. Groups were compared by χ^2 test for categorical variables. Differences between independent samples were evaluated using Student's *t* test and one-way ANOVA for normally distributed data or the Mann-Whitney *U* test for skewed data.

Multiple logistic regression was used to evaluate the association between abnormal PFT and biological and genetic variables. Explanatory variables were sex, age, diabetes duration, A1C, BMI, SBP, cholesterol, and PON1 genotypes (MM vs. ML/LL for p.Leu54Met; QQ vs. RQ/RR for p.Gln192Arg, and TT vs. CT/CC for c.-107C>T). Results are expressed as odds ratios and 95% CI. $P \leq 0.05$ indicated statistical significance.

RESULTS — Clinical characteristics are summarized in Table 1. Patients with abnormal PFT had higher SBP and BMI percentiles and were more likely to be male. PON1 activity was not significantly different between those with or without abnormal PFT for any substrate.

Table 2 shows genotype distributions and allele frequencies (all mutations were in Hardy-Weinberg equilibrium). Activities for phenylacetate and paraoxon substrates were higher for patients carrying LL alleles at PON1 p.Leu54Met versus those with the MM genotype. Similarly, those with CC alleles at c.-107C>T had higher enzyme activity for both substrates versus those with the TT genotype. At p.Gln192Arg, enzyme activity for hydrolysis of paraoxon was higher in those with the RR versus the QQ genotype, but phenylacetate activities did not differ.

The p.Leu54Met genotype distribution differed between the two PFT groups. The MM genotype was less frequent among those with thickened aponeurosis (normal PFT 20% vs. abnormal PFT 8%, χ^2, $P = 0.01$). There was no difference in frequency of p.Gln192Arg or c.-107C>T genotype distribution by PFT (Table 3).

In the multiple regression, LL/ML at p.Leu54Met, male sex, and BMI and SBP percentiles were associated with increased PFT (Table 4). There was no interaction between sex and BMI, sex and PON1 variants, or BMI and PON1 variants. There was strong linkage disequilibrium between p.Leu54Met and p.Gln192Arg and between p.Leu54Met and c.-107C>T genotypes (not shown).

Table 2—*Allele frequencies and enzyme activity of PON1 genotypes for hydrolysis of paraoxon and phenylacetate as substrates*

Polymorphism	Genotype (n)	Frequency (Hardy-Weinberg)	Paraoxon (units/ml)	Phenylacetate (units/ml)
n	331		144	144
p.Leu53Met	LL (135)	0.40 (0.39)	77.8 (46.2–106.5)	73.4 (64.9–87.7)
	ML (149)	0.45 (0.46)	39.1 (28.4–64.7)	66.2 (53.0–80.9)
	MM (47)	0.14 (0.13)	21.0 (16.7–30.4)	56.0 (39.5–63.0)
P value			<0.001	<0.001
p.Gln191Arg	RR (29)	0.09 (0.08)	99.8 (73.0–185.0)	68.2 (32.2–85.8)
	RQ (127)	0.38 (0.39)	80.3 (63.4–106.1)	68.7 (54.6–80.1)
	QQ (175)	0.53 (0.52)	30.5 (24.5–39.8)	66.7 (53.1–81.7)
P value			<0.001	0.81
c.-107C>T*	CC (90)	0.27 (0.26)	61.4 (37.9–90.3)	77.4 (68.4–90.2)
	CT (154)	0.49 (0.49)	40.3 (28.7–82.3)	70.3 (59.4–81.6)
	TT (75)	0.24 (0.24)	34.6 (20.8–73.6)	54.0 (39.7–63.2)
P value			0.017	<0.001

Data are median (interquartile range) unless otherwise indicated. *For c.-107C>T, genotyping was performed in 319 individuals and PON1 activity measured in 139 subjects.

CONCLUSIONS — This is the first report demonstrating an association between PFT, a marker of tissue glycation and/or oxidation, and PON1 gene polymorphisms in type 1 diabetes. In this cross-sectional study, the L allele at the p.Leu54Met gene was associated with abnormal PFT, or, conversely, the M allele had a protective effect. These results support the association between PON1 gene polymorphisms and plantar fascia changes. Previously, our group showed that the LL genotype was closely associated with microvascular complications (9,11).

After a relatively short median diabetes duration of 7 years, approximately half of the cohort had abnormal plantar fascia measurements. The early appearance of abnormal PFT, although unrelated to A1C measured at the time of the assessment, does not exclude the possibility that early glycemic variability could leave an imprinting in target organs, including changes in collagen, predisposing these organs to the future development of complications. In support of this possibility, we have recently demonstrated that PFT predicts retinopathy, early elevation of albumin excretion rate, and nerve abnormalities in young people with type 1 diabetes (6).

Oxidative stress and abnormalities of lipoprotein quantity and quality are implicated in the pathogenesis of microvascular complications (3). We hypothesize that genetic variants at the PON1 gene, for an antioxidant enzyme, could also predispose to collagen abnormalities via advanced glycation end product (AGE) formation, which involves glycation and oxidation. Tissue glycation and/or oxidation via intra- and extracellular generation of AGEs may promote diabetes complications. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) demonstrated in skin biopsies that collagen AGEs predict microvascular disease (12). Skin collagen methionine sulfoxide, a marker of oxidative damage independent of glycemia, has also been associated with type 1 diabetes complications (13).

There are divergent reports of PON1 activity and genotype and their relationship to microvascular complications. Our group described a higher allelic frequency of leucine 54 among type 1 diabetic subjects with versus without retinopathy (14). Similar findings were subsequently confirmed in a larger cohort of 372 type 1

Table 3—*Distribution of PON1 genotype in subjects with type 1 diabetes with and without abnormal PFT*

	Normal PFT	Abnormal PFT	*P* value
p.Leu54Met			
LL	66 (38)	69 (43)	
ML	72 (42)	77 (49)	0.01
MM	34 (20)	13 (8)	
p.Leu54Met			
MM	34 (20)	13 (8)	
ML/LL	138 (80)	146 (92)	0.003
p.Gln192Arg			
RR	14 (8)	15 (9)	
RQ	64 (37)	63 (40)	0.81
QQ	94 (55)	81 (51)	
p.Gln192Arg			
QQ	94 (55)	81 (51)	
RQ/RR	78 (45)	78 (49)	0.58
c.-107C>T			
TT	41 (25)	34 (22)	
CT	76 (46)	78 (51)	0.65
CC	49 (29)	41 (27)	
c.-107C>T			
TT	41 (25)	34 (22)	
CT/CC	125 (75)	119 (78)	0.69

Data are n (%).

Table 4—*Factors associated with abnormal PFT in young subjects with type 1 diabetes using multiple regression analysis*

	Odds ratio (95% CI)	*P* value
p.Leu54Met (ML/LL vs. MM)	3.84 (1.49–9.82)	0.005
Sex (male)	3.29 (1.98–5.46)	<0.001
BMI (percentile)	1.02 (1.01–1.03)	0.007
SBP (percentile)	1.01 (1.001–1.02)	0.03

The variables explained 19% of variation of abnormal PFT.

diabetic adolescents in whom the LL genotype increased risk for early retinopathy by almost threefold (8). The presence of the LL genotype and two other PON1 polymorphisms was found to influence urinary albumin excretion in 156 Caucasian type 1 diabetic adolescents (9). In contrast, others found no correlation between microvascular complications and PON1 polymorphisms in adults with type 1 diabetes (15). Divergent results may be explained by differences in ethnicity, age, sample size, smoking, diet, concomitant medications (16), PON1 assays, and differing relationships between PON activity or genotype for initiation and progression of complications.

Conversely, there is strong evidence showing that "high-expressor" PON1 alleles influence macrovascular disease. Homozygosity for the L allele doubled cardiovascular disease risk after adjustment for other risk factors in diabetes (17).

If PON1 protects lipids from oxidation, one might expect a higher expressor allele and a higher enzymatic activity to be protective against oxidative stress, AGE formation, and diabetes complications. However, the artificial nature of the substrates in this study is recognized and may not represent physiological substrates. A recent report demonstrated that the primary activity of the paraoxonases is that of a lactonase (18). As yet, there are no studies relating lactonase activity to diabetes complications.

Although PON1 activity was measured in a subgroup of subjects, PON1 polymorphisms influenced at least one of the two measured activities, in agreement with published data (19). PON1 activity was higher in the abnormal PFT group but did not achieve statistical significance. There is a large interindividual variation in PON activity that mostly depends on functional and promoter variations at the PON gene. Lower PON activity has been reported in type 1 diabetic subjects versus control subjects regardless of differences in PON1 phenotype (20). Hyperglycemia may influence the in vivo concentration and in vitro activity of PON1. Kordonouri et al. (11) showed that higher PON1 activity was associated with high glucose levels but not with A1C. With adjustment for blood glucose and diabetes duration, PON1 activity was higher in subjects with different stages of retinopathy versus those without retinopathy.

Our findings suggest that high-expressor alleles and a higher enzymatic activity are associated with increased susceptibility to microvascular complications (8,9,11). One explanation could be that although paraoxonase hydrolyzes harmful lysolipids produced by peroxidation, it might also increase their production from phospholipid peroxidation products and create a more harmful lipoprotein profile. The LL genotype has been shown to be least protective against oxidation (21). Another possibility is that relatively reduced enzyme activity rather than increased absolute PON1 activity promotes vascular complications. Some have reported that a higher LDL cholesterol–to-PON concentration ratio may indicate a reduced capacity of the enzyme to limit LDL oxidation (22). The low-activity allele at the PON1 gene has also been associated with a less harmful lipoprotein profile (23). Data on the LDL cholesterol–to-PON concentration ratio or levels of LDL cholesterol, triglycerides, and apolipoprotein B were not available for this study.

Male sex presented a threefold increased risk for thickened aponeurosis independent of other risk factors. The reasons for this are unclear, but men have a greater risk of lower limb diabetes complications (24). Hormonal variation and different recreational activities may be contributors. Although level of physical activity was not measured, it is unlikely that plantar fasciitis, a common condition among athletes, is the cause of fascia thickness. Fasciitis is associated with heel pain, and its ultrasonographic changes

are limited to the proximal insertion of the aponeurosis (25).

Higher BMI and SBP were associated with abnormal PFT. Although BMI may increase mechanical load on the plantar aponeurosis, overweight is associated with microvascular complications in diabetes, insulin resistance, hypertension, and an atherogenic profile.

In summary, this study underlines the association between p.Leu54Met variants and PFT, implicating PON1 in the pathogenesis of diabetes-related collagen changes. Although relationships between PON1 genes and collagen abnormalities merit further investigation, these initial findings support the concept of PON1 genetic variants as a link predisposing to development of complications in type 1 diabetes.

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