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ORIGINAL RESEARCH

Association of Diabetes Mellitus With Health Status Outcomes in Patients With Peripheral Artery Disease: Insights From the PORTRAIT Registry

Krishna K. Patel, MD, MSc; Hani Alturkmani, MD; Kensey Gosch, MS; Carlos Mena-Hurtado, MD; Mehdi H. Shishehbor, DO, MPH, PhD; Poghni A. Peri-Okonny, MD, MSc; Mark A. Creager, MD; John A. Spertus, MD, MPH; Kim G. Smolderen, PhD

BACKGROUND: Patients with peripheral artery disease (PAD) and coexisting diabetes mellitus (DM) have greater PAD progression and adverse limb events. Our aim was to study whether PAD-specific health status differs by DM.

METHODS AND RESULTS: The PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) trial is a 16-center international registry that includes patients with recent exacerbations or new-onset symptomatic PAD presenting to specialty clinics. We assessed PAD-specific health status initially and at 3, 6, and 12 months (Peripheral Artery Questionnaire [PAQ]). We used hierarchical, multivariable, linear regression, and repeated measures analyses to study the association between DM and baseline health status initially and over 3 to 12 months. Models were adjusted for demographics, socioeconomic factors, PAD severity, comorbidities, and psychosocial characteristics. The interaction of DM with PAD revascularization on 3- to 12-month health status was also tested. Of 1204 patients, 398 (33%) had DM (94% type 2). Patients with versus those without DM had lower unadjusted PAQ summary scores at baseline and 3, 6, and 12 months (46.1 versus 50.8, 63.6 versus 68.2, 65.7 versus 71.7, and 65.4 versus 72.6; $P \leq 0.01$). In fully adjusted models, the effect of DM on baseline (mean difference, −0.65; 95% CI, −2.86 to 1.56 [$P=0.56$]) and over 3- to 12-month PAQ summary scores (mean difference, −1.59; 95% CI, −4.06 to 0.88 [$P=0.21$]) was no longer significant. Twelve-month health status gains following revascularization were similar in both groups ($P=0.69$).

CONCLUSIONS: Patients with PAD with coexisting DM have poorer health status, mostly explained by the differences in their psychosocial and other comorbidity burden. Patients with PAD and DM versus those without DM experience similar health status benefits following PAD revascularization.

Key Words: diabetes mellitus ■ health-related quality of life ■ peripheral artery disease

After smoking, diabetes mellitus (DM) is the strongest risk factor for peripheral artery disease (PAD).[1] DM is present in 20% to 30% of patients with PAD,[2,3] and patients with DM have a 2- to 4-fold greater risk of developing PAD.[4,5] Patients with DM and PAD present with more advanced disease and have an increased rate of disease progression, peripheral vascular complications, and amputations compared with patients with PAD without DM.[6–10] These patients also have greater functional impairment from PAD in terms of shorter walking velocities and distance[11] and greater rates of cardiovascular events compared with those with PAD and no DM.[2,3,12]

While there are small single-center reports suggesting a worse quality of life in patients with PAD and DM,[13–15] these studies are limited by their small

Correspondence to: Krishna K. Patel, MD, MSc, Department of Cardiology, Saint Luke's Mid America Heart Institute, University of Missouri––Kansas City, Kansas City, MO. E-mail: patelkris@umkc.edu

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CLINICAL PERSPECTIVE

What Is New?

- Among 1204 patients with symptomatic peripheral artery disease (PAD), 33% with coexisting diabetes mellitus (DM), those with DM had poorer health status compared with patients without DM, mostly related to a higher burden of psychosocial and other comorbidities.
- Symptomatic patients with PAD and DM experience similar health status benefits following PAD revascularization compared with those without DM.

What Are the Clinical Implications?

- Better management of psychosocial and medical comorbidities in patients with PAD and coexisting DM may help improve their health status.
- Symptomatic patients with PAD and DM should have equal access to PAD revascularization, as it is associated with a significant improvement in health status, similar to those without DM.

Nonstandard Abbreviations and Acronyms

DM	diabetes mellitus
EQ-5D	Euro-Quality of Life 5 Dimension Questionnaire
ESSI	ENRICHD Social Support Inventory
GAD-2	2-Item Generalized Anxiety Disorder Scale
PAQ	Peripheral Artery Questionnaire
PHQ-2	Patient Health Questionnaire-2
PORTRAIT	Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories
PSS	Perceived Stress Scale

sample size, cross-sectional design, absence of a control group, and potential confounding factors that were not adjusted for. There are no current data regarding the effect of comorbid DM on PAD-specific health status and how it changes with time, which is important given the growing prevalence of DM. There is also lack of data regarding how patients' health status outcomes are affected by PAD treatment, specifically revascularization, based on their DM status. To address this gap in knowledge, we used an international multicenter registry of patients with symptomatic PAD to: (1) examine whether health status differs by DM status when patients present with new or worsening symptoms of PAD; (2) examine the trajectories of health status changes in patients with PAD over the course of a year according to their DM status; and (3) examine the effect of invasive PAD treatment on health status according to patient DM status. Documenting health status differences in patients with PAD who have comorbid DM can enable providers to better inform patients of their prognosis and can help identify strategies to potentially improve their health status.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The PORTRAIT (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) study is a multicenter, international prospective registry that enrolled patients presenting with new or worsening PAD symptoms to 16 specialty clinics (Data S1) across the United States, the Netherlands, and Australia from June 2011 to December 2015. Study details have been previously described.[16] Briefly, adults with new or worsening claudication and an abnormal resting ankle-brachial index (≤0.90) or a significant drop in postexercise ankle pressure of ≥20 mm Hg were included. Patients with noncompressible ankle-brachial index (≥1.3), a recent episode of critical limb ischemia, or recent peripheral revascularization and those who were incarcerated; hard of hearing; unable to speak English, Dutch, or Spanish; or unable to provide informed consent were excluded.

Patients with an established diagnosis of DM were identified through medical record review at the time of their initial visit. DM type, treatment with insulin or oral hypoglycemics, glycemic control as measured by fasting plasma glucose and glycated hemoglobin (HbA_{1c}), and quality-of-care measures related to DM were abstracted from the patient's medical record. Demographic, socioeconomic (insurance, marital status, finances, employment, cost of care), symptom status (typical versus atypical symptoms), and lifestyle (activity level and smoking and alcohol use) factors were collected through patient interviews at the initial visit. Psychosocial factors such as depression, anxiety, social support, and perceived stress were assessed through standardized patient questionnaires, which included the Patient Health Questionnaire-2 (PHQ-2),[17] 2-Item Generalized Anxiety Disorder Scale (GAD-2),[18] ENRICHD Social Support Inventory (ESSI),[19] and Perceived Stress

Scale (PSS)[20] at baseline visit and at 3, 6, and 12 months of follow-up. Other comorbidities, laboratory, performance measure adherence, medication, and diagnostic test information was collected from the medical record by trained study personnel. For all patients, serial health status and lifestyle factors were collected at 3, 6, and 12 months by telephone conducted by trained interviewers. PAD treatment was defined as receipt of supervised exercise therapy or revascularization (peripheral endovascular intervention or surgery; symptom-driven) or medical therapy (antiplatelet and statin) within the first 3 months of follow-up.

All study participants provided either written or telephonic informed consent. The study protocol was approved by the institutional review boards of all participating sites.

Health Status Assessment

Disease-specific health status was assessed using the Peripheral Artery Questionnaire (PAQ),[21] and generic health status was assessed using the Euro-Quality of Life 5 Dimension Questionnaire (EQ-5D).[22] Trained study personnel administered both questionnaires in-person at the initial visit and via telephone at 3, 6, and 12 months of follow-up. The PAQ is a 20-item validated, multidimensional, PAD-specific health status instrument that measures the following health domains in patients with PAD: physical limitation, symptoms, symptom stability, social limitation, treatment satisfaction, and quality of life.[21] Scores for all subdomains range from 0 to 100 with higher scores correlating with better health status. A summary score is calculated by averaging PAQ physical limitation, symptom, social limitation, and quality-of-life subscales and also ranges from 0 to 100. A difference of 8 points in the PAQ summary score has been proposed to be clinically important.[23] The EQ-5D is a generic health status instrument that assesses health status among 5 dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety/depression and has a visual analog scale (VAS) component that rates an individual's perception of their overall health on a scale of 0 to 100, where higher scores indicate better health status.[22]

Statistical Analysis

Baseline characteristics were compared between patients with PAD who did and did not have DM using Student *t* test or Wilcoxon rank sum test for continuous variables and chi-square or Fisher exact tests for categorical variables. Health status was compared between patients with PAD with and without DM at baseline, 3-, 6-, and 12-month time points using Student *t* tests, including an omnibus test to assess for any differences over all time points.

A hierarchical, multivariable, linear regression model, with a random effect for site, was used to assess the association between DM and health status at baseline. This model was performed in a stepwise fashion, with the first step only adjusting for DM to generate unadjusted effect estimates of patient health status. In the second step, the model was partially adjusted for differences in demographic characteristics of age, sex, race, and country. To account for other patient and treatment characteristics that could affect the association of DM with patients' health status, the following characteristics (Table S1) were adjusted for in the third step to generate fully adjusted estimates: (1) socioeconomic factors (education, current work for pay, insurance, avoidance of care because of cost); (2) PAD disease severity (ankle-brachial index, proximal versus distal location, laterality [bilateral versus unilateral disease], exacerbation versus new diagnosis, duration of pain, history of ulcer, amputation, or prior peripheral intervention); (3) comorbidities (hypertension, dyslipidemia, cerebrovascular accident, coronary artery disease, chronic heart failure, chronic kidney disease, chronic lung disease, musculoskeletal problems, sleep apnea, obesity/body mass index); and (4) psychosocial factors (ESSI score, PSS score, GAD-2 score, PHQ-2). In each step, all variables listed above were entered at the same time (simultaneous forced entry). Effect of DM on PAQ outcomes were presented as mean estimates with 95% CIs. Covariates were chosen a priori based on previously published literature and clinical judgement and supplemented with a random forest approach.

Additionally, another hierarchical, multivariable, linear model was used to examine the independent association of DM status with health status over follow-up (3, 6, and 12 months). A random effect for site was included along with a Cholesky-structured covariance matrix to account for repeated measurements. DM status and follow-up time in months were included as fixed effects and a 2-way interaction term was tested for differences in DM effect over time on health status. This repeated measure analysis was also performed in a similar stepwise fashion as the baseline health status analysis previously presented. In addition to the variables described above, fully adjusted repeated measures models for follow-up health status were also adjusted for antiplatelet and statin receipt, referral to supervised exercise therapy within the first 3 months, and receipt of revascularization (endovascular PAD intervention or surgical PAD treatment) within 3 months, to adjust for differences in treatment at follow-up among patients with and without DM.

To evaluate whether any specific group of patient factors would most explain the difference in health status among patients with and without DM beyond demographic factors, sensitivity analyses were

Table 1. Baseline Characteristics of the Study Population

	DM (n=398) Mean (SD) or n (%)	No DM (n=806) Mean (SD) or n (%)	*P* Value
Demographics			
Age, y	67.4±9.0	67.6±9.6	0.79
Men	239 (60.1)	514 (63.8)	0.21
White race	297 (74.6)	692 (85.9)	<0.001
Country			<0.001
United States	286 (72)	462 (57.3)	
The Netherlands	77 (19.3)	289 (35.9)	
Australia	35 (8.8)	55 (6.8)	
Socioeconomic factors			
At least a high school education	286 (72.0)	539 (67.6)	0.12
Insurance	394 (99.0)	801 (99.4)	0.49
Currently work for pay			0.03
No	316 (79.8)	595 (74.0)	
Yes, full-time	44 (11.1)	136 (16.9)	
Yes, part-time	36 (9.1)	73 (9.1)	
Not taking medication because of cost			0.5
Always or frequently	10 (2.6)	14 (1.8)	
Occasionally	30 (7.6)	36 (4.5)	
Rarely or never	355 (89.9)	753 (93.7)	
PAD severity			
Ankle-brachial index	0.7±0.2	0.7±0.2	0.41
Onset			0.003
New-onset PAD	186 (46.7)	448 (55.6)	
Exacerbation of PAD	212 (53.3)	358 (44.4)	
Unilateral disease	168 (42.2)	420 (52.1)	0.001
Location			0.13
Proximal	155 (38.9)	340 (42.2)	
Distal	223 (56)	412 (51.1)	
Other	17 (4.3)	52 (6.5)	
Duration of pain			0.45
<1 mo	5 (1.5)	22 (3.2)	
1–6 mo	99 (29.5)	208 (30.0)	
7–12 mo	60 (17.9)	122 (17.6)	
>12 mo	172 (51.2)	341 (49.2)	
Nonhealing ulcer	11 (2.8)	5 (0.6)	0.002
Amputation	8 (2.0)	6 (0.7)	0.08
Prior peripheral vascular intervention	128 (32.2)	200 (24.8)	0.01
Comorbidities			
Current smokers	118 (29.7)	328 (40.7)	<0.001
Hypertension	355 (89.2)	612 (75.9)	<0.001
Dyslipidemia	352 (88.4)	605 (75.1)	<0.001
Cerebrovascular accident	52 (13.1)	86 (10.7)	0.22
Coronary artery disease	212 (53.3)	320 (39.7)	<0.001
Congestive heart failure	53 (13.3)	71 (8.8)	0.02
Chronic kidney disease	63 (15.8)	69 (8.6)	<0.001
Current depression	40 (10.1)	55 (6.8)	0.05
Chronic lung disease	58 (14.6)	148 (18.4)	0.1

(*Continued*)

Table 1. Continued

	DM (n=398) Mean (SD) or n (%)	No DM (n=806) Mean (SD) or n (%)	*P* Value
Body mass index, kg/m^2	31.7±7.4	27.6±5.3	<0.001
Musculoskeletal problems	79 (19.8)	165 (20.5)	0.8
Psychosocial factors			
PHQ-8 depression score	5.2±5.2	4.5±4.9	0.02
GAD-2 score	3.8±5.1	3.5±4.5	0.47
ESSI score	21.9±4.7	22.1±4.7	0.47
PSS stress score	4.3±3.6	3.8±3.3	0.04
Baseline health status measures			
PAQ physical limitation	33.9±25.7	40.8±26.3	<0.001
PAQ symptom stability	42.6±20.0	43.8±21.6	0.32
PAQ symptoms	41.8±23.9	45.0±22.2	0.02
PAQ treatment satisfaction	81.7±21.4	83.7±20.8	0.13
PAQ quality of life	47.6±26.3	52.0±25.6	0.005
PAQ social limitation	59.7±30.7	65.2±29.6	0.003
PAQ summary	46.1±22.3	50.8±21.3	<0.001
EQ-5D: score your health today	65.1±19.4	66.6±19.3	0.21
Laboratory values			
Fasting plasma glucose (median [IQR]), mg/dL	135.5 (107.0–174.5)	96.0 (88.2–107.0)	<0.001[w]
Hemoglobin (median [IQR]), g%	13.0 (11.5–14.3)	13.9 (12.5–15.0)	<0.001[w]
Serum creatinine (median [IQR]), mg/dL	1.0 (0.8–1.3)	0.9 (0.8–1.1)	<0.001[w]
PAD treatment			
Antiplatelet prescription	357 (89.7)	688 (85.4)	0.16
Statin prescription	345 (86.7)	652 (80.9)	0.01
Smoking cessation advice/counseling/treatment	86 (74.8)	242 (77.3)	0.70
Supervised exercise program referral	61 (16.0)	202 (26.8)	<0.001
Invasive treatment within 3 mo	73 (19.6)	155 (20.2)	0.83

Continuous variables compared using Student *t* test, except [w] Wilcoxon rank sum test. Categorical variables compared using chi-square or Fisher exact test. DM indicates diabetes mellitus; EQ-5D, Euro-Quality of Life 5 Dimension Questionnaire; ESSI, ENRICHD Social Support Inventory; GAD-2, 2-Item Generalized Anxiety Disorder Scale; IQR, interquartile range; PAD, peripheral arterial disease; PAQ, Peripheral Artery Questionnaire; PHQ-8, Patient Health Questionnaire-8; and PSS, Perceived Stress Scale.

conducted, where mean estimates, 95% Cis, and change in R^2 were evaluated after addition of patient factors related to each covariate group noted above separately, into a multiple regression model with DM and demographic patient characteristics.

To estimate whether patients with DM and PAD responded differently to PAD revascularization in terms of their health status outcomes on follow-up, an interaction between DM status and revascularization was entered into the fully adjusted follow-up health status model. A statistically significant interaction of DM×revascularization in the models would suggest that follow-up health status differs based on receipt of invasive PAD treatment among patients with PAD who do and do not have DM.

To assess the effect of glycemic control on health status in patients with DM, we conducted a sensitivity analysis evaluating PAQ and EQ-5D outcomes in a subgroup of patients with PAD and DM according to glycemic control at baseline (subdivided into groups by baseline HbA_{1c} of <6%, 6%–6.9%, 7%–7.9%, 8%–8.9%, and >9%).

Covariate data were largely complete with >90% of patients missing ≤1 covariate. The covariates with the largest number of missing data were body mass index (21.7%), duration of pain (14.5%), and treatment at 3 months (5.2%). Missing data were imputed using sequential regression imputation that included all of the variables from the multivariable model. All analyses were performed using SAS version 9.4 (SAS Institute). A 2-tailed $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

Of the 1275 eligible patients with PAD enrolled in the PORTRAIT registry, we excluded 71 who were missing either all follow-up interviews (n=70) or baseline PAQ

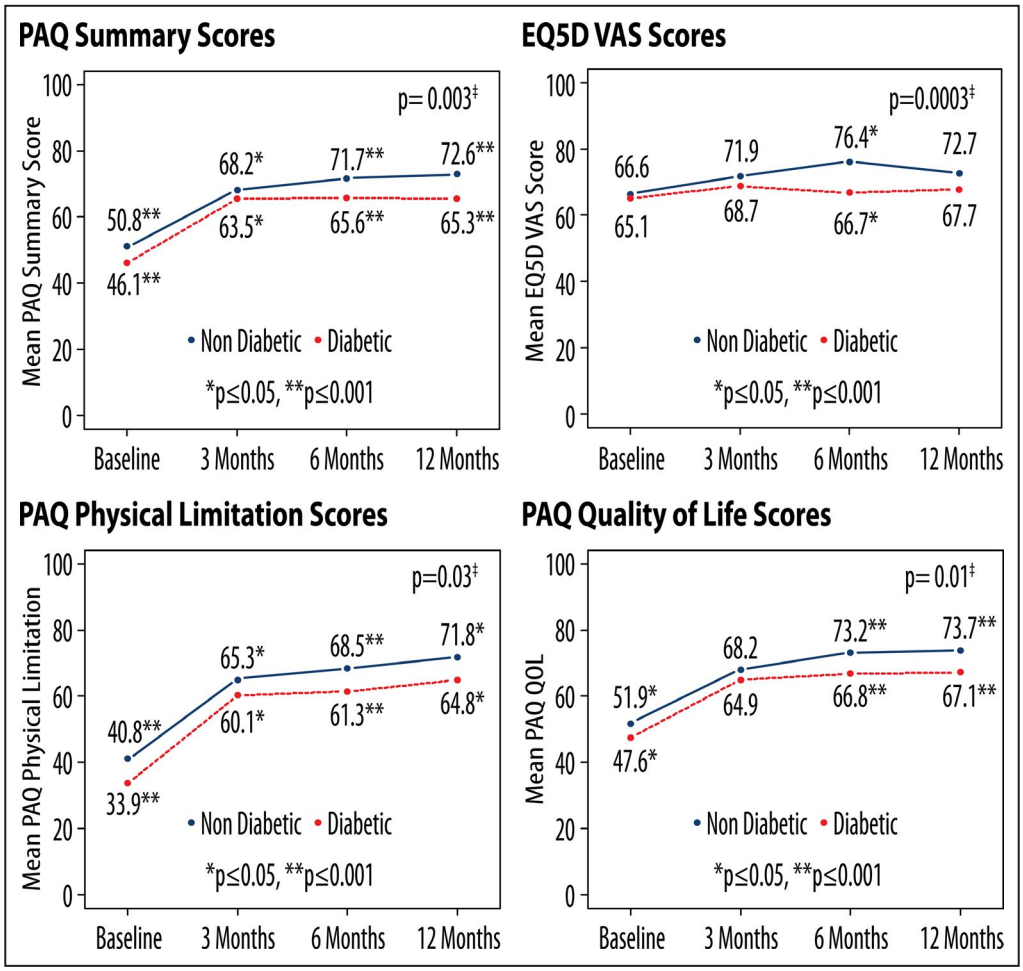

Figure 1. Unadjusted mean Peripheral Artery Questionnaire (PAQ) and Euro-Quality of Life 5 Dimension Questionnaire (EQ-5D) visual analog scale (VAS) scores over a year after presentation with symptomatic peripheral artery disease (PAD) in those with and without comorbid diabetes mellitus (DM).
P values represent those for interaction of DM status of the patient with time on health status and are adjusted for age, sex, race, and country. Nonsignificant *P* values for interaction of DM status with time suggests a statistically similar magnitude of improvement in health status over time of follow-up in patients with PAD with and without DM. All comparisons of PAQ and EQ-5D scores at each time point between patients with PAD with and without DM were significant ($P \leq 0.05$) except EQ-5D VAS scores at baseline and 3 months ($P=0.2$) and PAQ quality-of-life (QOL) score at 3 months ($P>0.05$). ‡*P* value for difference over time points using omnibus test.

assessments (n=1). Of the remaining 1204 patients, 398 (33.1%) had DM at the time of their baseline visit, a majority of whom had type 2 DM (n=375, 94.2%). The median HbA_{1c} of patients with DM was 6.9% (interquartile range, 6.1–7.9), 140 (35.4%) patients were on insulin therapy, 255 (64.6%) were on oral hypoglycemic therapy, and 76 (19.3%) were taking both oral hypoglycemics and insulin for treatment of their DM. A quarter of these patients (n=103, 25.9%) reported receiving DM education, 79 (19.8%) reported receiving diet counseling, and 24 (6%) reported receiving weight management counseling before baseline visit. Diabetic neuropathy was present in 40 patients (10.1%) and nephropathy was present in 10 patients (2.5%). Baseline characteristics of the study population are shown in Table 1. Patients with PAD and comorbid DM were more likely to be non-White and unemployed. They were also more likely to present with worsening symptoms of PAD and have bilateral and distal PAD disease, nonhealing ulcers, and prior peripheral interventions. The patients with DM also had more cardiovascular comorbidities but were less likely to be current smokers. They were more likely to have greater levels of depression and perceived stress but similar levels of anxiety and social support.

Health Status According to DM Status on Initial Presentation

On initial presentation, patients with DM reported significantly worse PAD-specific physical and social

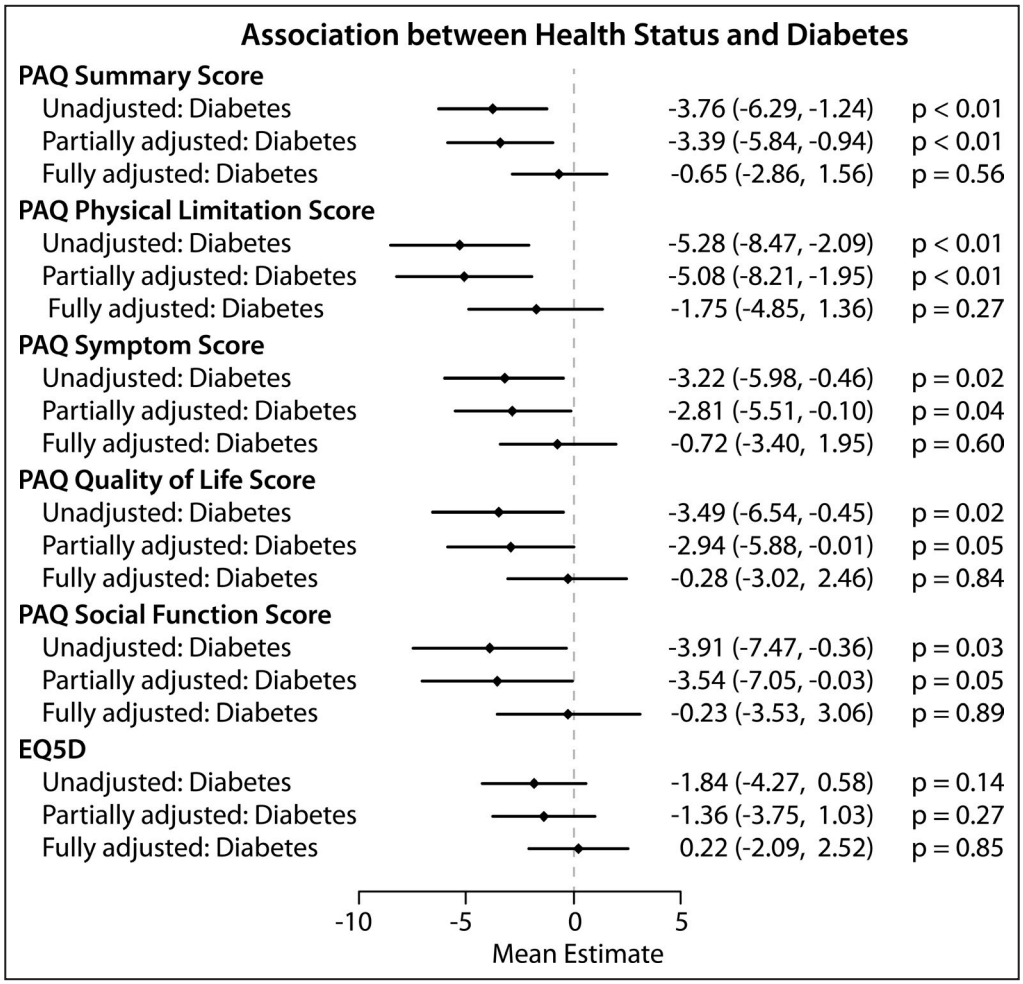

Figure 2. Mean difference in health status scores among patients with symptomatic peripheral artery disease (PAD) with and without diabetes mellitus (DM) on initial presentation to a vascular clinic. Presented as adjusted mean difference and 95% CI at 12 months in the Peripheral Artery Questionnaire (PAQ) summary and subdomain scores and Euro-Quality of Life 5 Dimension Questionnaire (EQ-5D) visual analog scale scores for PAD. Unadjusted model: only DM; partially adjusted model: adjusted for age, sex, race, country, and DM; fully adjusted model: adjusted for demographics, socioeconomic factors, PAD severity, comorbidities, and psychosocial factors.

limitations, poorer quality of life, and higher symptom burden but similar general health status compared with patients without DM (Table 1). Figure 1 and Figure S1 and Table S2 show mean unadjusted PAQ and EQ-5D scores at baseline in patients with and without DM. After adjusting for age, sex, race, and country, patients with DM had worse PAQ summary scores at baseline (partially adjusted mean difference, −3.39; 95% CI, −5.84 to −0.94 [*P*=0.006]). After additionally adjusting for socioeconomic, comorbidities, psychosocial characteristics, and PAD severity (fully adjusted), the effect of DM on PAQ summary score at baseline (adjusted mean difference, −0.65; 95% CI, −2.86 to 1.56 [*P*=0.56]) was no longer significant. A similar pattern was noted for PAQ physical limitation, symptom, social limitation and quality-of-life subscales (Figure 2). There was no difference in general health status at baseline, as measured by the EQ-5D VAS, between patients with and without DM, in unadjusted or adjusted models.

Health Status Outcomes on Follow-Up According to DM Status

In the unadjusted model, patients with DM had a significantly lower PAQ summary score over the follow-up period of 1 year (average over 3-, 6-, and 12-month time points) compared with those without DM, with a mean difference of −4.07 (95% CI, −6.59 to −1.54; *P*=0.002), which persisted after adjusting for difference in patient demographics (mean difference, −3.68; 95% CI, −6.19 to −1.18 [*P*=0.004]). Upon further adjustment for socioeconomic factors, PAD severity, comorbidities, psychosocial factors, quality-of-care measures, and treatment, the estimate for average PAD-specific health status

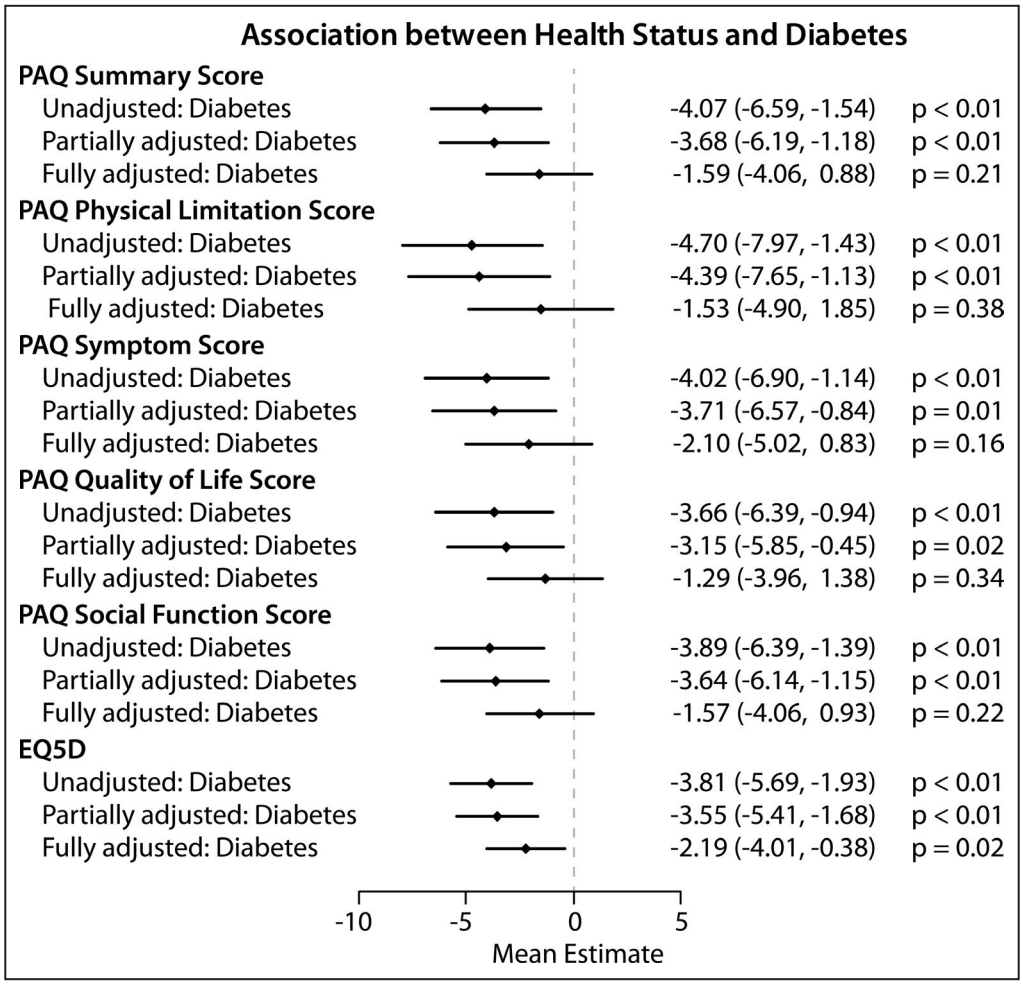

Figure 3. Mean difference in health status scores among patients with symptomatic peripheral artery disease (PAD) with and without diabetes mellitus (DM) at 3- to 12-month follow-up.
Presented as adjusted aggregated mean difference and 95% CI at 3, 6, and 12 months in the Peripheral Artery Questionnaire (PAQ) summary and subdomain scores and Euro-Quality of Life 5 Dimension Questionnaire (EQ-5D) visual analog scale scores for PAD unadjusted model: only DM; partially adjusted model: adjusted for age, sex, race, country, and DM; fully adjusted model: adjusted for demographics, socioeconomic factors, PAD severity, comorbidities, psychosocial factors, primary PAD treatment strategy (invasive vs medical), and PAD quality-of-care (statin, antiplatelet, supervised exercise) measures.

differences over a year as measured by PAQ summary score between patients with and without DM was marginal and nonsignificant, with a mean difference of –1.59 (95% CI, –4.06 to 0.88; *P*=0.21) (Figure 2). A similar pattern between patients with and without DM was noted for other PAQ subdomains on follow-up (Figure 3).

In contrast to baseline, general health status as measured by EQ-5D VAS was lower in patients with PAD who had DM compared with those without DM, on unadjusted, demographic-adjusted, and fully adjusted models (mean difference, –2.19; 95% CI, –4.01 to –0.38 [*P*=0.02]) over the follow-up (Figure 3).

Sensitivity Analyses

Sensitivity analyses exploring patient factors that most explain the differences between health status (PAQ summary score) among patients with and without DM at baseline (Table 2) showed a greater burden of psychosocial factors and comorbidities in patients with DM and that adjusting for this contributed most to the attenuation of the difference in PAQ summary scores between the 2 groups. For follow-up health status over 3 to 12 months (Table 3), greater burden of comorbidities in patients with DM partially attenuated the difference in the follow-up PAQ summary score.

A sensitivity analysis in a subset of patients with DM who had HbA_{1c} available at baseline (226 of 398, 56.8%) showed no difference in PAD-specific or general health status at baseline or follow-up among subgroups divided by glycemic control at baseline, except that patients with poor glycemic control ≥8% had worse PAQ symptom stability scores at baseline compared with those with HbA_{1c} <8% (Table S3).

Table 2. Mean Difference in Health Status Scores (PAQ Summary Score) at Initial Visit (Baseline) in Patients With and Without DM and Symptomatic PAD

Model	Covariate Category	Mean Estimate (95% CI)	*P* Value	Adjusted R^2
1	DM (unadjusted)	−3.76 (−6.29 to −1.24)	0.004	0.12
2	1+demographics	−3.38 (−5.83 to −0.93)	0.007	0.18
3	1, 2+socioeconomic factors	−3.25 (−5.67 to −0.82)	0.009	0.22
4	1, 2+PAD severity	−3.22 (−5.66 to −0.78)	0.01	0.21
5	1, 2+comorbidities	−2.24 (−4.81 to 0.33)	0.09	0.21
6	1, 2+psychosocial factors	−1.81 (−4.01 to 0.39)	0.11	0.44
7	1, 2, 3, 4, 5, 6 (fully adjusted)	−0.65 (−2.86 to 1.56)	0.56	0.43

Derived using hierarchical multivariable linear regression (baseline). Adjusted for covariates described in column 2. DM indicates diabetes mellitus; PAD, peripheral arterial disease; and PAQ, Peripheral Artery Questionnaire.

Effect of Treatment on Health Status Outcomes According to Patient DM Status

Receipt of PAD revascularization within the first 3 months postbaseline was associated with a significant improvement in PAQ summary score and EQ-5D for all patients (mean difference in PAQ summary score with 3-month revascularization, 5.75 [95% CI, 3.01–8.49] $P<0.0001$; mean difference in EQ-5D score, 3.03 [95% CI, 1.02–5.04] $P=0.003$), but there was no difference between patients with and without DM (interaction for DM×revascularization for PAQ summary score: $P=0.69$; EQ-5D VAS, $P=0.35$). Similar results were obtained for other PAD subdomains (Table 4).

DISCUSSION

In addition to improving survival, a key goal of PAD management is to improve symptoms, function, and quality of life of patients. In this large multicenter registry of patients presenting with symptoms related to PAD, presence of DM with PAD was associated with worse disease-specific health status at presentation and in the year thereafter, even after accounting for demographic differences. This difference could potentially be explained by greater psychosocial and comorbidity burden in patients with DM, as the differences in health status were attenuated and no longer significant after accounting for those. Patients with DM had similar improvements in health status over a year with revascularization procedures as compared with their counterparts without DM.

Coexisting DM in patients with PAD is associated with significant clinical and economic morbidity[10,24]; however, its association with health-related quality of life has not been previously delineated. Comorbid DM presents some unique challenges in PAD management, which could potentially affect health-related quality of life. Patients with DM often present later in the disease course with more advanced disease and atypical symptoms.[2,3,24] These patients often have diffuse, small-vessel, and distal disease with significant calcium burden in their atherosclerotic plaques making intervention technically difficult.[2] These patients have greater rates of restenosis postrevascularization compared with their counterparts without DM but with PAD.[2,25–28] DM is also associated with increased rates of postintervention complications, including infections, amputations, and major adverse limb events.[8,25,29] This is not only associated with a longer length of stay and higher hospital costs,[30] but can potentially have a significant effect on patient health status and quality of life.

Few studies have attempted to examine the effect of coexisting DM on quality of life in patients with PAD. In a small single-center analysis of 92 patients with PAD, those with DM had shorter walking distance and walking speed and poorer general health status and quality of life compared with patients with PAD who did not have DM.[13] A study by Amer et al[14] also reported poorer general health status in patients with

Table 3. Mean Difference in Health Status Scores (PAQ Summary Score) on 3 to 12 Months of Follow-Up in Patients With and Without DM and Symptomatic PAD

Model	Covariate Category	Mean Estimate (95% CI)	*P* Value
1	DM (unadjusted)	−4.07 (−6.59 to −1.54)	0.002
2	1+demographics	−3.68 (−6.19 to −1.18)	0.004
3	1, 2+socioeconomic factors	−3.60 (−6.06 to −1.14)	0.004
4	1, 2+PAD severity	−3.37 (−5.86 to −0.88)	0.008
5	1, 2+comorbidities	−2.59 (−5.22 to 0.05)	0.06
6	1, 2+psychosocial factors	−2.79 (−5.08 to −0.50)	0.02
7	1, 2+QOC measures	−3.84 (−6.35 to −1.33)	0.003
8	1, 2+invasive treatment	−3.34 (−5.89 to −0.80)	0.01
9	1, 2, 3, 4, 5, 6, 7, 8 (fully adjusted)	−1.59 (−4.06 to 0.88)	0.21

Derived using hierarchical multivariable repeated measures model. Adjusted for covariates described in column 2. DM indicates diabetes mellitus; PAD, peripheral arterial disease; PAQ, Peripheral Artery Questionnaire; and QOC, quality-of-care.

Table 4. Effect of Invasive PAD Treatment Within First 3 Months After Baseline on Follow-Up PAQ Subdomain Scores and Differential Effect of Treatment on Follow-Up Health Status Based on Patient DM Status

Health Status Measure	Adjusted Mean Difference in 3–12 mo PAQ Scores With Invasive PAD Treatment Mean Difference (95% CI)	*P* Value	Interaction DM×Invasive Treatment on 3–12 mo PAQ
PAQ: summary score	5.75 (3.01–8.49)	<0.0001	0.69
PAQ: physical limitation	8.52 (4.79–12.24)	<0.0001	0.89
PAQ: symptoms	6.70 (3.46–9.94)	<0.0001	0.97
PAQ: social limitation	4.04 (1.29–6.80)	0.004	0.26
PAQ: quality of life	4.88 (1.93–7.84)	0.001	0.75
PAQ: EQ-5D VAS	3.03 (1.02–5.04)	0.003	0.35

Derived from hierarchical, multivariable, and repeated measures models, adjusted for demographics, socioeconomic factors, peripheral artery disease (PAD) severity, comorbidities, psychosocial factors, primary PAD treatment strategy (invasive vs medical), and PAD quality-of-care (statin, antiplatelet, supervised exercise) measures. DM indicates diabetes mellitus; EQ-5D; Euro-Quality of Life 5 Dimension Questionnaire; PAQ, Peripheral Artery Questionnaire; and VAS, visual analog scale.

DM and PAD compared with patients with DM alone. In 920 patients with intermittent claudication, over half of whom had DM, Lozano et al[15] reported slightly lower Walking Impairment Questionnaire scores and EQ-5D scores in those with DM. All of these studies, however, were cross-sectional in nature, had few patients with symptomatic PAD and DM,[13,14] and did not account for multiple coexisting comorbidities, socioeconomic and psychosocial factors, and PAD severity.

Our study is the first to report longitudinal health status outcomes over the course of a year in patients with PAD who did and did not have DM in a large multicenter cohort. Patients with DM had worse PAD-specific health status at baseline and at 12 months of follow-up. Our study suggests potential mechanisms that could explain this difference in health-related quality of life. Sensitivity analyses suggest that greater prevalence of psychosocial factors such as depression and stress and other cardiac and noncardiac comorbidities in patients with PAD and DM compared with those without DM is a possible mechanism explaining the worse PAD-specific health status noted in these patients. The health status differences between patients with and without DM were not significant after adjustment for these characteristics. Recognizing and adequately controlling coexisting comorbidities, especially psychosocial factors such as depression and stress, should be tested as potential interventions to improve the quality of life of patients with PAD and DM. Importantly, while initial PAD revascularization by itself was associated with significant improvements in PAD-specific and general health status measures, there was no evidence of a differential effect of treatment with PAD interventions on the health status after a year of follow-up in patients with DM. This suggests that both patients with and without DM should be offered similar treatment options for their PAD, including revascularization, as both groups experience similar gains in health status with treatment over time. DM status should not be a barrier to adopting an aggressive management approach in patients with PAD. Whether this pattern of improvement in health status is sustained longer than a year should be studied. A noteworthy finding of our study was that while patients with PAD with and without DM did not have any difference in generic health status at the time of their initial visit, patients with DM had significantly worse generic health status as measured by EQ-5D VAS at 12 months compared with those without DM, even after accounting for many other patient and treatment characteristics that could affect the association of DM with patients' health status. This could be reflective of poor clinical outcomes following procedural treatment such as increased complications or readmissions. This could not be evaluated in the present study, but needs to be explored further in the future.

Our study results should be interpreted in the context of the following potential limitations. First, DM status was ascertained by medical record review and patient self-report and not confirmed with laboratory testing. Second, given the observational nature of the study, there might be residual or unmeasured confounding in our results, even though we adjusted extensively for sociodemographic, clinical, psychosocial, and treatment factors. Third, we also could not assess whether health status outcomes differed with duration of DM. Since a majority of patients in our study had type 2 DM, whether patients with type 1 DM who have much more long-standing DM and are on long-term insulin also have similar health status outcomes is unknown. As follow-up was limited to 1 year after the initial visit to a PAD provider, we could not determine the long-term effect of DM status on PAD-specific health status outcomes beyond a year. We were not able to assess the effect of glycemic control postbaseline on follow-up PAD health status outcomes for all patients. However, sensitivity analysis showed no difference in health status based on glycemic control in a subset of

patients with DM who had HbA_{1c} available at baseline. Finally, the health status perspectives of patients with PAD and comorbid DM were restricted to those with compressible ankle-brachial index and those without critical limb ischemia, and our findings are not to be extended to patients with more severe disease.

CONCLUSIONS

We found that patients with DM and PAD have worse health status compared with those without DM when they present with symptoms of PAD and throughout a year of follow-up thereafter. This may be explained by the differences in their psychosocial characteristics such as greater prevalence of psychosocial and cardiovascular comorbidities in patients with DM and PAD. However, they experience similar improvement in health status with revascularization as their counterparts without DM. Our results can help inform patients with PAD and DM and their providers regarding how their symptoms, function, and health-related quality of life would be affected by their DM, how they can expect it to change over time, and how it is affected by PAD revascularization.

ARTICLE INFORMATION

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Affiliations

From the University of Missouri-Kansas City, Kansas City, MO (K.K.P., H.A., P.A.P.-O., J.A.S., K.G.S.); Saint Luke's Mid America Heart Institute, Kansas City, MO (K.K.P., K.G., P.A.P.-O., J.A.S., K.G.S.); Truman Medical Centers, Kansas City, MO (H.A.); Yale School of Medicine, New Haven, CT (C.M.-H.); University Hospital Cleveland Medical Center and Case Western Reserve University School of Medicine, Cleveland, OH (M.H.S.); and Dartmouth-Hitchcock Heart and Vascular Center, Lebanon, NH (M.A.C.).

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Drs Patel and Smolderen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Patel and Smolderen; acquisition, analysis, or interpretation of data: all authors; drafting of the initial article: Patel; critical revision of the article for important intellectual content: all authors; statistical analysis: Gosch; administrative, technical, or material support: Smolderen; and study supervision: Smolderen.

Disclosures

Dr Spertus owns copyright for the Peripheral Artery Questionnaire. He serves as a consultant to United Healthcare, Bayer, Janssen, AstraZeneca, and Novartis. He is the principal investigator of an analytic center for the American College of Cardiology. He has an equity interest in Health Outcomes Sciences. Dr Mena-Hurtado serves as a consultant for Abbott, Cardinal Health, Boston Sci, Cook, Medtronic, and Bard BD. Dr Shishehbor is a consultant and serves on the global advisory board of Medtronic, Abbott Vascular, Terumo, Boston Scientific, and Philips. Dr Creager is supported by the American Heart Association Strategically Focused Research Network in Vascular Disease under award number 18SFRN339008. Dr Smolderen receives grant support from Boston Scientific, Abbott Vascular, and Terumo.

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Supplementary Material

Data S1
Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Data S1.

Appendix: List of participating investigators in the PORTRAIT study

Key Personnel

Name	Role	Institution/Organization
Dave Safley, MD	site PI	Saint Luke's Hospital
Mehdi Shishehbor, MD	site PI	University Hospitals of Cleveland
Mansoor Qureshi, MD	site PI	St Joseph Mercy
Peter Soukas, MD	site PI	Miriam Hospital
Dawn Abbott, MD	site PI	Rhode Island Hospital
Carlos Mena-Hurtado, MD	site PI	Yale New Haven Hospital
Ed Touhy, MD	site PI	Bridgeport Hospital
Christopher White, MD	site PI	Ochsner Health System
Manesh Patel, MD	site PI	Duke University Health System
Glenn Talboy, MD	site PI	Truman Medical Center
Kim Smolderen, PhD	PI	Saint Luke's Hospital/UMKC
John Spertus, MD	co-investigator	Saint Luke's Hospital/UMKC
Will Hiatt, MD	OSMB	University of Colorado School of Medicine
Mark Creager, MD	OSMB	Dartmouth-Hitchcock Heart and Vascular Center
Greg Moneta, MD	OSMB	Oregon Health and Science University
Herb Aronow, MD	Physician Expert Panel	Rhode Island Hospital
Tom Tsai, MD	Physician Expert Panel	University of Colorado Hospital

Table S1. Covariates including for adjustment for models for baseline health status and follow-up health status outcomes between 3-12 months for patients with peripheral artery disease (PAD) and comorbid diabetes compared to non-diabetics.

Model	Covariate category	Covariates included in the model
1	Diabetes status	Diabetes status
2	Demographics	Age, Sex, Race, Country
3	Socio-Economic Factors	Education, Current work for pay, Insurance, Avoid care due to cost
4	PAD Disease Severity	Ankle Brachial Index, Proximal vs. Distal location, Unilateral vs. bilateral disease, Exacerbation vs. New diagnosis, Duration of claudication pain, History of ulcer, amputation or peripheral intervention
5	Comorbidities	Hypertension, Dyslipidemia, Cerebrovascular Accident, Chronic heart failure, Chronic Kidney Disease, Chronic Lung Disease, musculoskeletal problem, Sleep apnea, Obesity/Body mass index
6	Psychosocial Factors	ENRICHD Social Support Inventory score, Perceived Stress Scale score, Generalized Anxiety Disorder-2 score, Patient Health Questionnaire-2 score
7)	PAD Quality of Care Measures	Statin, Antiplatelets, Supervised Exercise Therapy

Table S2. Unadjusted mean health status scores in patients with symptomatic peripheral arterial disease based on diabetes status.

Health status measure	Diabetes N=398	No Diabetes N=806	p-value
PAQ: Physical limitation (Baseline)	33.9 ± 25.7	40.8 ± 26.3	< 0.001
PAQ: Physical limitation (3 months)	60.2 ± 30.8	65.3 ± 30.0	0.02
PAQ: Physical limitation (6 months)	61.4 ± 30.9	68.4 ± 30.4	0.001
PAQ: Physical limitation (12 months)	64.9 ± 31.8	71.8 ± 29.7	0.002
PAQ: Symptom stability (Baseline)	42.6 ± 20.0	43.8 ± 21.6	0.32
PAQ: Symptom stability (3 months)	56.9 ± 24.8	60.9 ± 26.7	0.01
PAQ: Symptom stability (6 months)	53.6 ± 23.2	55.8 ± 23.6	0.14
PAQ: Symptom stability (12 months)	47.5 ± 21.9	51.4 ± 22.5	0.01
PAQ: Symptoms (Baseline)	41.8 ± 23.9	45.0 ± 22.2	0.02
PAQ: Symptoms (3 months)	54.3 ± 29.3	59.5 ± 28.1	0.003
PAQ: Symptoms (6 months)	58.2 ± 29.8	63.0 ± 28.7	0.01
PAQ: Symptoms (12 months)	57.1 ± 30.8	64.4 ± 29.3	< 0.001
PAQ: Treatment satisfaction (Baseline)	81.7 ± 21.4	83.7 ± 20.8	0.13
PAQ: Treatment satisfaction (3 months)	79.1 ± 26.4	82.8 ± 22.8	0.01
PAQ: Treatment satisfaction (6 months)	80.0 ± 26.1	83.2 ± 23.0	0.04
PAQ: Treatment satisfaction (12 months)	79.7 ± 27.4	82.5 ± 24.1	0.09
PAQ: Quality of life (Baseline)	47.6 ± 26.3	52.0 ± 25.6	0.005

PAQ: Quality of life (3 months)	65.0 ± 28.2	68.1 ± 27.3	0.07
PAQ: Quality of life (6 months)	66.9 ± 28.1	73.2 ± 26.3	< 0.001
PAQ: Quality of life (12 months)	67.2 ± 28.8	73.8 ± 26.8	< 0.001
PAQ: Social limitation (Baseline)	59.7 ± 30.7	65.2 ± 29.6	0.003
PAQ: Social limitation (3 months)	78.8 ± 26.6	82.0 ± 24.7	0.05
PAQ: Social limitation (6 months)	80.0 ± 25.0	85.6 ± 22.4	< 0.001
PAQ: Social limitation (12 months)	78.6 ± 27.8	85.0 ± 22.7	< 0.001
PAQ: Summary (Baseline)	46.1 ± 22.3	50.8 ± 21.3	< 0.001
PAQ: Summary (3 months)	63.6 ± 25.8	68.2 ± 24.0	0.002
PAQ: Summary (6 months)	65.7 ± 25.2	71.7 ± 23.8	< 0.001
PAQ: Summary (12 months)	65.4 ± 26.7	72.6 ± 24.4	< 0.001
EQ5D Visual Analog Scale (Baseline)	65.1 ± 19.4	66.6 ± 19.3	0.21
EQ5D Visual Analog Scale (3 months)	68.8 ± 29.2	71.8 ± 38.5	0.17
EQ5D Visual Analog Scale (6 months)	66.8 ± 18.9	76.3 ± 64.0	0.006
EQ5D Visual Analog Scale (12 months)	67.7 ± 18.3	72.8 ± 35.1	0.01
PAQ: Peripheral Artery Questionnaire, EQ5D: Euro-Quality of Life 5 Dimensions			

Table S3. Unadjusted mean health status scores in patients with diabetes and symptomatic peripheral arterial disease based on glycemic control at baseline (N=226/398; 56.8%).

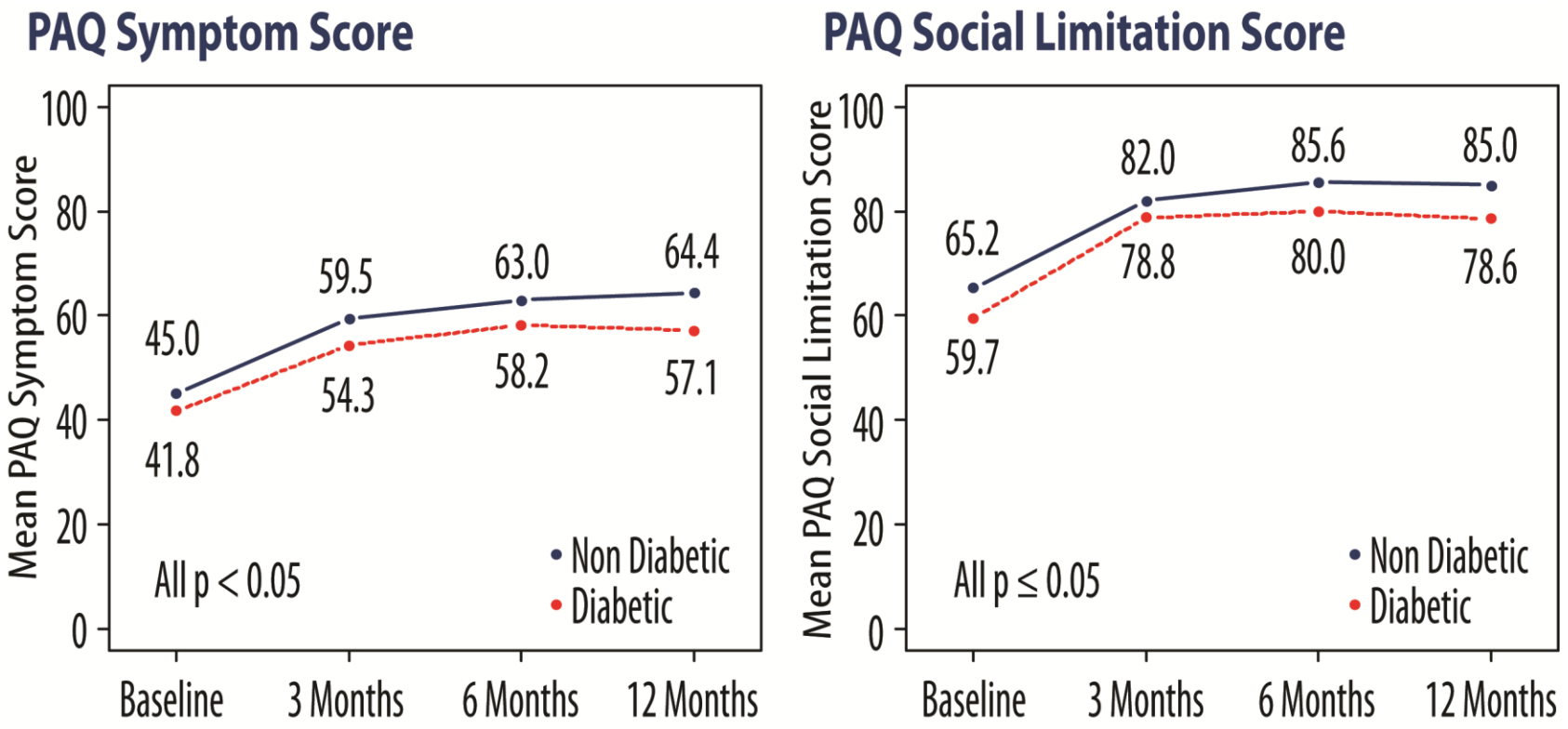
	HbA1c at/prior to baseline					
	< 6% n = 46	**6 – 6.9% n = 78**	**7 – 7.9% n = 47**	**8 – 8.9% n = 25**	**≥9% n = 30**	**P-Value**
PAQ: Physical limitation (Baseline)	38.6 ± 29.2	39.5 ± 27.3	34.6 ± 22.9	31.5 ± 29.1	31.5 ± 25.8	0.56
PAQ: Physical limitation (3month)	62.1 ± 28.6	65.1 ± 27.1	61.8 ± 32.1	53.3 ± 36.4	54.4 ± 34.0	0.50
PAQ: Physical limitation (6month)	67.8 ± 29.2	62.4 ± 32.7	63.5 ± 28.5	63.9 ± 31.3	56.9 ± 36.0	0.82
PAQ: Physical limitation (12month)	69.8 ± 31.6	68.8 ± 29.7	66.3 ± 34.6	65.4 ± 31.5	67.0 ± 34.4	0.99
PAQ: Symptom stability (Baseline)	47.8 ± 15.7	45.8 ± 21.5	42.6 ± 20.8	35.0 ± 21.7	37.5 ± 21.5	0.04
PAQ: Symptom stability (3month)	58.5 ± 26.9	59.1 ± 22.9	58.5 ± 24.7	64.8 ± 26.3	49.1 ± 22.4	0.25
PAQ: Symptom stability (6month)	46.3 ± 18.2	52.9 ± 22.1	57.1 ± 28.2	58.3 ± 21.7	52.1 ± 25.4	0.20
PAQ: Symptom stability (12month)	41.1 ± 23.3	50.7 ± 18.3	45.6 ± 24.6	47.8 ± 19.8	47.7 ± 24.3	0.26
PAQ: Symptoms (Baseline)	44.7 ± 22.5	42.1 ± 23.1	47.0 ± 26.2	41.1 ± 28.1	38.2 ± 23.9	0.58
PAQ: Symptoms (3month)	56.8 ± 29.5	55.1 ± 27.6	54.3 ± 31.6	57.2 ± 33.0	54.8 ± 24.0	0.99
PAQ: Symptoms (6month)	57.2 ± 29.0	55.8 ± 28.9	63.4 ± 31.8	65.2 ± 27.4	50.5 ± 33.2	0.32
PAQ: Symptoms (12month)	57.0 ± 30.8	56.8 ± 27.3	62.0 ± 32.6	60.3 ± 29.5	52.9 ± 35.1	0.80
PAQ: Treatment satisfaction (Baseline)	82.4 ± 23.4	84.2 ± 19.4	80.7 ± 19.6	78.7 ± 26.6	85.0 ± 24.1	0.75
PAQ: Treatment satisfaction (3month)	82.1 ± 25.4	80.4 ± 25.3	80.3 ± 24.1	81.4 ± 22.1	74.1 ± 28.1	0.75
PAQ: Treatment satisfaction (6month)	77.7 ± 30.3	80.0 ± 25.4	86.1 ± 21.9	81.9 ± 20.7	79.9 ± 27.2	0.62
PAQ: Treatment satisfaction (12month)	81.5 ± 27.5	79.2 ± 28.3	82.6 ± 29.7	85.5 ± 13.8	71.0 ± 32.6	0.46

	HbA1c at/prior to baseline					
	< 6% n = 46	**6 – 6.9% n = 78**	**7 – 7.9% n = 47**	**8 – 8.9% n = 25**	**≥9% n = 30**	**P-Value**
PAQ: Quality of life (Baseline)	48.2 ± 28.2	50.9 ± 25.3	54.1 ± 27.5	46.7 ± 28.6	41.4 ± 25.7	0.32
PAQ: Quality of life (3month)	70.8 ± 26.8	66.8 ± 27.6	65.6 ± 27.2	69.7 ± 28.0	54.9 ± 29.1	0.19
PAQ: Quality of life (6month)	67.9 ± 28.2	68.0 ± 28.1	68.8 ± 28.9	68.1 ± 27.1	58.0 ± 31.7	0.61
PAQ: Quality of life (12month)	67.2 ± 31.2	68.8 ± 26.1	67.4 ± 31.6	68.8 ± 26.9	59.8 ± 33.8	0.80
PAQ: Social limitation (Baseline)	62.1 ± 37.0	65.3 ± 25.9	62.0 ± 30.9	62.7 ± 33.2	52.2 ± 28.2	0.42
PAQ: Social limitation (3month)	85.2 ± 16.8	82.1 ± 22.7	76.6 ± 29.3	74.0 ± 31.8	75.5 ± 27.5	0.28
PAQ: Social limitation (6month)	79.7 ± 20.7	82.7 ± 22.5	80.5 ± 23.5	81.4 ± 22.8	73.0 ± 32.9	0.59
PAQ: Social limitation (12month)	78.3 ± 30.9	84.4 ± 22.1	79.4 ± 30.3	79.2 ± 22.2	68.9 ± 36.3	0.33
PAQ: Summary (Baseline)	48.5 ± 23.4	49.5 ± 21.1	49.8 ± 23.3	46.2 ± 25.4	41.1 ± 22.9	0.46
PAQ: Summary (3month)	67.4 ± 23.7	66.7 ± 22.9	63.1 ± 26.1	64.4 ± 29.8	58.0 ± 25.0	0.53
PAQ: Summary (6month)	65.9 ± 26.0	66.4 ± 23.6	68.1 ± 26.7	68.6 ± 23.4	58.4 ± 30.4	0.61
PAQ: Summary (12month)	65.6 ± 27.9	67.9 ± 23.1	67.6 ± 30.1	66.5 ± 23.3	59.3 ± 31.7	0.76
EQ5D: Visual Analog Scale (Baseline)	61.4 ± 20.2	65.8 ± 18.2	65.1 ± 21.5	63.5 ± 21.8	60.5 ± 22.5	0.68
EQ5D: Visual Analog Scale (3month)	66.7 ± 17.3	69.6 ± 18.0	77.3 ± 68.2	65.8 ± 23.2	72.7 ± 13.5	0.61
EQ5D: Visual Analog Scale (6month)	67.4 ± 15.2	70.8 ± 16.9	66.0 ± 19.7	65.2 ± 16.6	62.7 ± 22.1	0.33
EQ5D: Visual Analog Scale (12month)	67.5 ± 15.9	69.0 ± 18.0	70.3 ± 17.2	62.2 ± 15.9	64.4 ± 23.7	0.38
PHQ-8 Depression Score (Baseline)	5.0 ± 5.3	4.2 ± 4.1	4.7 ± 5.0	6.6 ± 6.7	6.3 ± 5.4	0.16
PHQ-8 Depression Score (3month)	2.8 ± 4.3	3.7 ± 4.3	3.6 ± 4.1	4.4 ± 5.1	4.9 ± 4.4	0.40

	HbA1c at/prior to baseline					
	< 6% n = 46	**6 – 6.9% n = 78**	**7 – 7.9% n = 47**	**8 – 8.9% n = 25**	**≥9% n = 30**	**P-Value**
PHQ-8 Depression Score (6month)	3.3 ± 4.2	3.8 ± 4.2	3.3 ± 3.4	3.8 ± 3.9	5.0 ± 6.4	0.55
PHQ-8 Depression Score (12month)	3.1 ± 4.3	3.1 ± 3.6	4.0 ± 4.4	3.8 ± 4.0	3.5 ± 4.4	0.79

PAQ: Peripheral Artery Questionnaire, EQ5D: Euro-Quality of Life 5 Dimensions, PHQ: Patient Health Questionnaire.
Continuous variables compared using one-way analysis of variance. Categorical variables compared using chi-square or Fisher's exact test.

Figure S1. Unadjusted mean PAQ symptom and PAQ social limitation over a year after presentation with symptomatic peripheral artery disease in those with and without comorbid diabetes.



P-values in the figures represent those for interaction of diabetes status of the patient with time on health status and are adjusted for age, sex, race and country. Non-significant p-values for interaction of diabetes status with time suggests statistically similar magnitude of improvement in health status over time of follow-up in PAD patients with and without diabetes. All comparisons of PAQ scores at each time point between PAD patients with and without diabetes significant ($p \leq 0.05$). PAQ= Peripheral Artery Questionnaire, EQ5D-VAS- EuroQOL-5 Dimension Visual Analaog Scale.