DOI: 10.4081/aiua.2024.12690

ORIGINAL PAPER

Combining ultrasound and elastography for the detection of a non-palpable, non-sonographically visualized Peyronie's plaques. Our experience

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Summary ***Background: B-mode ultrasound (US) medical imaging is very effective in localizing and describing Peyronie's disease (PD). Moreover, elastography is a new technique used to evaluate tissue elasticity to detect penile Peyronie's plaques that are not visible using standard B-mode US.***

Objective: The main objective of this study was to evaluate the diagnostic efficacy of real-time elastography (RTE) or strain elastography (SE) in PD patients and to determine whether its combined use with standard US improved diagnostic accuracy. Additionally, this study aimed to assess whether RTE was useful for monitoring PD patients undergoing conservative treatment.

Methods: A group of 37 patients with PD in the active phase was selected based on US examination showing isoechoic or hypo-isoechoic plaques, with or without associated hyperechoic or calcified plaque areas. All patients underwent traditional US combined with RTE before starting conservative treatment with antioxidants, during treatment and after treatment. After each examination with RTE, a specific "Strain Ratio"(SR) was used to identify the specific elasticity of the tissue.

Results: Using B-mode US with RTE, we detected all 13 non-palpable penile plaques present in the 37 PD patients (100% of cases). Using only B-mode US, we detected only 8 of the 13 non-palpable plaques (61.5% of cases). The Deformation Index (DI) of the plaque decreased during and after treatment in all cases, indicating that RTE is effective for monitoring conservative PD treatment. A statistically significant correlation was found between the DI and plaque volume in all patients ($p = 0.002$).

Conclusions: Our study has shown that the combination of US and RTE methods allowed for a more accurate diagnosis in PD patients.

KEY WORDS: B-mode ultrasound; Peyronie's disease; Penile plaques; Elastography; Strain imaging.

Submitted 26 May 2024; Accepted 13 June 2024

INTRODUCTION

Peyronie's disease (PD) is a pathological condition that affects the tunica albuginea of the penis in males with a genetic predisposition, causing the formation of fibrous plaques (1, 2). The occurrence of PD is more common in Western countries (3.2-13.1%) and less common in Asian countries (0.6-5.0%) and among populations of black African origin (0.1-3.5%). These differences are probably related to genetic, environmental, and lifestyle factors (3-12). It is hypothesized that the prevalence of PD in men is much higher due to the underreporting of symptoms, as patients may feel embarrassed and choose not to report their embarrassing problem (3). PD can result in penile deformity, penile pain, erectile dysfunction, and psychological distress (anxiety and depression); penile deformities may involve curvature, shortening, torsion, indentations, and hourglass deformity (13-17). The precise cause of PD is not completely understood, but it is generally believed to be initiated by a local injury (18-20). Although it can be triggered by traumatic sexual experience or injury, 70% of cases have no specific cause, and patients do not remember a traumatic event (21). When an injury occurs, fibrin is deposited and a small hematoma forms. In people without a genetic predisposition to the disease, the hematoma is absorbed back into the penile corpora cavernosa. In individuals with a genetic predisposition, the hematoma causes the activation of inflammatory cells and proinflammatory cytokines, resulting in the formation of chronic inflammatory tissue that progresses to fibrosis over time (22-24). In the last two decades, studies have demonstrated that *oxidative stress* (OS) is crucial in the development of plaque and the progression of this disease (22-29).

Diagnosing PD involves a medical history, physical examination, penile palpation, photographic documentation of penile curvature, dynamic penile color Doppler US, computed tomography, and Magnetic Resonance Imaging (30-32).

Computed tomography and radiography are excellent at visualizing penile plaque calcifications, while MRI is accurate at identifying plaques in complex locations, such as the corporal septum.

B-mode US medical imaging is highly useful for localizing and characterizing Peyronie's plaque. Regarding the ultrasound appearance, penile plaques are typically observed as localized areas of hyperechoic thickening of the tunica albuginea, showing strong echogenicity with significant attenuation of the acoustic beam.

Moreover, elastography is a new and emerging method

that studies the elastic properties of tissue to identify penile plaques that may not be visualized with traditional B-mode US studies. Furthermore, elastography is the most suitable imaging modality in PD because it allows for non-invasive highlighting of penile plaques and monitoring of the therapeutic response to various treatments. In addition, elastography has recently been suggested as a diagnostic tool for PD. Palpation of the penis is essential in the evaluation of the patient, as most patients with Peyronie's disease have a palpable plaque that is clearly distinguishable from the rest of the penile corpora cavernosa. However, documentation with a diagnostic imaging method is often necessary to support the clinical diagnosis. B-mode US examination can identify the location, number, size, and echogenicity of the plaques.

The main bias and disadvantage of this method is that traditional US can only detect between 40% and 84.2% of palpable plaques (33-36). Elastography is a non-invasive technique that uses an ultrasound probe to measure the mechanical properties of tissue, which can be affected by a disease process, making the tissue more rigid.

The different levels of tissue elasticity under the pressure of the ultrasound probe are expressed in a more or less relevant way and evaluated using a color scale.

Elastography diagnostic approaches were first developed at the end of the last century and, subsequently, numerous scientific studies have been published (37).

Elastography is primarily used to diagnose soft tissue pathologies in the liver, breast, prostate, thyroid, pancreas, nerves, tendons, muscles, and other conditions. Furthermore, elastography has also been suggested for studying PD (32-36, 38-44).

The World Federation of Ultrasound Medicine and Biology categorized "*elastographic techniques*" as *strain elastography* (SE), transient elastography, and *acoustic radiation force impulse* (ARFI). The ARFI techniques can be subcategorized into point *shear wave elastography* (SWE), 2D SWE, and 3D SWE techniques (45).

SE, also known as *real-time elastography* (RTE), is a qualitative method that assesses the relative stiffness of various tissues and examines how tissues can deform when subjected to external forces and then return to their original shape. SE assesses tissue deformation using manual compression or natural motion. SE measures the strain caused by "*quasi-static*" methods, such as manual compression or cardiovascular/respiratory pulsation, and displays the distributions of the strain or normalized strain values within the *region of interest* (ROI). Tissue deformation can be achieved by manually applying micro-pressure with the ultrasound probe or by using ultrasound pulses of appropriate intensity (44). In the second method of excitation, the ultrasound remains stationary while tissue displacement is induced via internal physiological movements such as cardiac and arterial pulsations and respiratory motion. In both cases, the ultrasound images are compared before and after the compression, and the equipment produces a color map that indicates the relative elasticity of the various tissue components, ultimately displaying a specific *Strain Ratio* (SR). SR is calculated by comparing the strain index of a lesion to that of healthy tissue at the same level. SR therefore indicates a measurement of the stiffness of the sampled tissue.

SE measures the relative stiffness of tissues within the elastographic *region of interest* (ROI) overlaid on a B-mode US image; therefore, the ROI must be accurately aligned with the Peyronie's plaque. The color map is shown in real time, overlaid on an ultrasound image of the tissues being examined. Usually, the color blue is utilized to indicate low strain (i.e., stiff tissue), while red is used to indicate high strain (i.e., soft tissue), although the exact color scale may differ depending on the manufacturer of the ultrasound equipment (35). Strain elastography is also used for the diagnostic study of PD. In the literature, there are four articles on this topic (33-35, 42). The objective of this study was to evaluate the diagnostic efficacy of RTE in patients with Peyronie's disease and to determine whether its combined use with traditional ultrasound imaging improves diagnostic accuracy. This study aimed to determine whether this diagnostic combination could detect nonpalpable and/or isoechoic Peyronie's plaques with or without hyperechoic or calcified plaque areas, which cannot be detected with a simple standard US examination. This study also aimed to evaluate whether US associated with RTE was effective for monitoring patients with PD undergoing conservative treatment.

The secondary objective of this study was to examine the relationship between plaque stiffness and the degree of curvature and plaque volume, as well as to detect the prevalence of anxiety and depression in patients with PD.

Materials and methods

The authors conducted this study by collecting and analyzing existing data of 249 patients who visited our Peyronie's Care Center and underwent US and elastography of the penis from January 1, 2018, to December 31, 2023, and were found to be affected by PD.

After applying the inclusion and exclusion criteria, 212 PD patients who were in the stabilized or active phase of the disease and presented exclusively hyperechoic and/or calcified plaques were excluded from the main study.

Objectives

The main objective of this retrospective study was to assess the diagnostic efficacy of RTE, also known as SE, in patients with *Peyronie's disease* (PD) and investigate if its integration with conventional *ultrasound* (US) imaging enhances diagnostic precision. Since this study primarily aimed to determine whether the diagnostic combination of US and RTE could detect non-palpable Peyronie's plaques that cannot be detected via physical examination of the PD patient or via a simple standard US, inclusion criteria were determined for the in-depth study of those PD patients in whom RTE could potentially increase the diagnostic level.

Evaluation and diagnosis

The diagnosis of Peyronie's disease was made for all patients after conducting the following assessments: palpation of the penis; photographic documentation of penile deformity (according to Kelâmi) with a goniometric measurement of the angulation; penile US with RTE or penile color Doppler US with RTE (only for patients with

associated erectile dysfunction) with plaque measurements (in three dimensions, in mm) and volume calculation (mm3) using the ellipsoid formula (volume = 0.524 × length × width × thickness); and completion of the *International Index of Erectile Function* (IIEF) questionnaire for measuring erectile function, the visual analog scale (VAS) questionnaire for measuring pain, the *Generalized Anxiety Disorder Questionnaire-7* (GAD-7, for anxiety), and the *Patient Health Questionnaire-9* (PHQ-9, for depression) (46-52). Regarding the last two questionnaires, we decided to also study the psychological condition of these patients, as we believe that psychological distress is a symptom of PD, just like curvature, pain, and erectile dysfunction.

To identify and confirm the presence of penile plaque, along with its location and volume, we subjected all 37 patients to combined US and RTE examination of the penis at the time of initial diagnosis and during the planned follow-up assessments during conservative treatment. A single andrologist operator performed and evaluated conventional US and SE of the penis on all patients in one session using the same ultrasound device, the *Philips Affinity 70 G*, and a high-frequency linear array transducer, the *Philips Linear Probe L12-5* (*Philips, Washington, United States*). The elasticity values were calculated and color-coded to represent tissue elasticity. The color scale ranged from red (i.e., soft tissue) to blue (i.e., stiff tissue), with components showing average strain displayed as green. Finally, a calculation indicating a specific SR was displayed on the equipment monitor. The areas included in the Strain Ratio calculation are selected by the operator by pointing the probe at the stiffest area and then at the normal tissue (soft).

Inclusion criteria

Patients with Peyronie's disease in the active phase who underwent US examination and presented isoechoic or hypo-isoechoic plaques, with or without associated hyperechoic or calcified plaque areas.

Exclusion criteria

Patients with Peyronie's disease in the stabilized or active phase who underwent US examination and presented exclusively hyperechoic and/or calcified plaques.

After applying the inclusion and exclusion criteria, 212 PD patients who were in the stabilized or active phase of the disease and presented exclusively hyperechoic and/or calcified plaques were excluded from the main study. Finally, a group of 37 patients with Peyronie's disease in the active phase was selected based on US examination and RTE (in the same diagnostic session) showing isoechoic or hypo-isoechoic plaques, with or without associated hyperechoic or calcified plaque areas.

Treatment and follow up

As previously indicated, in this study, we specifically focused on the analysis of data relating to US and RTE combination examinations in patients with PD to evaluate whether US associated with RTE is effective for monitoring PD patients undergoing conservative treatment. Therefore, after the first visit of the patients to our andrological center, we performed a combined diagnostic US and RTE on 37 PD patients before starting conservative treatment with antioxidants. Patients underwent US and RTE every six months during and after treatment. Conservative treatments to which these patients were subjected were retrospectively identified from the data in our clinical archive and are not the subject of this article. Some of these patients have undergone multiple treatment cycles. For completeness, we describe our standard conservative medical treatment: oral L-carnitine 1000 mg + propolis 700 mg + silymarin 400 mg + coenzyme Q-10 100 mg + bilberry 180 mg + ginkgo biloba 240 mg + vitamin E 48 mg + vitamin C 50 mg + superoxide dismutase 11000 IU/g 10 mg/daily and topical diclofenac gel 4%/2 times daily + peri-plaque penile injections (only in the case of plaques with volume ≥ 100 mm^3) with pentoxifylline 100 mg (30 G needle) every month for 6 months.

Statistical analysis

We utilized *CalculatorSoup®* software (*version of Mar 07, 2023, Ashland, MA,USA*) to conduct the statistical analysis involving the calculation of standard deviation and mean, median, and *interquartile range* (IQR). The Pearson correlation coefficient was calculated using Statistics Kingdom statistical software (*version 2017, Melbourne, Australia, http://www.statskingdom.com*) and *Excel* (*version 2011, MS Office, Redmond, WA, USA*). In the statistical analyses, a significance level of 5% for alpha error (p-value < 0.05) was considered to demonstrate statistical significance.

This study was carried out in accordance with the principles outlined in the Declaration of Helsinki (*Fortaleza, 2013*). All participants were contacted and gave their informed consent for the study. However, sensitive data were anonymized in accordance with privacy regulations as per legislative decree 10 August 2018, n. 101 adapted to the *General Data Protection Regulation/GDPR* (*Official Gazette of the Italian Republic, General Series n. 205, dated 4 September 2018*).

Results

The 37 patients with Peyronie's disease who were selected for this study (with isoechoic or hypo-isoechoic plaques, with or without associated hyperechoic or calcified plaque areas) were aged between 23 and 74 years, with a mean age = 51.3 years (SD ± 14.7).

The plaque volume in the 37 selected patients ranged from 11.5 to 2660 mm^3.

Table 1 shows the physical and echo-elastographic characteristics of the plaques of the 37 patients.

Non-palpable plaques

Using B-mode US with RTE, we detected all 13 non-palpable penile plaques present in the 37 selected PD patients (100% of cases). Using only B-mode US, we detected only 8 of the 13 non-palpable plaques (61.5% of cases).

Soft plaques

When using US examination on 37 PD patients, only one out of seven barely palpable (soft) plaques were detected (14.2%). However, with RTE, all seven soft plaques were detected (100%).

Table 1.
Physical and echo-elastographic characteristics of the plaques of the 37 patients.

Palpatory features of the plaque	N. cases (out 37) (%)
Non-palpable	13 (35.1)
Soft	7 (18.9)
Fibrous	11 (29.7)
Fibrocalcific	6 (16.2)
Ultrasound imaging of the plaque	
Hypo-isoechoic	12 (32.4)
Isoechoic	10 (27.0)
Iso-hyperechogenicity (mixed plaque)	1 (2.7)
Iso-hyperechogenicity associated with calcification (mixed plaque)	3 (8.1)
Hypo-isoecogenicity associated with hyperechogenicity (mixed plaque)	2 (5.4)
Hypo-isoecogenicity associated with calcification (mixed plaque)	9 (24.3)
Plaque volume (mm^3)	
Up to 100	6 (16.2)
From 101 to 300	10 (27.0)
From 301 to 500	5 (13.5)
From 501 to 1000	10 (27.0)
From 1001 to 2000	5 (13.5)
> 2000	1 (2.7)
Strain Ratio of the plaque detected via strain elastography (SE)	
> 1 to 2	18 (48.6)
> 2 to 3	16 (43.2)
> 3 to 4.4	3 (8.1)

The Strain Ratio is considered pathological when it is greater than 1.

Isoechoic or hypo-isoechoic plaques

When using US examination, 29 out of 37 isoechoic or hypo-isoechoic plaques, with or without associated hyperechoic or calcified plaque areas, were identified (78.3%), while the remaining 8 plaques (21.6%) were not identified. Specifically, the eight plaques that were not identified were completely isoechoic. Therefore, using US, entirely isoechoic plaques were found in only 2 out of 10 cases (20%). All 37 plaques were instead identified with RTE (100%).

Ultrasound findings in relation to the volume of PD plaques

Out of 21 plaques with a volume up to 500 mm^3, 19 plaques (90.4%) were identified, and 2 plaques (9.5%) were not identified using only US, while all 21 plaques were identified with RTE (100%). All 16 remaining larger PD plaques over 500 mm^3 were identified with US (100%) and also with RTE.

A statistically significant correlation was found between the Deformation Index (Strain Ratio) and plaque volume in the 37 selected patients, p-value = 0.002 ($p < 0.05$). Figure 1 shows the graph that highlights this correlation.

No statistically significant correlation was found between the Strain Ratio and the degree of angulation of the penile curvature of the 37 selected patients: r = 0.2848, r2 = 0.08109, p-value = 0.08759 ($p > 0.05$).

In Figure 2 below, we present four examples of plaques that were not detected with traditional US but were instead detected with RTE. Please note that during each elastography scan, circles (light blue color) were placed by the operator on the stiffer (blue) and normal (soft) areas corresponding to the ROI. At the end of this procedure, the elastography software provided the Strain Ratio after the relative calculation.

Treatment and follow up

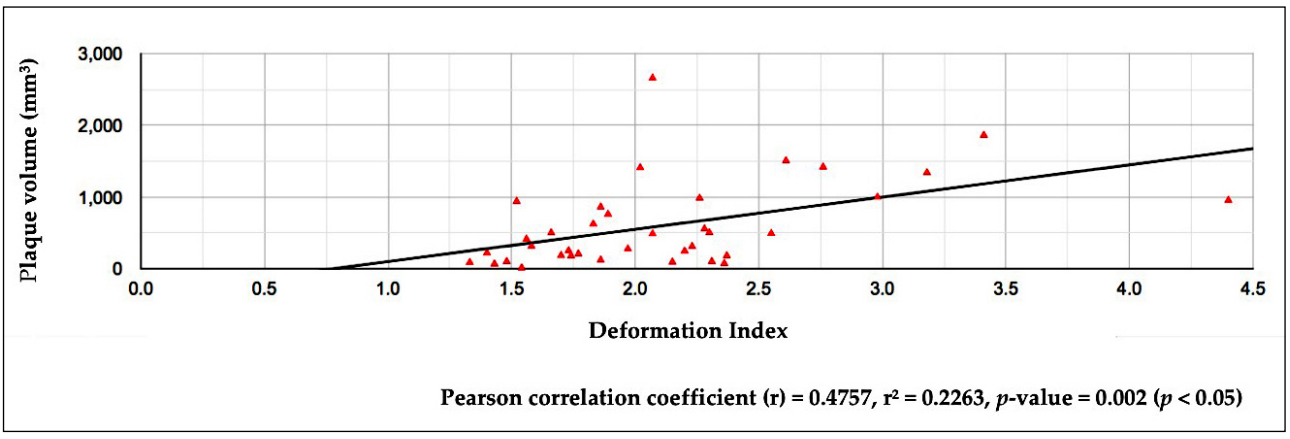
Figure 3 shows the Deformation Index (or Strain Ratio) values of the plaques before, during, and after the treatments The results presented demonstrate that the Strain Ratio decreased during the monitoring at each follow-up assessment.

The Strain Ratio value is considered pathological when it is greater than 1. RTE measurements were performed every 6 months during the course of conservative treatment. The 37 selected patients underwent multiple treatment cycles, ranging from two to four cycles. Some patients underwent a greater number of follow-up assessments because they were observed before the others.

Psychological assessment

The results of the GAD-7 and PHQ-9 questionnaires showed that in the 37 patients with Peyronie's disease, significant anxiety was present in 70.2% of cases and severe anxiety in 18.9% of cases. Significant depression was present in 45.9% of cases, with no cases of severe depression.

Figure 1.
Graph highlighting the relationship between plaque volumes and Deformation Index (or Strain Ratio) values.



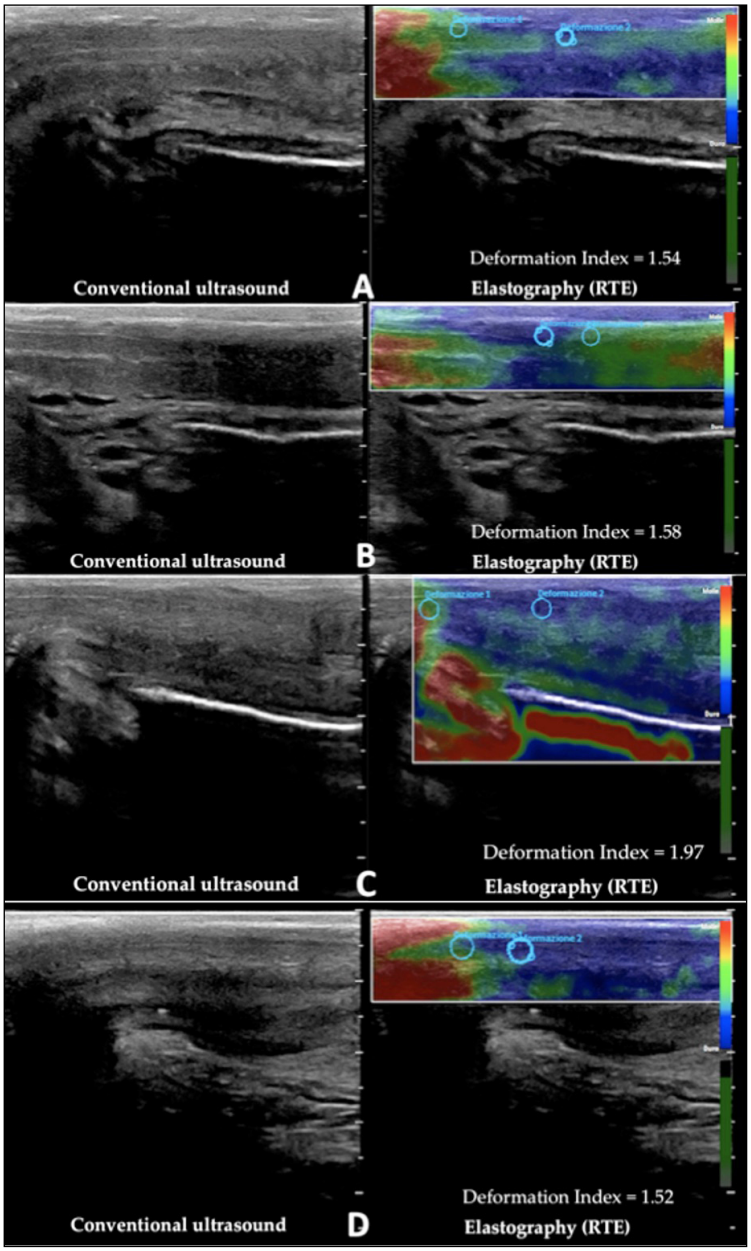


Figure 2.
Examples of four non-palpable and isoechoic Peyronie's plaques that were not detectable with traditional ultrasound (US) but identified with real-time elastography (RTE).

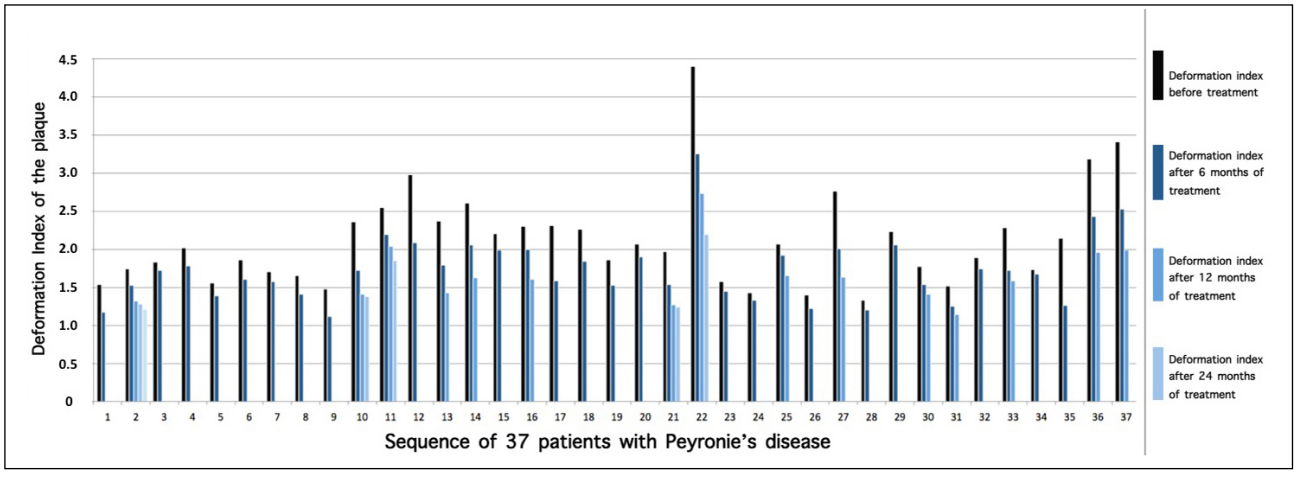
Discussion

The authors specify that, for the elastography study, they preferred to use SE, also known as RTE. SE is preferable for studying superficial pathologies such as plaques that develop in Peyronie's disease because it has high spatial resolution. In fact, in this pathology, SE, owing to its high sensitivity, is important for visualizing the area of fibrosis associated with it, even in the absence of detectable B-mode images. We should also add that in order to use SE correctly, it is essential for the procedure to be conducted by an experienced operator and to use the latest technology to achieve the correct visualization of Peyronie's plaque.

Using B-mode US with RTE, we detected all 13 non-palpable penile plaques present in the 37 selected PD patients (100% of cases). Using only B-mode US, we detected only 8 of the 13 non-palpable plaques (61.5% of cases). In 11 out of these 13 cases, a penile curvature was present. Furthermore, in two of these patients with non-palpable penile plaque who did not report penile pain or erectile dysfunction problems, there was a penile deformity, including both penile curvature and shortening. In these two cases the ultrasound diagnosis would have been completely negative without performing RTE. We believe that the penile plaques could not be palpated, mainly due to their small size, which in most cases never exceeded a volume of 300 mm^3.

In a study by *Dell'Atti et al.*, using only B-mode

Figure 3.
Deformation Index (Strain Ratio) values of penile plaques in 37 patients with Peyronie's disease, before and after treatment.



US to detect non-palpable Peyronie's plaques, small plaque volumes and fairly similar ultrasound features were found; however, they found 41 non-palpable penile plaques in 386 patients with PD (10.6% of cases) (53). In our study, using only B-mode US, we detected non-palpable plaques in 8 out of 37 cases (21.6% of cases). Regarding the incidence of non-palpable plaques in patients with Peyronie's disease, other authors using only B-mode US studies, although with different ultrasound machines, have reported detection rates of 6.0%, 22.5%, and 32.4% in PD cases (33, 54, 55).

Referring to the ultrasound appearance of the plaques (isoechoic or hypo-isoechoic, with associated hyperechogenicity or calcification) using only B-mode US, we detected penile plaques in 29 out of 37 cases (78.3% of cases). However, when using B-mode US with RTE, we detected all 37 penile plaques (100% of cases) in the respective 37 patients.

Penile plaques appear as localized areas of thickening in the tunica albuginea on ultrasound, showing strong echogenicity and significant attenuation of the acoustic beam. However, in our study, almost all noncalcified penile plaques were found to be isoechoic or slightly hyperechoic compared to the surrounding cavernous tissue. The peculiarity of our results is due to the selection of patients due to the inclusion criteria of our study.

Nevertheless, there are few articles in the literature that specifically discuss the possibility of the existence of isoechoic plaques (56-58).

In our study, the isoechoic penile plaques detected using only B-mode US were only 2 out of 10 (20% of cases). Instead, using B-mode US with RTE, we detected all 10 isoechoic penile plaques (100% of cases) in the respective 10 patients. However, when the penile plaques were not isoechoic, B-mode US was consistently able to detect all the penile plaques. This demonstrates that when B-mode US is combined with RTE, the diagnostic accuracy is significantly improved.

Similar results were obtained by other authors who used elastography associated with conventional B-mode US (33-36, 42). Our study has shown a strong statistical correlation between the Strain Ratio values of the plaque and its volume (p-value = 0.002). Of course, it seems logical that increasing the size of the plaque also increases its rigidity; however, this correlation had never been demonstrated in Peyronie's disease.

Otherwise, we did not find any statistically significant correlation between the Strain Ratio and the degree of angulation of the penile curvature angle ($p > 0.05$). It should be noted that, in our case series, 3 out of 37 patients did not have penile curvature due to the central location of the plaque (between the two corpora cavernosa), and this may have resulted in the absence of this correlation. However, other authors, using a different method of elastography (*shear wave elastography*, SWE), have shown a relationship between the stiffness of the selected plaque area (expressed in kPa) and the curvature angle of the penis (41).

Our study has shown that RTE combined with traditional US is very useful for monitoring patients with Peyronie's disease during conservative treatment with antioxidants and antifibrotics. In this way, in addition to the reduction in plaque volume, which we could have demonstrated using traditional US alone, we were also able to observe the progressive reduction in the stiffness of the affected area. A very similar observation has been made by other authors who, using another elastography method (SWE), have analyzed the changes in elastography after administering a compound made up of *Ecklonia bicyclis*, *Tribulus terrestris*, and water-soluble *Chitosan (Biovis)* (39).

After researching the prevalence of anxiety in patients with PD, we found that 70.2% of cases had significant anxiety, and 18.9% of cases had severe anxiety. There are no precise data in the literature regarding the incidence of anxiety symptoms during PD; however, a study by Smith and colleagues found that 81% of PD patients reported "*emotional difficulties*" (59). After researching the prevalence of depression in PD patients, we found that significant depression was present in 45.9% of cases, with no cases of severe depression. Nelson and colleagues found that 48% of PD patients exhibited clinically significant depression (14, 60). We believe that depressive and anxiety symptoms, if not investigated in PD patients using specific questionnaires, may remain unknown or at least be underestimated in terms of severity and prevalence. Our data on the prevalence of anxiety in patients with PD confirm that the anxious and depressive states represent important symptoms of PD, as well as penile pain, penile curvature/deformation, and erectile dysfunction. In uro-andrological clinical practice, psychologists should be involved in providing supportive treatment to patients with PD. In this way, we could reduce the psychological impact of PD, which has been described by some important authors as a psychologically and physically devastating disease (61-65). Although our findings are quite interesting, the limitation of our study is that the sample size was not very large. However, our limited sample was determined by very selective inclusion criteria.

Conclusions

RTE is a modern non-invasive technique that can accurately identify penile plaques in patients with Peyronie's disease, complementing B-mode US. Furthermore, RTE is very useful for diagnosing the disease at an earlier stage (isoechoic plaque) than B-mode US alone. Additionally, RTE is especially valuable when palpation and B-mode US are unable to identify a plaque. RTE can also accurately assess plaque stiffness, size, and volume. RTE offers an additional method for uro-andrologists to monitor conservative treatment in patients with Peyronie's disease. More extensive prospective studies are needed to determine the diagnostic accuracy and clinical utility of this imaging technique.

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Conflict of interest: The authors declare no potential conflict of interest.