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ORIGINAL PAPER

Calcification in Peyronie's disease: Its role and clinical influence on the various symptoms and signs of the disease, including psychological impact. Our study of 551 patients

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Summary ***Background: The aim of study was to evaluate the impact of plaque calcification on symptoms of patients with Peyronie's disease (PD) and to evaluate mental health in PD patients with or without calcification. Methods: We performed a retrospective analysis of the clinical database of a single andrology clinic. We extracted 551 PD patients, and we sorted them into two groups: the first group included 201 PD patients with plaque calcification; the second group included 350 PD patients without plaque calcification. The inclusion criteria for both groups were as follows: aged between 21 and 81 years; thorough and available data on clinical history; baseline levels of blood glucose, glycosylated hemoglobin, cholesterol, and triglycerides; photographic documentation of the penile curvature; dynamic penile eco-color Doppler ultrasound with plaque measurements and volume calculation; and completion of the generalized anxiety disorder—7 questionnaire, patient health questionnaire—9 (for depression), visual analog scale for penile pain measurements, and the International Index of Erectile Function (IIEF) questionnaire. Results: Plaque calcification was present in 36.4% of cases. The presence of calcification affects the presence and severity of penile curvature. Calcification is associated with the presence of hypertension. In PD patients, the prevalence of significant anxiety and significant depression was 89.1% and 57.3%, respectively. Calcification is associated with the presence of anxiety and depression but does not lead to an increase in their prevalence. Conclusions: In PD patients, the calcification was present in more than one third of cases. The size of the plaque calcification was < 15 mm in most cases. Calcification influences the presence of the curve and influences its severity. There was a prominent prevalence of anxiety and depression in PD patients.***

KEY WORDS: Peyronie's disease; Plaque calcification; Depression; Anxiety.

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INTRODUCTION

Peyronies's disease (PD) is a chronic inflammatory disease that affects the tunica albuginea of the corpora cavernosa of the penis. PD has a genetic origin; however, it requires the concomitance of some risk factors. Among these are penile trauma, diabetes mellitus, hypertension, congenital penile curvature, radical pelvic surgery, erectile dysfunction, obesity, smoking, hypertension, autoimmune diseases (rheumatoid arthritis, psoriatic arthritis, psoriasis), alcohol consumption, and dyslipidemia (1-11). The prevalence of PD ranges from 3.2 to 13.1% in Western countries (12-17). However, PD prevalence is influenced by the geographic location of patients; prevalence in the Asian region seems to be lower, with 5.0% in *Japan* and 0.6% in *China* (18, 19).

PD takes place in two phases, the first of which represents the active phase of the disease; the second phase represents the phase of stabilization. In the first phase, which has a duration of about 12-18 months, inflammation causes an overproduction of collagen with the relative formation of a fibrotic plaque which causes penile deformation (curvature, shortening, dip, indentation, hourglass, etc.) (20-22).

The fibroblasts and myofibroblasts present in the disease area (plaque) can transform into osteoblasts with a relative production of calcified areas (22, 23). *Vernet et al.* (2005) demonstrated that progenitor cells are present in the fibrotic plaque tissue of PD and in the normal tunica albuginea of the penis, which, in culture, can differentiate into other cell lines (23). During PD, the differentiation of these progenitor cells into osteoblasts and myofibroblasts is stimulated by the profibrotic cytokine *transforming growth factor beta-1* (TGF-β1). This cell differentiation can also be activated during chronic inflammation, oxidative stress, and fibrosis, where TGF-β1 is upregulated (23). This cell differentiation into osteoblasts and the related plaque calcification in PD occurs in about 20-43% of cases (22-26). The stabilization phase represents the end of the progression of the disease; in this phase, there is no more penile pain and penile deformation has ceased to progress. The diagnosis of plaque calcification necessarily requires a penile ultrasound or other imaging methods (MRI, CT) as the simple penile palpation is not able to recognize the calcification for sure (27-32).

The aim of our study is to evaluate the impact of plaque calcification on the clinical symptoms of patients with PD.

Materials and methods

Study design

We performed a retrospective analysis of the clinical database of a single andrology clinic. From the database, we extracted 551 PD patients who were examined in our urology/andrology clinic between January 2013 and April 2023. We divided all PD patients into two groups: the first group included 201 patients diagnosed with *Peyronie's disease* (PD) and with plaque calcification; the second group included 350 PD patients without plaque calcification. All data were obtained from the available patient records. The diagnosis of penile calcification was made in all cases with a penile ultrasound examination performed by the same andrologist operator with a high-resolution ultrasound device, Philips HD 15 until the year of 2018, and thereafter with Philips Affinity 70 G (*Philips, Washington, United States*). The diagnosis of penile calcification was made when the hyperechoic area presented characteristic acoustic shadowing (33).

This retrospective observational study was conducted in compliance with the principles contained in the Declaration of Helsinki: all study subjects were contacted to provide their informed consent to participate in the study. Sensitive data were anonymized to respect privacy according to Legislative Decree, 10 August 2018, n. 101, adapted to the GDPR (*Official Gazette of the Italian Republic, General Series n.205, dated 04-09-2018*).

Inclusion criteria

The inclusion criteria for both groups were as follows: aged between 21 and 81 years and available data of thorough clinical history examination (comprising all diseases) and the availability of the following blood tests: baseline blood glucose, glycosylated hemoglobin, cholesterol, and triglycerides.

The diagnosis of Peyronie's disease was made as follows: performing penile palpation for all PD patients and availability of a (i) photographic documentation of the penile deformation (according to Kelâmi) with a goniometric measurement of the angulation and evaluation of the possible presence of the multiplanarity of the curvature (34) and a (ii) dynamic penile eco-color Doppler ultrasound with plaque measurements and volume calculation (mm^3, in three dimensions in mm) using an ellipsoid formula (volume = 0.524 x width x length x thickness) (35, 36).

Exclusion criteria

The exclusion criteria were as follows:

- For both groups, PD patients and non-PD patients aged under 21 years or over 81 years;
- All patients who had not undergone the tests listed above.

Clinical data

All clinical data (including the presence of concomitant diseases) were obtained from the clinical records of the 551 PD patients. In the clinical records of the 551 PD patients, the results of the following blood tests were searched: baseline blood glucose, glycosylated hemoglobin (hemoglobin A1c), cholesterolemia, and triglyceridemia. All PD patients were asked to complete the following questionnaires: *visual analog scale* (VAS) questionnaire for pain measurement (37, 38); *International Index of Erectile Function* (IIEF) for erectile function measurement (39); and two validated psychometric tests: the generalized anxiety disorder—7 questionnaire (GAD-7, concerning anxiety) and the patient health questionnaire—9 (PHQ-9, concerning depression) (40, 41). The VAS questionnaire consists of a 10 cm line drawn on paper, and each 1 cm point corresponds to a degree of pain intensity; the patient indicates their perceived pain point on this line. Scores range from 0 (no pain) to 10 (most intolerable pain) (37). We considered the following interpretation VAS: 1-5, mild/moderate pain; 6-7, severe pain; and 8-10, very severe pain (38).

The IIEF erectile function questionnaire (for measuring possible erectile dysfunction) consists of 15 questions with 5 answers, and the final score varies from a minimum of 0 to 30. The interpretation of the score is: severe ED, from 0 to 10; moderate ED, 11 to 16; mild to moderate ED, 17 to 21; mild ED, 22 to 25; and no erectile dysfunction, 26 to 30 (39). We considered ED as present when the score was < 26.

The GAD-7 anxiety questionnaire consists of seven questions with four answers, and the final score ranges from 0 to 21. We interpreted this score as follows: least anxiety, 0-4; mild anxiety, 5-9; moderate anxiety, 10-14; and severe anxiety, 15-21 (40). In this study, we considered the presence of "*significant*" anxiety when the GAD-7 score was > 9.

The PHQ-9 questionnaire (patient health questionnaire—9) includes 9 questions with 4 answers, and the final score ranges from 0 to 27. We interpreted this score as follows: minimal depression, 0-4; mild depression, 5-9; moderate depression, 10-14; moderately severe depression, 15-19; and severe depression, 20-27 (41). We considered the presence of "*significant*" depression when the PHQ-9 score was > 9 (moderate to severe depression).

In accordance with the classification of *Levine et al.* (24), the size of the calcification (measured in mm) was stratified into three groups according to the maximum size of the calcified zone: grade 1= punctiform or ≤ 3 mm; grade 2= > 3 mm and < 15 mm; and grade 3 = ≥ 15 mm or ≥ 2 plaques > 10 mm.

Study endpoints

The primary endpoints of the study were the impact of calcification in PD patients on presence and severity of penile curvature, penile curve multiplanarity, presence and severity of ED, presence and severity of penile pain, presence and severity of anxiety, and presence and severity of depression.

The secondary endpoints of the study were the impact on the presence of calcification of diabetes mellitus, hypertension (high blood pressure), dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia), cardiovascular diseases, and obesity and the prevalence of anxiety an depression in Peyronie's disease patients.

Statistical analysis

We used MedCalc statistical software (Version 16.4.3, 2016) for the following statistical studies: Chi-square two tailed test, *relative risk* (RR) test, *odds ratio* (OR) test, and two-tailed t-test. For the statistical study of logistic regres-

sion, we used *AgriMetSoft's software (2019)*. For the statistical study of the Mann-Whitney-Wilcoxon test, we used *Statistics Kingdom software (2017)*. For the statistical study of standard deviation, median, and interquartile range calculation (IQR), we used *CalculatorSoup® software (2006-2023)*.
The impact of calcification on penile curvature severity in PD patients was investigated via a *relative risk* (RR) test after stratification of PD patients with calcification into two groups (Group A, ≤ 45 degrees; Group B, > 45 degrees).
The impact of multiple calcifications on the multiplanarity of the penile curvature (when present) in PD patients was investigated using the *odds ratio* (OR) test.
The effect of calcification on the presence of ED in PD patients was investigated by comparing the median IIEF scores of patients with and without calcification. To calculate this comparison, we employed the two-tailed Mann-Whitney-Wilcoxon test as well as the calculation of the median IIEF scores and the *interquartile range* (IQR). Furthermore, to investigate the impact of calcification on ED presence in PD patients, we employed a logistic regression study.
The impact of calcification on penile pain in PD patients, was investigated by comparing the median VAS scores of patients with and without calcification. To calculate this comparison, we employed the two-tailed Mann-Whitney-Wilcoxon test as well as the calculation of the median VAS scores and the IQR.
Furthermore, to investigate the impact of calcification on penile pain in PD patients, we employed a logistic regression study.
The impact of calcification on the presence of anxiety in PD patients was investigated by comparing the mean and *standard deviation* (SD) of the GAD-7 scores (of significantly anxious patients both with and without a calcification). To calculate this comparison using the GAD-7 scores, we used the two-tailed Mann-Whitney-Wilcoxon test as well as the calculation of the median scores and the IQR.
Furthermore, to investigate the impact of calcification on anxiety in PD patients, we employed a logistic regression study.
The impact of calcification on the presence of depression in PD patients was investigated by comparing the mean and SD of the scores (PHQ-9) of significantly depressed patients with and without a calcification. To calculate this comparison using the PHQ-9 scores, we employed the two-tailed Mann-Whitney-Wilcoxon test as well as the calculation of the median scores and IQR.
Furthermore, to investigate the impact of calcification on depression in PD patients, we employed a logistic regression study.
The influence of diabetes mellitus, hypertension, hypercholesterolemia, cardiovascular diseases, and obesity on the presence of calcification in PD patients was investigated using the OR test.
In all statistical analyses, a 5% threshold for an alpha error was used to define statistical significance (significant p-value < 0.05).

Results

In total, 551 patients with PD met the inclusion criteria for this study. The mean age was 49.55 years ± 12.17 years, range 21-81. We found that in the 551 patients affected by Peyronie's disease, calcification was present in 36.4% of cases (201 cases). After dividing all PD patients into two groups according to the presence of plaque calcification, the first group included 201 PD patients with plaque calcification (mean age 49.57 years ± 12.19 years, range 21-81) and the second group included 350 patients diagnosed as PD patients without plaque calcification (mean age 49.54 years ± 12.18 years, range 21-73).
In 107 cases, the penile calcifications were multiple (53.2% out of 201 cases, and 19.4% of all PD patients).
Having stratified the calcifications of 201 PD patients according to the classification proposed by *Levine et al.* (23), we found the following results: grade 1 calcifications, 23 cases (11.4%); grade 2 calcifications, 130 cases (64.6%); and grade 3 calcifications, 48 cases (23.8%).
The plaque calcification was < 15 mm (grade 1 and grade 2) in 76.1% of cases.
Out of a total of 551 PD patients, 499 had penile curvature (90.05% of cases), and the bend angle ranged from 5 to 100 degrees (mean 35.6 degrees ± 17.67). In the 201 PD patients with plaque calcification (group 1) the angle of curvature ranged from 5 to 100 degrees (mean 38.37 degrees ± 17.72); in the 350 patients with PD and without plaque calcification (group 2) the angle of curvature ranged from 5 to 100 degrees (mean 34.09 degrees ± 17.48).
Out of a total of 551 PD patients, 169 cases had a complex curve (multiplanarity) (30.67%), 217 erectile dysfunction (39.38% of cases), 296 penile pain (53.72% of cases), 491 significant anxiety (89.1% of cases), 317 significant depression (57.3% of cases), 32 diabetes mellitus (5.8% of cases), 103 hypertension (18.69% of cases), 56 dyslipidemia (10.16% of cases), 41 cardiovascular diseases (7.44%), and 31 were obese (5.6%).
The clinical characteristics of the 551 PD patients, as a whole and divided by group 1 and group 2 are shown in Table 1.
The impact of plaque calcification on the presence and severity of penile curvature in PD patients
The mean penile curvature degree of group 1 and group 2 were significantly dufferent (p = 0.009) (Table 1).
Using the two-tailed Mann-Whitney-Wilcoxon test, the medians of penile angulation degrees in patients with or without calcification were statistically different (with calcification = 39, IQR = 15; no calcification = 30, IQR = 25, p = 0.004) (p < 0.05).
Using the logistic regression test and considering the penile angulation degrees of all PD patients with or without calcification, the results we obtained are as follows: Odds ratio = 1.013, (95% CI, 1.003 to 1.024), deviance 643.5, and p-value = 0.009 (p < 0.05).
All statistical studies indicate that calcification has an influence on the presence and severity of penile curvature.

The influence of calcification on penile curvature severity in PD

PD patients with calcification were stratified into two groups (Group A, ≤ 45 degrees; Group B, > 45 degrees). There were 161 patients with calcification with a curve ≤ 45 degrees (80.09%), 40 with a curve > 45 degrees (19.90%); 309 patients without calcification had a curve ≤ 45 degrees (88.28%), and there were 41 patients with a curve > 45 degrees (11.71%). The resulting relative risk

Table 1.
Clinical characteristics and results of the 551 PD patients, and the two subdivided groups (PD patients with and without calcifications).

	All n. 551 PD patients	**Group 1 n. 201 PD patients with calcified plaque**	**Group 2 n. 350 PD patients without calcified plaque**	**Statistical analysis Group-1 *versus* Group-2 P-value (t-test)**
Mean age (SD)	49.55 years (± 12.17)	49.57 years (± 12.19)	49.54 years (± 12.18)	0.977
Means of the degrees of penile curvature (SD)	35.6 degrees (± 17.67)	38.37 degrees (± 17.72)	34.09 degrees (± 17.48)	0.009
Variable	**All n. 551 PD patients**	**Group 1 n. 201 PD patients with calcified plaque n. cases (%)**	**Group 2 n. 350 PD patients without calcified plaque n. cases (%)**	**P-value (χ^2-test)**
Plaque calcification	201 (36.4)	201 (100.0)	0 (0)	/
Penile curvature	499 (90.05)	178 (88.5)	321 (91.7)	0.285
Curvature multiplanarity	169 (30.67)	69 (34.3)	132 (37.7)	0.482
Erectile dysfunction (ED)	217 (39.38)	77 (38.3)	140 (40.0)	0.763
Penile pain	296 (53.7)	113 (56.2)	183 (52.2)	0.422
Significant anxiety *	491 (89.1)	183 (91.04)	308 (88.0)	0.335
Severe anxiety *	216 (39.2)	82 (40.79)	134 (38.28)	0.623
Significant depression **	317 (57.3)	125 (62.18)	192 (54.8)	0.112
Severe depression **	25 (4.5)	7 (3.48)	18 (5.1)	0.491
Diabetes mellitus	32 (5.8)	11 (5.4)	21 (6.0)	0.947
Hypertension	103 (18.69)	47 (23.38)	56 (16.0)	0.042
Dyslipidemia	56 (10.16)	11 (5.4)	45 (12.8)	0.008 ***
Cardio-vascular diseases	41 (7.4)	13 (6.4)	28 (8.0)	0.623
Obesity	31 (5.6)	14 (6.9)	17 (4.8)	0.400

SD = standard deviation.
* *Significant anxiety is present when Generalized Anxiety Disorder-7 (GAD-7) questionnaire score > 9. Severe anxiety is present when GAD-7 score ≥ 15 (40).*
** *Significant depression is present when Patient Health Questionnaire-9 (PHQ-9) questionnaire score > 9. Severe depression is present when PHQ-9 score ≥ 20 (41).*
*** *Although the P-value was found to be significant, this must be interpreted in favor of cases without calcification; in fact, in the 201 cases with calcification, dyslipidemia was present in 11 cases (5.47% of cases), while in the 350 cases without calcification, dyslipidemia was present in 45 cases (12.8% of cases).*

of calcification on penile curvature severity was 0.22 (95% CI, 0.17 to 0.29, p < 0.0001). The Z statistic was 10.4 (p < 0.0001). It was found that calcification has an influence on penile curvature severity.

The impact of multiple calcifications on the multiplanarity of penile curvature in PD patients

There were 35 patients with multiple calcifications and multiplanarity of the curve, and 72 without multiplanarity; there were 134 patients without multiple calcifications and with multiplanarity of the curve, and there were 310 without multiplanarity.
The resulting odds ratio (OR) was 1.12 (95% CI, 0.71 to 1.76, p = 0.610). The Z-statistic was 0.509 (p > 0.05). These results indicate that calcification has no impact on the multiplanarity of curvature.

The impact of calcification on the presence of erectile dysfunction (ED) in PD patients

Using the two-tailed Mann-Whitney-Wilcoxon test the medians of the IIEF scores in patients with or without calcification were not statistically different (with calcification = 26, IQR = 2; no calcification = 26, IQR = 3, p = 0.1123) (p > 0.05).
Using the logistic regression test and considering the IIEF scores of all PD patients with or without calcification, odds ratio was 1.034, (95% CI, 0.971 to 1.102), deviance = 721.9, and p-value = 0.284 (p > 0.05).
We found no correlation between the presence of calcification and IIEF score.

The impact of calcification on the presence of penile pain in PD patients

Using the two-tailed Mann-Whitney-Wilcoxon test the medians of the VAS scores in patients with or without calcification were not statistically different (with calcification = 1, IQR = 4; no calcification = 1, IQR = 4, p = 0.536) (p > 0.05). Using the logistic regression test and considering the VAS scores of all PD patients with or without calcification, odds ratio was 1.019, (95% CI, 0.952 to 1.091), deviance = 722.7, and p-value = 0.572 (p > 0.05).
We found no correlation between the presence of calcification and VAS score.

The impact of calcification on the presence of anxiety in PD patients

Using the two-tailed Mann-Whitney-Wilcoxon test the medians of the GAD-7 scores in patients with or without calcification were not statistically different (with calcification = 14, IQR = 7; no calcification = 14, IQR = 7, p = 0.764) (p > 0.05).
Using the logistic regression test and considering the GAD-7 scores of all PD patients with or without calcification, odds ratio was 1.015 (95% CI, 0.976 to 1.056), deviance = 720.6, and p-value = 0.438 (p > 0.05).
We found no correlation between the presence of calcification and GAD-7 score.

The impact of calcification on the presence of depression in PD patients

Using the two-tailed Mann-Whitney-Wilcoxon test the

Table 2.
Results for primary and secondary endpoints of the study.

PRIMARY ENDPOINTS		IMPACT Yes or No	Statistical analysis P-value
The impact of plaque calcification on the	presence and severity of penile curvature	Yes	< 0.05
	presence and severity of erectile dysfunction	No	> 0.05
	presence and severity of penile pain	No	> 0.05
	presence and severity of anxiety	No	> 0.05
	presence and severity of depression	No	> 0.05
The impact of multiple calcifications on	penile curvature multiplanarity	No	> 0.05
SECONDARY ENDPOINTS	The impact of diabetes mellitus on the presence of calcification	No	> 0.05
	The impact of hypertension on the presence of calcification	Yes	< 0.05
	The impact of dyslipidemia on the presence of calcification	No	< 0.05 *
	The impact of cardio-vascular diseases on the presence of calcification	No	> 0.05
	The impact of obesity on the presence of calcification	No	> 0.05

The results regarding the prevalence of anxiety and depression in PD patients (secondary endpoints) are shown in Table 1.
** Although the P-value was found to be significant, this must be interpreted in favor of cases without calcification; in fact, in the 201 cases with calcification, dyslipidemia was present in 11 cases (5.47% of cases), while in the 350 cases without calcification, dyslipidemia was present in 45 cases (12.8% of cases).*

medians of the PHQ-9 scores in patients with or without calcification were not statistically different (with calcification = 12, IQR = 7; no calcification= 10, IQR = 8, p = 0.308) (p > 0.05). Furthermore, using the logistic regression test and considering the PHQ-9 scores of all PD patients with or without calcification, odds ratio was 1.015, (95% CI, 0.979 to 1.052), deviance = 719.4, and p-value = 0.404 (p > 0.05).
We found no correlation between the presence of calcification and PHQ-9 score.

Diabetes, hypertension, dyslipidemia, cardiovascular disease, obesity in PD patients with plaque calcification
In our study 32 PD patients had diabetes mellitus (5.8%); 26 were affected by type-2 diabetes; and 6 were affected by type-1 diabetes. The resulting OR was 0.90 (95% CI, 0.428 to 1.922, p = 0.799) and Z-statistic was 0.255 (p > 0.05). After separately studying the impact of type-1 and type-2 diabetes on the presence of calcification, the result of the p-value was always > 0.05 (0.494 and 0.536, respectively).
These results indicate that diabetes mellitus has no impact on calcification.
Among the 551 PD patients, 103 had hypertension (18.69%). In the 201 cases with calcification, hypertension was present in 47 cases (23.38% of cases), while in the 350 cases without calcification, hypertension was present in 56 cases (16.0% of cases). The resulting OR was 1.6 (95% CI, 1.038 to 2.473, p = 0.03) and the Z-statistic was 2.129 (p < 0.05). These results indicate that calcification is associated with the presence of hypertension.
In our study 56 PD patients had dyslipidemia (high cholesterol and/or hypertriglyceridemia) (10.16%).
The resulting OR was 0.39 (95% CI, 0.191 to 0.777, p = 0.007) and Z-statistic was 2.68 (p < 0.05). P-value was significant, but odds was lower in cases with calcification; in fact, in the 201 cases with calcification, dyslipidemia was present in 11 cases (5.47% of cases), while in the 350 cases without calcification, dyslipidemia was present in 45 cases (12.8% of cases).
These results indicate that dyslipidemia has no positive impact on calcification.
Among the 551 PD patients, 41 had cardiovascular diseases (7.44%). The resulting OR was 0.79 (95% CI, 0.402 to 1.572, p = 0.510) and Z-statistic was 0.659 (p > 0.05). These results indicate that cardiovascular diseases have no impact on calcification.
In our study 31 PD patients were obese (5.6%). The resulting OR was 1.46 (95% CI, 0.706 to 3.042, p = 0.303) and Z-statistic was 1.028 (p > 0.05). These results indicate that obesity has no impact on calcification.
The impact of PD on anxiety and depression.

Anxiety
- 4 out of 551 patients (0.7%) had minimal anxiety (GAD-7 scores ranging from 0 to 4).
- 54 out of 551 patients (9.8%) had mild anxiety (GAD-7 scores ranging from 5 to 9).
- 275 out of 551 patients (49.9%) had moderate anxiety (GAD-7 scores ranging from 10 to 14).
- 216 out of 551 patients (39.2%) had severe anxiety (GAD-7 scores ranging from 15 to 21).

The prevalence of "significant anxiety" was 89.1% (491 out of 551 patients) (40).

Depression
- 63 out of 551 patients (11.4%) had minimal depression (PHQ-9 scores ranging from 0 to 4).
- 171 out of 551 patients (31.0%) had mild depression (PHQ-9 scores ranging from 5 to 9).
- 201 out of 551 patients (36.4%) had moderate depression (PHQ-9 scores ranging from 10 to 14).
- 91 out of 551 patients (16.5%) had moderately severe depression (PHQ-9 scores ranging from 15 to 19).
- 25 out of 551 patients (4.5%) had severe depression (PHQ-9 scores ranging from 20 to 27).

The prevalence of "*significant depression*" was 57.3% (317 out of 551 patients) (41).
The prevalence of severe anxiety and severe depression in PD patients with or without plaque calcification are shown in Table 1.
Results for the primary and secondary endpoints of the study are shown in Table 2.

Discussion

In our study, in 551 patients affected by Peyronie's disease, plaque calcification was present in 36.4% of cases. Our results do not differ much from the percentage detected by *Levine et al.* (34.1%) (24). Unfortunately, the literature lacks studies focusing on the prevalence of calcification in Peyronie's disease.

Two other classifications of penile calcifications in PD patients have been proposed. The classification proposed by Bekos et al. categorizes patients according to the severity of calcification and echogenicity. This classification divides patients into three groups: A, B, and C. Group A: a solitary hyperechoic zone without acoustic shadow; group B: multiple scattered moderately hyperechoic calcifications with acoustic shadow; and group C: densely calcified hyperechoic plaques with acoustic shadow (42). *Pawlowska* and *Bianek-Bodzak* proposed the following classification of PD plaques: type 1 = thickening of the tunica albuginea without acoustic shadow; type 2 = moderately calcified plaque with a typical acoustic shadow; and type 3 = severely calcified plaques with complete shadowing (43).

However, we believe that the classification proposed by *Levine et al.* is more precise because it mainly considers the size of the calcifications. Having stratified the calcifications of 201 PD patients according to the classification proposed by *Levine et al.* (24), we found the following results: grade 1 calcifications, 23 cases (11.4%); grade 2 calcifications, 130 cases (64.6%); and grade 3 calcifications, 48 cases (23.8%). The calcification was < 15 mm (grade 1 and grade 2) in 76.1% of cases.

Our results differ markedly from those reported in *Levine's* study that reported grade 1 calcifications in 40.8%, grade 2 calcifications in 27.6%, and grade 3 calcifications in 31.6%. We believe that the difference in the results of the two studies is due to the numerical difference in the two samples (201 *versus* 98 cases of *Levine's* study) (24).

However, when examining the two studies, we noticed that grade 3 calcifications are less frequent (our study 23.8%; *Levine's* study 31.6%) than the total sum of grade 1 and grade 2 calcifications.

In our study, it was found that calcification has an influence on the presence and severity of penile curvature ($p < 0.05$); this correlation is also present in the study conducted by *Levine et al.* (24).

Our study found that the presence of calcifications in PD patients has no influence on the presence of erectile dysfunction and its severity, penile pain and its severity, and anxiety and depression and their severity. Our study also found that the presence of multiple calcifications in PD patients has no influence on the presence of multiplanarity of penile curvature.

In *Levine's* study, the correlation between plaque calcification and multiplanar penile curvature or erectile dysfunction was not investigated. Also in *Levine's* study, no correlation was found between plaque calcification and penile pain (24), as well as no correlation was found between plaque calcification and emotional distress/anxiety (24).

Our study found that the presence of calcification in PD patients is not influenced by the presence of diabetes mellitus, dyslipidemia, cardiovascular diseases, and obesity. Our results differ from those of the study by *Levine et al.* where diabetes mellitus was found to influence the presence of plaque calcification (*Levine* study, $p = 0.012$ *versus* our study, $p = 0.799$) (24).

However, our study found that calcification in PD patients is associated with the presence of hypertension ($p = 0.03$); in contrast, in *Levine's* study, hypertension did not appear to influence the presence of plaque calcification ($p = 0.865$) (24).

The prevalence of "*significant anxiety*" that we have found in PD patients (89.1% of cases) appears higher than the results of some studies which more generically refer to "*distress*" and "*emotional*" difficulties (80-81% of cases) (44, 45). In *Levine's* study, the presence of "*emotional distress*" was found in 83% of cases of PD patients (24).

In our study, we found the presence of "*significant depression*" in 57.3% of PD patients; this percentage is higher than that documented in *Nelson's* studies (48%) (46, 47). It is most likely that the greater number of cases in our study (551 cases) compared to the 92 cases in Nelson's study caused the disparity in the two results.

Conclusions

Our results indicate that in patients with Peyronie's disease, plaque calcification is present in more than 1/3 of cases (36.4% of cases); this does not differ much from the data in the literature. We found that the size of the plaque calcification was < 15 mm in the majority of cases. In our study, it was found that plaque calcification has an influence on the presence and severity of penile curvature. We also found that calcification in PD patients is associated with the presence of hypertension.

Our results indicate that anxiety and depression have an important prevalence in PD patients; moreover, we are especially alarmed by the high percentages of "*severe*" anxiety (39.2%).

We therefore believe that psychotherapy should be associated with the treatment of these patients in order to improve their quality of life and to avoid dropping out of ongoing medical therapies.

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