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Are Sonographic Characteristics Associated With Progression to Surgery in Men With Peyronie's Disease?

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Abstract

Purpose—Traditionally, diagnosis and treatment plans for Peyronie's disease have been based on history and physical examination. Penile ultrasound provides rapid, anatomical information to establish disease severity, and to monitor progression and response to medical therapy. We determined the relationship between ultrasound characteristics and progression to surgical intervention in men with Peyronie's disease.

Materials and Methods—We conducted a retrospective cohort study of 518 patients with Peyronie's disease. Patients completed a Peyronie's disease specific questionnaire detailing medical history, health related behaviors and Peyronie's disease characteristics, and underwent sonographic evaluation of the penis. Measurements of subtunical calcifications, septal fibrosis, tunical thickening (tunica thickness greater than 2 mm) and intracavernous fibrosis were made. Progression to surgery was determined from the medical record.

Results—In this cohort (mean patient age 53.8 years, range 20 to 78) 31% of patients had calcifications, 50% had tunical thickening, 20% had septal fibrosis and 15% had intracavernous fibrosis. Overall 25% of the cohort progressed to surgical intervention after an average followup of 1.25 years (range 0 to 7.6). Patients who underwent surgery were more likely to have subtunical calcifications present at the first clinic visit (OR 1.75, 95% CI 1.16–2.62). No other sonographic characteristics were associated with progression to surgery. After adjustment for age, marital status, degree of curvature, additional penile deformity, difficulty with penetration, ability to have intercourse and prior treatment for Peyronie's disease, calcifications were strongly associated with progression to surgery (OR 2.75, 95% CI 1.25–3.45).

Conclusions—In a large cohort of patients with Peyronie's disease the presence of sonographically detected sub-tunical calcifications during the initial office evaluation was independently associated with subsequent surgical intervention.

Keywords

calcification; physiologic; fibrosis; prevalence; ultrasonography; epidemiology

Peyronie's disease is an acquired condition arising from abnormalities in the connective tissues of the penis. A common disease affecting 3% to 9% of men,¹ PD results in a spectrum of penile deformities that often make intercourse painful or impossible.²

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Traditionally, diagnosis and treatment plans for PD have been based solely on patient history and physical examination of the penis.² Penile ultrasound has emerged as a valuable extension of the physical examination. Sonography permits noninvasive, objective and detailed study of penile anatomy that may help establish disease severity, monitor disease progression and track response to medical therapy.^{3,4}

Recent studies have described the clinical characteristics of men with PD and the relation to penile ultrasound findings.^{5,6} To our knowledge there have been no studies on the prognostic implications of ultrasound findings in PD. A clearer understanding of sonographic predictors of disease progression and/or eventual need for surgical intervention will enhance the usefulness of ultrasound in evaluating PD. In particular, ultrasound findings would be significantly more valuable if they could predict who would benefit from observation, medical therapy or immediate surgical intervention. We investigated the relationship between penile sonographic characteristics and the progression to surgical intervention in men presenting for evaluation of PD, hypothesizing that specific penile ultrasound findings would be associated with subsequent progression to surgical intervention.

METHODS

Study Design and Cohort Description

Before initiating the study institutional review board approval was obtained. This retrospective cohort study enrolled patients with PD from a single clinical practice. Patients completed a nonvalidated PD specific questionnaire gathering medical history, health related behaviors and details of PD. All men underwent sonographic evaluation of the penis at the first clinical evaluation. Exclusion criteria were congenital penile curvature and previous PD surgery.

Outcome Variables

The main outcome variable was surgical treatment for PD. Surgical intervention for PD was offered to men with stable deformity who desired correction after understanding the risks, benefits and alternatives of surgery. Each study participant chart with corresponding clinic note and operative report was examined to determine whether surgery was performed (yes/no).

Exposure Variables

Medical and demographic—Patients completed an intake clinic form that included age (categorized to younger than 40 years, 40 to 49, 50 to 59, 60 to 69, 70+), coronary artery disease (yes/no), marital status (married yes/no), diabetes (yes/no), hypertension (yes/no), current tobacco use (yes/ no), hypercholesterolemia (yes/no) and vascular disease (yes/no). Current and past treatment for PD was obtained from the medical history and PD questionnaire.

PD specific characteristics—Disease duration was defined as the date of symptom onset to the date of presentation. The PD questionnaire gathered self-reported answers to the questions do you have penile curvature? (yes/no), can you estimate the degree of curvature?, previous penile trauma or injury (yes/no), disease stability (yes/no), penile deformity (eg hourglass, yes/no), loss of penile length (yes/ no), current penile pain (yes/no), difficulty with penetration (yes/no), sexual function (yes/no, single question, “Able to have intercourse?”), and able to maintain erections (single question, yes/no). Curvature was categorized to 4 levels of less than 30 degrees, 30 to 59 degrees, 60 or more degrees and unknown. To minimize the effect of missing data curvature was included as a 4-level

categorical variable. The group of men with missing curvature data was not significantly different from men with curvature less than 30 degrees (OR 1.2, 95% CI 0.6–2.6).

Penile ultrasound—Penile imaging was performed with gray-scale ultrasonography using a 7.5 to 12 MHz small parts linear array probe by a single senior clinician or by a clinical fellow in sexual medicine with subsequent review by a senior clinician. Measurements of septal fibrosis, penile calcifications, tunical thickening (tunica thickness greater than 2 mm⁷) and intracavernous fibrosis were made. The categories were not mutually exclusive and some patients had multiple sonographic characteristics. Penile calcifications were measured by determining the length and width in the longitudinal and transverse axes. If more than 1 calcification was present the calcified area was summed to calculate an aggregate index of calcification burden. The presence or absence of ultrasound findings and measurement of the size of calcifications were obtained from the medical record by a urologist who reviewed ultrasound images and ultrasound reports.

Statistical Analysis

Descriptive statistics were used to characterize the study population. For all categorical variables a chi-square test was applied. ANOVA was used to assess differences among continuous variables. Odds ratios with 95% CI were reported to estimate the association between penile ultrasound characteristics and progression to surgical intervention. Multivariate logistic regression models were developed to explore this relationship. Predictor variables (ie age, marital status, duration of PD symptoms, degree of curvature, penile deformity, penetration difficulty, loss of penile length, ability to have intercourse and treatment for PD before enrollment in study) were selected a priori based on our clinical experience and understanding of the literature. In a backward stepwise approach other variables (ie penile injury, libido, medical comorbidities and demographic characteristics) were considered but were excluded for p values greater than 0.20. Statistical significance was set at p < 0.05 and all tests were 2-sided. STATA® 10 was used for all analysis.

RESULTS

A total of 518 patients were included in the study. Patient age ranged from 20 to 78 years (mean 53.8). Men undergoing surgery (130) were older than those who did not (56.7 vs 52.8 years, p = 0.02). The prevalence of comorbid conditions was similar between the surgery and nonsurgery groups (table 1).

The PD specific characteristics and ultrasound findings of the cohort are listed in table 1. Overall 25% of the cohort progressed to surgical intervention after an average followup of 1.25 years (range 0 to 7.6). Of 518 patients 196 (38%) underwent prior treatment. Some patients reported using more than 1 treatment. Before surgery patients used oral vitamin E (29%), potaba (7%), colchicine (7%), verapamil injection (6%), tamoxifen (1%), steroid injection (1%), anti-inflammatory medicines (1%) and interferon injection (1%). Of patients undergoing surgery the most common technique performed was penile plication (117, 81%) followed by plaque incision with graft placement (17, 12%) and penile prosthesis placement (10, 7%).

Bivariate analysis of the relationship of ultrasound and PD specific characteristics, and progression to surgery were examined (table 2). Men with sub-tunical calcifications at baseline had a 75% increase in the odds of progressing to surgical intervention (OR 1.75, 95% CI 1.16–2.62). Septal fibrosis (OR 0.84, 95% CI 0.51–1.41), intracavernous fibrosis (OR 0.75, 95% CI 0.42–1.36, p = 0.345) and tunical thickening (OR 1.25, 95% CI 0.84–1.87) were not statistically associated with the progression to surgery. Compared to men with curvature less than 30 degrees, men with curvature 30 to 59 degrees or 60+ degrees

were 2.3 (OR 2.32, 95% CI 1.11–4.84) and 5.9 (OR 5.93, 95% CI 2.79–12.58) times more likely to have surgery, respectively. Men unable to have intercourse (OR 1.77, 95% CI 1.1–2.82) or who had difficulty penetrating (OR 1.89, 95% CI 1.27–2.83) were also more likely to have surgical intervention.

The multivariate analysis revealed that the presence of sub-tunical calcifications during initial ultrasound was significantly associated with subsequent progression to surgery (OR 1.91, 1.24–23.95) in the unadjusted model and remained similar after adjustment for age (table 3). However, after adjustment for PD specific characteristics, baseline calcifications were associated with a 2.75-fold increase in the odds of progression to surgery.

DISCUSSION

High-resolution gray-scale ultrasound of the penis (with or without color and pulse wave Doppler) has emerged as an important extension of the penile physical examination for clinical and research purposes.^{3,4} The present study uses a large database of patients with PD, all of whom had an ultrasound on initial visit. Men with calcification at baseline were significantly more likely to progress to surgery relative to men without calcification. This relationship was maintained even after adjustment for other demographics, PD specific characteristics and observation time. No other sonographic findings were associated with progression to surgical repair of penile deformity.

The pathophysiology and natural history of PD remain poorly understood despite recent evidence suggesting that it is much more common than previously supposed.¹ Diverse causative agents of PD have been suggested including infections, autoimmune disease, beta-blockers, vitamin deficiency and genetic predisposition.⁸ The most commonly accepted theory of the etiology of PD is trauma. Devine et al postulated that acute and/or chronic trauma during intercourse may result in delamination of the tunica albuginea and hemorrhage.⁹ Subsequent fibrosis may lead to decreased elasticity, less effective wound healing and excessive collagen deposition.¹⁰ Over time, fibrotic lesions rich in collagen may develop into the calcifications typical of PD.¹¹ This theory underlies the prevailing opinion that calcification is in most cases an indicator of chronic phase PD.

Ultrasound of the penis has become increasingly popular because it provides detailed anatomical and vascular information that can be used to evaluate erectile dysfunction, penile cancer, priapism and PD.⁷ Ultrasound for PD has been most commonly used to localize and measure plaques, exclude patients with calcified plaques from clinical trials and assess vascular status when contemplating penile reconstructive surgeries.¹² Ultrasound is in many respects a superior imaging modality relative to magnetic resonance imaging and computerized tomography. Advantages include low cost, ease of access, minimization of exposure to radiation and contrast agents, and the capability to perform real-time examinations such as power Doppler to ascertain blood flow.^{3,13} Further refinements of ultrasound technology such as real-time compound spatial imaging will enhance image quality in penile ultrasound.¹⁴

There have been few published studies on sonographic characteristics of patients with PD over time.⁶ In a study of 78 men with PD Prando reported that up to 60% had densely echogenic and possibly calcified tunical lesions which were visualized on ultrasound.^{4,15} The clinical relevance of this finding was not reported in that study. Bekos et al reported on 95 men with PD who had penile ultrasounds at presentation and 1 year after presentation.⁶ Patients were classified into 1 of 3 groups as those with a solitary hyperechoic lesion without acoustic shadow, those with multiple moderately hyperechoic calcified lesions with acoustic shadows, and those with dense, calcified hyperechoic plaques with acoustic

shadow. It was concluded that the 3 groups represented different phases of PD (acute, intermediate and chronic disease, respectively). In the study men with progressively greater burdens of calcification had an increased risk of being unable to have intercourse. At the 1-year followup it was determined that clinical improvement (defined as decrease in curvature and plaque size) was most common in the group without baseline calcifications. The authors contend that surgery should be offered earlier to men who present with dense calcium deposits as this represents mature disease. These findings are in line with the results of our study, and suggest that patients with prominent calcifications may have mature disease that is refractory to medical management and requires surgery for correction of deformity.

Several limitations of this study are worth noting. Ultrasound is a user dependent modality and the ultrasounds in our study were performed by several different sonographers. This cohort is derived from a single urban quaternary referral center in the United States. Although these data can likely be generalized to other similar referral centers, until these results have been replicated in other clinical populations, they may reflect findings of our highly select population and not those of the broader Peyronie's disease population. Ultimately whether PD with calcification portends a greater need for surgery or simply a greater likelihood of being offered/ electing surgery cannot be definitively gleaned from these data.

To our knowledge this study is the first analysis of penile sonographic findings and their relationship to progression to surgery in PD. These findings may allow more accurate patient counseling after an initial office ultrasound. Given the greater likelihood of progression to surgery in the presence of penile calcifications, some men may elect to proceed to surgery sooner to resolve the clinical complaint more rapidly.

Future research on outcomes of PD related surgery in men with or without calcification will shed light on the true clinical implications of penile calcification in PD. Important future research could center on outcomes of surgical repair of PD in the setting of calcification. In addition, future work may explore the relationship among calcification, the degree of curvature, vascular flow on Doppler ultrasound and the need for future surgical interventions. Calcium burden or other ultrasound findings at initial visit may also predict surgical outcome success and/or optimal surgical approach. Future studies could develop risk assessment models or nomograms that stratify cases into low, medium and high risk for progression to surgical intervention.

CONCLUSIONS

In a large cohort of patients with PD the presence of sonographically detected calcifications during an initial office evaluation was associated with progression to surgical intervention even after adjusting for the most common reasons men elect to undergo surgical repair.

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Abbreviations and Acronyms

PD Peyronie's disease

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Table 1

Demographic, Peyronie's specific characteristics and ultrasound findings during initial visit of study participants

	No. Observation (%)	No. Surgery (%)	p Value
Age:			
Younger than 40	71 (18.3)	8 (6.2)	
40–49	50 (12.9)	17 (13.1)	
50–59	152 (39.2)	58 (44.6)	
60–69	98 (25.3)	42 (32.3)	
70+	17 (4.4)	5 (3.9)	0.02
Married	226 (58.3)	80 (61.5)	0.51
Yrs of PD:			
Less than 1	157 (42.2)	34 (27.2)	
1–2	101 (27.2)	39 (31.2)	
2 or Greater	114 (30.7)	52 (41.6)	0.01
Curvature (degrees):			
Less than 30	68 (17.5)	11 (8.5)	
30–59	104 (26.8)	39 (30)	
60+	49 (12.6)	47 (36.2)	
Unknown	167 (43.0)	33 (25.4)	<0.001
Prior treatment	289 (74.5)	108 (83.1)	0.05
Current treatment	353 (93.1)	82 (63.6)	<0.001
Previous penile injury	85 (32.7)	23 (26.1)	0.25
Able to have intercourse	256 (79.3)	74 (67.9)	0.02
Maintain erections	109 (50.9)	42 (55.3)	0.52
Loss of penile length	165 (42.5)	57 (43.9)	0.79
Current penile pain	85 (41.3)	38 (45.2)	0.53
Difficulty with penetration	148 (38.1)	70 (53.9)	0.002
Penile deformity	149 (40)	55 (43.7)	0.47
Ultrasound findings:			
Septal fibrosis	79 (20.4)	23 (17.7)	0.51
Intracavernous fibrosis	61 (15.7)	16 (12.3)	0.34
Tunical thickening	190 (49)	71 (54.6)	0.27
Calcification	107 (27.9)	52 (40)	0.01

Table 2

Bivariate analysis of the relationships between demographic and PD characteristics, and progression to surgical intervention

	OR	95% CI	p Value
Calcifications	1.75	1.16–2.62	0.01
Septal fibrosis	0.84	0.51–1.41	0.51
Intracavernous fibrosis	0.75	0.42–1.36	0.35
Tunica thickening	1.25	0.84–1.87	0.27
Age (/10-yr increase)	1.37	1.14–1.66	0.001
Married	1.14	0.76–1.72	0.509
Yrs of PD:			
Less than 1	1	Ref	Ref
1–2	1.78	1.06–3.01	0.03
2+	2.11	1.28–3.46	0.003
Curvature (degrees):			
Less than 30	1	Ref	Ref
30–59	2.32	1.11–4.84	0.03
60+	5.93	2.79–12.58	<0.001
Unknown	1.22	0.58–2.56	0.60
Prior treatment	2.23	1.49–3.34	<0.001
Current treatment	0.13	0.08–0.22	<0.001
Penile injury	0.73	0.42–1.25	0.25
Unable to have sex	1.77	1.1–2.82	0.02
Maintain erection	1.19	0.7–2.01	0.52
Loss of length	1.06	0.71–1.58	0.79
Penile pain	1.18	0.71–1.96	0.53
Difficulty penetrating	1.89	1.27–2.83	0.002
Other penile deformity	1.16	0.77–1.75	0.47

Table 3

Multivariate analysis of the relationship between sonographic characteristics and progression to surgery

	OR	95% CI	p Value
Unadjusted:			
Calcification	1.91	1.24–23.95	0.004
Tunica thickening	1.49	0.98–2.26	0.06
Septal fibrosis	0.9	0.53–1.51	0.68
Intracavernous fibrosis	0.78	0.43–1.41	0.41
Adjusted for age:			
Calcification	1.88	1.21–2.92	0.005
Tunica thickening	1.26	0.82–1.96	0.30
Septal fibrosis	0.95	0.56–1.61	0.86
Intracavernous fibrosis	0.81	0.44–1.5	0.51
Adjusted for age, marital status + PD specific characteristics: *			
Calcification	2.75	1.59–4.77	<0.001
Tunica thickening	1.49	0.87–2.57	0.15
Septal fibrosis	0.9	0.46–1.72	0.74
Intracavernous fibrosis	0.92	0.46–1.86	0.82

* Duration of PD symptoms, degree of curvature, penile deformity, penetration difficulty, loss of penile length, ability to have intercourse and treatment for PD before enrollment in study, in 481 patients.