Review

Implications of Calcification in Peyronie's Disease, A Review of the Literature

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A common characteristic of Peyronie's Disease (PD) is plaque calcification, which is associated with decreased response to treatments and higher rates of surgical intervention. Despite its prevalence in the PD population, the literature on plaque calcification is limited. While the diagnosis of PD is mostly clinical, imaging modalities such as ultrasound can be used to identify plaque calcification. The proper identification of plaque calcification is crucial for guiding management and setting therapeutic expectations for patients with PD. Herein we discuss what is known about PD plaque calcification, including epidemiology, etiology, diagnosis, and management. UROLOGY 00: 1–8, 2021. Published by Elsevier Inc.

Peyronie's disease (PD) is a benign condition characterized by acquired penile deformity often accompanied by pain and sexual dysfunction. PD curvature results from abnormal scarring and fibrous collagen buildup (plaque) in the tunica albuginea (TA) of the corpora cavernosa. [1] PD is estimated to have a worldwide prevalence of 0.3%-13.1%, with greater occurrence in men with risk factors such as diabetes, smoking, and alcohol consumption. [2,3] PD's pathophysiology has not been fully elucidated. Both genetic and environmental factors, such as microtrauma to the penis during intercourse, may be involved. A subset of men will develop calcification within the PD plaque. Calcification is associated with worse treatment outcomes, and greater need for surgical intervention. [4,5] However, little is known about the mechanisms of PD plaque calcification. In this review, we will discuss what is known about PD plaque calcification and how calcification affects treatment and outcomes.

EPIDEMIOLOGY

The epidemiology of PD has been a subject of debate for some time. Several studies have attempted to estimate the prevalence and age of affected individuals in the general population with varying results. A challenge in determining the true prevalence of PD is that many men do not seek care, possibly due to feelings of embarrassment or lack of bother. Nevertheless, it is estimated that the global prevalence lies somewhere between 0.3%-13.1 %, with a higher prevalence in certain sub-populations, such as men who were operated on for radical prostatectomy (16%) and men with diabetes mellitus erectile dysfunction (ED) (20%). [3] To date, the largest study on PD prevalence, by Schwartzer et al, suggests that the prevalence increases somewhat at each decade of life. Men 30-39 had a prevalence of 1.5%; men 40-59 had a prevalence of 3%; men 60-69 had a prevalence of 4.5%; with a maximum of 6.5% prevalence in men older than 70. Generally, patients in studies of PD calcification have a mean age somewhere in middle adulthood (approximately 50 years old). [3,6]

Similarly, it is difficult to ascertain the prevalence or incidence of plaque calcification in PD, and previous estimates suggest that 20%-25% of men with PD have calcification. [4] Some studies that characterized the lesions in patients with PD are case series using consecutive patients. [7,8] One previous study identified calcification radiographically in one-third of 66 consecutive patients with PD. [8] Another, more recent study by Bekos et al characterized PD in 95 consecutive patients using color Doppler ultrasonography and identified some degree of calcifications in 88% of patients. [7] A retrospective cohort study by Levine et al. of 834 men with PD found ultrasonographic evidence of calcification in 34%. Another large cohort study of 1500 men with PD and/or erectile dysfunction found evidence of calcification in 43%. [4]

There is no clear consensus across studies between patients with and without calcified plaque in terms of age at presentation, duration of disease, or chief complaint on presentation such as pain and/or curvature. However, the study by Levine et al. did report a statistically significant difference in some of these characteristics: men with plaque calcifications were found to be slightly older (mean age of 52.20 years old compared to 48.97 in their noncalcified plaque- counterparts, $P = .003$); duration of disease was shorter (17.70 vs 33.20 months $P = .011$); and they were more likely to have pain at the inciting event and pain since onset of PD compared to their noncalcified plaque counterparts.[4] Further investigation is needed to validate Levine's results.

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While the evidence on incidence is variable, calcification and degree of calcification has a more consistent association with disease severity, progression, and comorbid conditions. Multiple studies showed an association between calcification and cardiovascular disease risk factors such as smoking, hypertension, and diabetes. [3,4,7,9] Bekos et al divided patients into 3 groups depending on the extent of plaque calcification determined via ultrasonography. Patients in group A had a solitary hyperechoic lesion without acoustic shadow. Patients in group B had multiple, moderately hyperechoic, scattered calcified lesions with acoustic shadow. Group C patients had dense calcified hyperechoic plaque with acoustic shadow. The investigators then assessed patients for penile vascular disease (PVD) at baseline and at 12 months. Bekos et al found an increased incidence of PVD in the groups with plaque calcifications at baseline. Furthermore, more patients progressed to PVD in the groups with plaque calcifications (>50% of patients in group C had PVD at 12 months).

The association of cardiovascular disease and diabetes mellitus with plaque calcification may be related to wound healing mechanics. It is well established that diabetes and peripheral vascular disease lead to chronic ulcers (eg, foot ulcers) and delayed wound healing. Underlying vascular pathology may promote poor wound healing in response to trauma or microtrauma to the TA and the development of fibrosis and calcifications overtime. While the etiology of calcification in PD is incompletely understood, several early studies have suggested a link between vascular trauma and the formation of calcified plaque. [8,10] Meanwhile, other more recent studies point out that differences in gene expression may account for the observed variation in plaque calcification among men with PD.

GENETICS

Research on the role of genetics in PD and plaque calcification has included pedigree analyses, chromosomal studies, GWAS, and gene expression profile analyses. Some have suggested that PD is one manifestation within a spectrum of systemic fibrotic disorders with genetic and environmental factors. This is supported by associations between PD, Dupuytren's Disease (DD, fibrosis of the palmar fascia of the hands), and Ledderhose Disease (LD, fibrosis of the plantar fascia of the feet). In fact, perhaps as many as 10%-20% of men with PD also have manifestations of DD. [11,12]

Bias et al studied 3 families with PD and DD and found an autosomal dominant mode of inheritance with incomplete penetrance, with 1 family showing 3 generations of transmission from father to son. [13] Other studies of the PD and DD in men and their relatives demonstrated that autosomal dominant transmission is uncommon. [11] The co-incidence of PD and DD varies in the literature. This variability may be due to differences in gene expression, inconsistent diagnostic criteria for DD between studies, and differences in the ages of individuals included. [11] Although there appears to be an association between PD and other fibrotic disorders, further investigation is needed to better understand this relationship.

Cytogenetic studies of fibroblasts by Somers et al. revealed a variety of chromosomal abnormalities present in cultured PD plaques and not adjacent normal TA. [14] Further evidence for the correlation between PD plaques and chromosomal instability comes from a study of fibroblast passage in culture. Cultured fibroblasts from PD plaque developed a pattern of aneuploidy after the third passage, whereas cells from unaffected TA required more passages in culture before chromosomal defects could be detected, consistent with a field defect. [15]

Gene expression studies have also identified differences present in PD. Using DNA expression microarrays, Magee et al. identified a set of genes that were dysregulated in plaque from PD patients compared to normal TA from unaffected controls. [16-18] The most upregulated genes in plaque were pleiotrophin (*PTN*) followed by monocyte chemotactic precursor protein 1 (*MCP-1*) and alpha smooth muscle actin (*ASMA*). *PTN* codes for a growth factor that induces proliferation of fibroblasts, osteoblasts, and osteogenesis. [16,17] *MCP-1* is involved in activation of monocytes, driving the inflammatory cascade and osteogenesis. *ASMA* codes for a subtype of actin found in smooth muscle cells and myofibroblasts. Interestingly, genes that were downregulated were functionally in opposition to collagen accumulation, such as procollagenase IV.

The gene expression profile identified by Magee et al is a marker of inflammation, fibroblast proliferation, and tissue ossification. *PTN* overexpression is likely involved specifically with plaque calcification by recruiting osteoblasts and/or inducing stem cell differentiation within the plaque to osteoblast-like cells. Stimulation by exogenous transforming growth factor beta-1 (TGF-β1) induces differentiation into an osteogenic cell line, as evidenced by expression of alkaline phosphatase and increased expression of *PTN*, *POSTN*, and *BMP-2*. [17] Evidence of calcification in these cell lines was also observed on microscopy with immunohistochemistry staining.

PATHOPHYSIOLOGY

The pathophysiology of PD is incompletely understood, and the prevailing school of thought centers around poor wound healing in genetically susceptible individuals. [3] In this model, trauma or microtrauma to the penis secondary to axial stress during penetration leads to an injury which undergoes aberrant or exuberant scarring. [19-21] The injury disrupts the TA and triggers a cascade of cellular and molecular mediators. In normal healing the TA restores the original architecture and amount of extracellular matrix (ECM) present. [19] In contrast, PD fibrosis is the result of chronic inflammation, characterized by excessive ECM deposition. [22] Epigenetic pathways involving histone deacetylases have been implicated. [23]

The most well studied factors in the pathophysiology of PD include TGF-β1 myofibroblasts, and fibrin. [17] Tissue

healing begins with fibrin deposition causing degranulation with increases in Platelet Derived Growth Factor (PDGF) and TGF-β1. This is followed by vasodilation, increased vascular permeability and attraction of neutrophils and macrophages.[24,25] Overexpression of TGF-β1 in PD may lie at the heart of the mechanism of fibrosis, which may explain its overabundance in PD plaques.[17,26] PDGF and TGF-β1 induce differentiation of fibroblasts into myofibroblasts and deposition of aberrant collagen in the ECM. [27] Matrix metalloproteases breakdown fibrin and ECM components, allowing inflammatory cells to enter the damaged tissue. In normal tissue there is a balance between deposition and removal of ECM by matrix metalloproteinases and tissue inhibitors of metalloproteinases. [28,29] In PD, tissue inhibitors of metalloproteinases are increased, preventing the degradation of ECM [30] (Fig. 1).

The mechanism of plaque calcification has not been as extensively studied. In electron microscopy studies of calcified PD plaques, Vande Berg et al observed "lamellar calcifications" of connective tissue surrounding blood vessels and a matrix rich in collagen with random calcified aggregates. Cells observed within the calcified matrix resembled osteoblasts (referred to as osteoblast-like cells) residing in lacunar spaces containing hydroxyapatite crystal depositions, mimicking boney tissue. They interpreted that collagen is deposited near blood vessels and osteoblast-like cells enter the matrix of collagen and gradually calcify. [10,31] In a study that characterized gene expression in PD, Vernet et al also demonstrated that there are cells within the TA possessing osteogenic potential. [16] Many of the same morphological findings observed by Vande Berg et al in calcified plaque were also observed by Vernet et al. in cultures derived from PD plaque and TA tissue. These included calcification of a collagen matrix and concentric circles surrounding cells confirmed to be osteoblasts by histochemical staining and mRNA expression profiles. The differentiation into osteoblasts in cultured

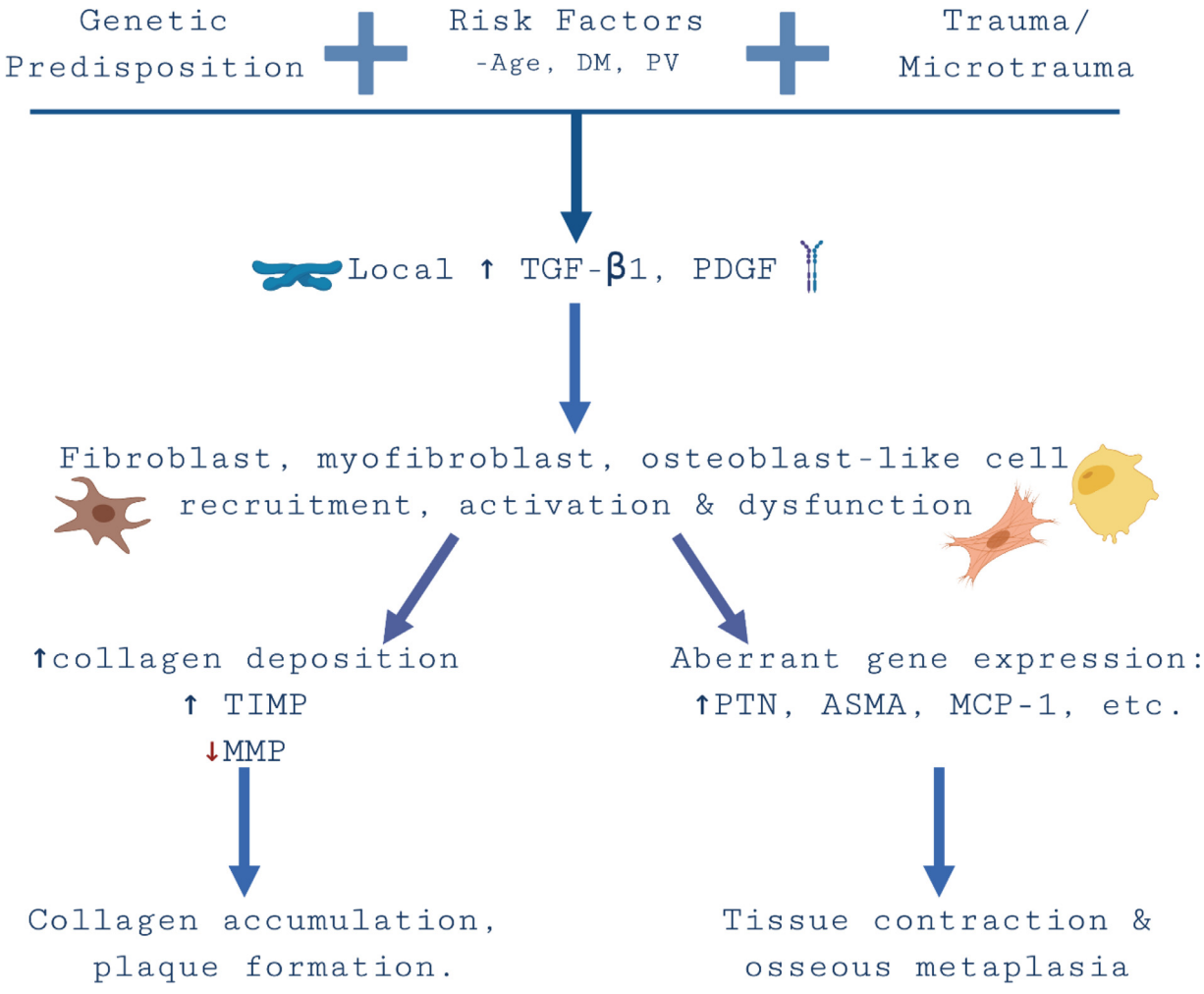

Figure 1. The development of Peyronie's disease plaques appears to involve increased local concentration of TGF-β1 and PDGF which cause differentiation of fibroblasts into myofibroblasts and deposition of aberrant collagen in the extracellular matrix. Additionally, there is a decrease in removal of ECM by matrix metalloproteinases (MMPs) and an increase in tissue inhibitors of metalloproteinases (TIMP). Taken together, this leads to plaque formation, tissue contraction and penile curvature. (Color version available online.)

PD plaque and TA was induced by TGF-β1. These findings are interesting and suggest the following: (1) TGF-β1 is not only a key mediator for fibrosis in PD, but for plaque calcification as well, (2) if normal TA could also be induced to make osteoblasts, then this supports the field defect model. The entire TA in a PD susceptible individual is capable of undergoing calcification and boney transformation, but these changes are observed in response to a trigger such as microtrauma or TGF-β1 stimulation. [12]

Hatfield et al. examined the histopathologic patterns in 71 biopsies of calcified PD.[32-35]They noted that nearly all of the cases identified in clinical imaging studies as containing calcifications were found to histologically represent metaplastic ossification, consistent with the descriptions of PD plaque histopathology in the earlier case series. The study by Hatfield et al. also represents perhaps the first attempt to classify PD plaque based on histopathology into 3 patterns: pattern 1 representing fibrosis only (the majority of cases), pattern 2 representing fibrosis with patchy areas of osseus metaplasia (35% of cases), and pattern 3 representing "predominantly metaplastic bone" (4% of cases). Notably, a plaque "ossification" rate of 39% (cases with patterns 2 and 3) is higher than the rate of calcification that has been reported previously in the literature, which the authors suggest may be due to referral bias of complex cases. Furthermore, Hatfield et al. argue that the nature of the histologic observations is consistent with previous models of plaque evolution supported by Vande Berg et al, in which ossification is a late-stage finding. [10,31,32]

The distinction between the terms "dystrophic calcification" and "osseus metaplasia" may have important implications on our understanding of PD pathophysiology, prognosis, and future therapeutic directions. Disease models or comparisons such as atherosclerosis and calcinosis in CREST syndrome may be less relevant than once thought. While research on the mechanism of plaque evolution in PD still has many unanswered questions, the 2020 study by Hatfield et al, along with the older pathology case series suggests that what is called dystrophic calcifications in PD represents osseus changes. This interpretation is consistent with past works showing that the molecular biology and genetics of plaque calcification in PD actually activates pathways of osteogenesis.[16-18] Although this presents opportunities for future investigation, it also presents challenges to our existing frameworks for PD pathogenesis. How do we reconcile a model of injury, poor wound healing, and fibrosis with the relatively high incidence of extensive plaque ossification? The answers could have a significant impact on our understanding of PD and other fibrotic disorders.

DIAGNOSIS

The diagnosis of PD relies on the clinical experience of the physician. PD can be distinguished from congenital chordee, another abnormality causing penile curvature, by the duration of symptoms. The American Urological Association guidelines recommend a careful clinical history and physical examination of the genitalia for evaluation of associated pain and palpable abnormalities. These recommendations include utilizing intracavernosal injection with or without duplex Doppler US prior to invasive intervention to measure and document the degree and direction of penile curvature. [36] The routine use of US imaging in the diagnosis of PD remains controversial as the European Association of Urology feels the results are operator dependent and may not affect management. [37] However, calcification can only be detected by imaging and as data grows regarding its importance, imaging may take on larger role. [38]

Multiple imaging modalities were studied in the diagnosis and work up of PD. Imaging enhances the ability to characterize PD plaques, providing information such as size, location, shape, and extent of calcification. US, magnetic resonance imaging, computed tomography (CT), and radiography can be utilized to quantify plaques. [39] Magnetic resonance imaging is excellent in the detection of plaques, but is unable to visualize calcification. [39] CT and radiography can detect calcification, but they are limited in their ability to identify non-calcified plaques and require ionizing radiation. [38] US is ideal because it has nearly 100% sensitivity for detecting calcifications, is non-invasive, relatively inexpensive, widely available, and avoids ionizing radiation. [40] US is also the most well studied modality when evaluating the impact of calcification on PD outcomes. [41]

On US, calcification appears as a dense white structure with posterior shadowing (**Fig. 2**). Several classification systems utilizing US have been proposed (**Table 1**). One system developed by Bekos et al categorized patients based on the severity of calcification and echogenicity on US. [7] Bekos' classification system divided patients into 3 groups A, B, and C. Group A patients had a solitary hyperechoic lesion without acoustic shadow, group B patients had moderately hyperechoic multiple scattered calcified lesions with acoustic shadows, and group C patients had densely calcified hyperechoic plaque with acoustic shadow. Interestingly, after 1-year follow-up of watchful waiting without any form of treatment, most patients in groups A and B demonstrated reduction in curvature, while group C did not.

Pawlowska and Bianek-Bodzak proposed a similar classification system of PD plaques: type 1, 2, and 3. Type 1 plaques appear as a thickening of the TA without acoustic shadowing, type 2 is moderately calcified plaque with a typical US shadow, and type 3 are severely calcified plaques with complete shadowing. This system is also potentially useful in research and clinical description.[40]

Levine et al. devised a classification system by grading the linear amount of calcification into grades 1, 2, or 3. Whereas previous system looked at the characteristics of US shadowing, Levine's grading system assessed linear amount of calcification. Grade 1 consisted of calcification <0.3 cm, grade 2 was >0.3 cm but <1.5 cm, and grade 3 was >1.5 cm or ≥2 plaques >1.0 cm. [4] In their study, the

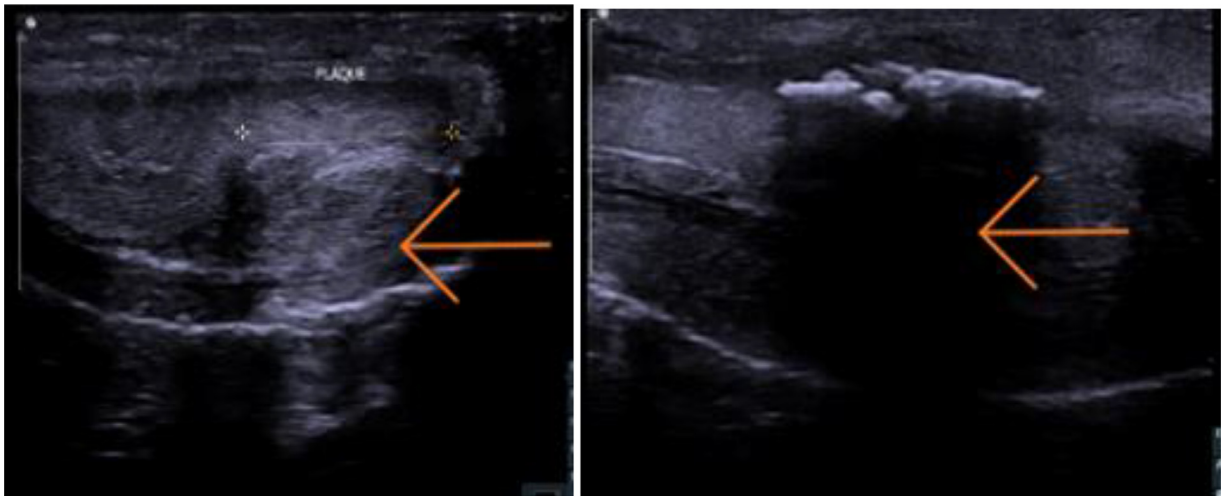

Figure 2. Representative image of Ultrasound detected Peyronie's disease plaques in 2 patients. Left, a noncalcified plaque without acoustic shadowing. Right, a calcified plaque with posterior acoustic shadowing. (Color version available online.)

frequency of surgical intervention directly correlated to grade, where 55% of men with grade 3 elected for surgical intervention, opposed to only 23% in grade 1.

Unfortunately, no system has been adopted into routine clinical practice. It seems essential that any standardized system for evaluating PD includes a classification system of calcification as it can impact treatment outcomes.

CLINICAL IMPLICATIONS

Men with calcified PD plaques have historically poor response to nonsurgical treatment options.[42] Clostridium histolyticum (CCH) is the only the Food and Drug Administration (FDA) approved medication for the treatment of PD since 2013. CCH gained approval after the completion of 2 large randomized placebo-controlled trials. [43,44] In some of these trials, only patients with stippling or calcification which did not physically interfere with CCH injections were included. *Post-hoc* subgroup analysis conducted by Lipshultz et al examined the efficacy of CCH and identified greater improvement in men with certain clinical characteristics, one of them being no plaque calcification. [45] A subsequent prospective study from March 2014 to January 2017 conducted by Wymer et al retrospectively examined a cohort of 115 patients treated with CCH for at least 2 cycles (along with penile traction for 1-3 hours daily), 34 (30%) of which had identifiable calcified plaques on US. [5] This study found that patients with non-calcified plaques achieved significantly greater improvements in curvature (measured during physical exam after an intracavernosal injection) after treatment with CCH when compared to those with moderate (echogenic shadowing <1 cm) or severe (>1 cm). Among the group with non-calcified plaques 67% of patients demonstrated a >20% improvement in curvature, compared to 41% in the group with calcified plaques (Table 2). Additionally, when expanding the study to

Table 1. Summary of calcification systems used to describe the severity of calcified plaques in PD patients [4,7,40]

Ultrasound PD Plaque Calcification Classification Systems			
Classification System	Categories and Descriptions		
Bekos et al.	A Solitary hyperechoic lesion without acoustic shadow	B Moderately hyperechoic multiple scattered calcified lesions with acoustic shadows	C Densely calcified hyperechoic plaque with acoustic shadow
Pawlowska and Bianek-Bodzak	Type 1 Plaque appearing as a thickening of the TA without acoustic shadowing	Type 2 Moderately calcified plaque with a typical US shadow	Type 3 Severely calcified plaque with typical US shadowing
Levine et al.	Grade 1 Calcification <0.3 cm	Grade 2 Calcification >0.3 cm but <1.5 cm	Grade 3 Calcification >1.5 cm or ≥2 calcified plaques >1.0 cm

PD, Peyronie's disease; TA, tunica albuginea; US, ultrasound.

Table 2. Comparison of patients who had >20% improvement in curvature after at least 2 cycles of collagenase clostridium histolyticum with encouraged penile traction for 1-3 hours daily, calcified versus noncalcified plaques[5]

	Significant Improvement (>20% improvement in curvature)	Non-significant Improvement (<20% improvement in curvature)
Calcified Plaque (*n*=34)	14 (41%)	20 (59%)
Non-calcified Plaque (*n*=81)	54 (67%)	27 (33%)

include patients with at least 1 cycle of CCH, it was found that 47 out of 192 reported restoration of the ability to penetrate after treatment. Of these 47 patients, only 10 (21%) were found to have calcified plaques, meaning 78% of patients with noncalcified plaques reported successful penetration after treatment, compared to 40% in the calcified plaques group. This study suggests that calcified PD plaques may be resistant to treatment with CCH.

A retrospective study by Bajic et al from October 2014 to October 2019 demonstrated that of 573 new PD consultations presenting to a urology clinic, 67 (11.7%) had CCH treatment prior; of these 67, 26 (38.8%) had calcifications present on US in clinic. [46] Of these 26 patients, 26.1% had grade 3 calcifications, per the Levine grading system. [4] Nearly half of these post-CCH patients (49.3%; 33/67) ultimately elected for surgery due to lack of satisfactory improvement from injection therapy.

Another common non-surgical method of PD treatment includes penile traction therapy (PTT), which utilizes mechanical stretch to induce mechanotransduction (the translation of mechanical stimuli into a chemical signal which actives cell proliferation). [47-49] According to a 2013 study examining the Andropeyronie (Andromedical, S.L., Madrid, Spain) with a recommended use for 6-9 hours daily for at least 6 months in patients with acute phase calcification (progressive penile curvature >15° and/or pain at rest or at erection in the last 12 months), calcified plaques remained stable after PTT and the presence of plaques and calcifications were inversely proportional to the success of PTT. [50] However, after classifying the 18 patients with calcification into grades 1, 2, or 3 (as described by Levine at al [4]) and reassessing after 6 months of treatment, the number of patients with grade 1 calcification increased from 10 (55.6%) to 14 (77.7%), grade 2 decreased from 4 (22.2%) to 3 (16.6%) patients, and grade 3 decreased from 4 (22.2%) to 1 (5.7%) patient. These data suggest that some patients in grade 2 and 3 may have decreased to grade 1 after PTT; although no patient displayed complete resolution of their calcification after 6 months of PPT. [50] Further investigation with larger prospective studies is needed to validate these results.

Pentoxifylline (PTX), is a nonspecific phosphodiesterase inhibitor that may increase levels of NO in the penis and/or block the TGF-β pathways. [51] A 2010 retrospective cohort study conducted by Smith et al. examined 71 men with PD and evidence of penile calcification on US at initial presentation. Of these men, 62 were treated with PTX (mean treatment duration of 1.2 years), the remaining 9 never took PTX. [52] Of those 9, 4 used vitamin E, and 5 never attempted medical treatment. Men who took PTX were more likely to have improvement in their mean area of calcification when compared to men who did not take PTX (69.4% vs 33.3%). Furthermore, men in the PTX group reported either a stabilization or a subjective sense of clinical improvement at greater rates than the control (78.3% versus 25.0%). Although the results of this experiment are promising and were statistically significant, the study had many limitations including small sample size and no randomization. Objective data, such as change in penile curvature, plaque volume, erectile function, and erectile pain were not included and thus not analyzed.

When Levine et al analyzed calcification in 334 men (98 calcified, 236 noncalcified) by grade and progression to surgery from nonsurgical intervention, 34.7% of noncalcified, 23% of grade 1, 32% of grade 2, and 55% of grade 3 patients eventually underwent surgical intervention.[4] Only grade 3 (>1.5cm linear calcification) had a statistically significant progression compared to the noncalcified group. Furthermore, Breyer et al reported in a retrospective cohort study that men with sub-tunical calcifications had a 75% increase in the odds of undergoing elective surgical interventions. [53] No other sonographic characteristics, including septal fibrosis, tunical thickening (tunica thickness greater than 2 mm), or intracavernous fibrosis demonstrated an associated progression to surgery. Given that both studies were retrospective and unblinded, it is difficult to determine the effect counseling had on each patient's choice to pursue surgery versus more conservative treatment options.

Similar to medical trials, surgical trials often exclude or make minimal analysis for treatment outcomes in patients with calcified plaques. An algorithm developed in 1997 by Levine and Lenting, which is still commonly utilized, noted that plaque calcification can be identified during a patient's workup but did not include calcification as a factor in their algorithm. [54] When considering tunica albuginea plication vs plaque excision and grating in the context of calcification, plaque excision and grating is the preferred method. [55] Surgical excision of bone and densely calcified plaques can be challenging, a retrospective chart review conducted by Ostrowski et al in 2015 reviewed 100 consecutive PD patients who underwent surgery at their medical center between October 1996 and December 2012. Of these 100 patients, 6 patients' plaques were too densely calcified to be cut with a blade and instead a TPS sagittal bone saw (Striker Corporation, Portage, Michigan) was used to cut through ossified plaques to the

cavernous tissue. Four of the resulting 6 patients underwent grafting with submucosal intestinal substance and the remaining 2 underwent inflatable penile prosthesis (IPP) placement after plaque incision. Both IPP patients retained function of their prothesis 4 and 7.3 years after surgery. One submucosal intestinal substance-graft patient required another operation for removal of more proximal curvature 11 months after his surgery, ultimately requiring multiple plaque incisions and placement of an IPP. [56] This study demonstrates that surgery and IPP placement can be successful even in difficult cases of plaque calcification.

Taken together, these studies highlight the importance of evaluating calcification in PD patients. Patients without calcification appear better suited for CCH whereas patients with severe calcification may be better counseled toward surgery. Common off label treatments such as colchicine, verapamil injections, and vitamin E, while not recommend in routine treatment of PD, have not been evaluated regarding their effectiveness in the setting of calcification. [57,58] Most PD trials do not explicitly assess for calcification or use calcification as an exclusion criterion for enrollment. According to a 2017-2018 survey in Europe emailed to members of various andrology and urology societies, only 74% of the respondents conduct US to assess patients with ED, and of the total respondents 36% are dissatisfied with the currently available treatment options and 64% report that they have the impression that patients are dissatisfied with available treatment options. [59] It should be noted that this survey was conducted before 2019, when CCH injections were discontinued in Europe. Establishing a standardized protocol for evaluating PD for features such as severity of calcification may help tailor more effective treatments and abate such dissatisfaction.

CONCLUSION

Despite ongoing research, the pathophysiology of PD remains undefined, especially as it pertains to plaque calcification. Calcification could have substantial implications on the natural history and treatment options for PD. Regardless of the true pathophysiology of calcification in PD, it remains apparent that it is predictive of a patient's clinical course and treatment outcomes. PD patients with calcification respond poorly to CCH, the only medication currently FDA approved for treatment of PD, and they undergo surgery at higher rates than those without calcification. For this reason alone, we argue that imaging to evaluate calcification is an essential component of evaluation for PD patients. Currently the American Urological Association and European Association of Urology do not strongly recommend US in the evaluation of patient's with PD, even though US is safe and can be of high diagnostic value for detecting calcification.

DECLARATION OF COMPETING INTEREST

No competing financial interests exist.

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