

## Peer Review File

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### Reviewer A

The article submitted is interesting and concerns a problem that unfortunately is increasingly more and more feedback. Authors are advised to make the objectives clearer, particularly in the abstract. Also please make the table legends more readable. It would also be useful to enrich the discussion with the following articles:

Calace FP, Napolitano L, Langella NA, Baron B, Trama F. Peyronie's disease: where are we at? J Basic Clin Physiol Pharmacol. 2022 Nov 9;34(1):1-4. doi: 10.1515/JBCPP-2022-0206. PMID: 36351265.

Trama F, Illiano E, Iacono F, Ruffo A, di Lauro G, Aveta A, Crocetto F, Manfredi C, Costantini E. Use of penile shear wave elastosonography for the diagnosis of Peyronie's Disease: a prospective case-control study. Basic Clin Androl. 2022 Aug 16;32(1):15. doi: 10.1186/S12610-022-00164-W. PMID: 35971058; PMCID: PMC9380314.

**Comment 1:** Authors are advised to make the objectives clearer, particularly in the abstract.

**Reply 1:** Thank you for this feedback. We appreciate the importance of a clear objective, and therefore, we have modified this in the abstract and introduction and included below:

**Changes in the text:**

Abstract, lines 36-39: Our study objective was to measure the rate of the development of Peyronie's disease among patients that receive penile rehabilitation (PR) regimen prior to and immediately after radical prostatectomy.

Introduction, lines 91-97:

our primary objective was to evaluate the rate of PD among our prostate cancer patients who have undergone a formal, multi-modal PR program that utilizes oral pharmacological agents (PDE5 inhibitors and L-citrulline, and ICI if indicated), mechanical intervention with vacuum erectile device (VED), and lifestyle counseling.

**Comment 2:** Also please make the table legends more readable.

**Reply 2:** We have revised Table 1 for numbers to be more clear. We hope you find this easier to read.

**Changes in the text:** See Table 1.

**Comment 3:** It would also be useful to enrich the discussion with the following articles: Calace FP, Napolitano L, Langella NA, Baron B, Trama F. Peyronie's disease: where are we at? J Basic Clin Physiol Pharmacol. 2022 Nov 9;34(1):1-4. doi: 10.1515/JBCPP-2022-0206. PMID: 36351265.

Trama F, Illiano E, Iacono F, Ruffo A, di Lauro G, Aveta A, Crocetto F, Manfredi C,

Costantini E. Use of penile shear wave elastosonography for the diagnosis of Peyronie's Disease: a prospective case-control study. *Basic Clin Androl.* 2022 Aug 16;32(1):15. doi: 10.1186/S12610-022-00164-W. PMID: 35971058; PMCID: PMC9380314.

**Reply 3:** Thank you for your suggestions. We also believe that these citations could help the readers to learn more about PD and the issues discussed in this paper. We have added the citations to our manuscript.

**Changes in the text:** Please see line 65-69 and lines 192-196.

## **Reviewer B**

The authors conduct a retrospective analysis of a specific cohort to assess the incidence of Peyronie's disease. Some major issues are needed:

As long and patients with previous ED were excluded, how was ED pre and postop measured? Any validated tools?

Methods section is detailed about the rehabilitation therapy but scarce about PD diagnosis of the cohort. How were patients assessed and diagnosed as PD? Kelami test, penile doppler, on-site ICI test? If only curvature not previously present reported by the patient, were those without proper rigidity excluded for the analysis, as proper curvature assessment is not possible?

Lines 109-130 of the discussion fit better in the introduction.

Control appropriate referencing (page 4, line 94)

**Comment 4:** As long and patients with previous ED were excluded, how was ED pre and postop measured? Any validated tools?

**Reply 4:** Thank you for this question. We excluded 3 patients that were previously diagnosed with PD at our institution. We did not review previous diagnoses of ED pre and post-radical prostatectomy in this manuscript. All patients who follow-up with the Men's health team discuss their sexual function and ED with their provider. Patients have the option to fill out validated questionnaires, such as International Index of Erectile Function, but in our cohort patients chose to not fill out surveys and preferred to speak with their doctor or APP.

**Changes in the text:** N/A

**Comment 5:** Methods section is detailed about the rehabilitation therapy but scarce about PD diagnosis of the cohort. How were patients assessed and diagnosed as PD? Kelami test, penile doppler, on-site ICI test? If only curvature not previously present reported by the patient, were those without proper rigidity excluded for the analysis, as proper curvature assessment is not possible?

**Reply 5:** Thank you for your comment. At our clinic, PD is diagnosed based on clinical history and examination. If patient provided history of bending of the penis, or penile pain without sexual activity, then we inquired about signs and symptoms of peyronie's disease. When patients felt comfortable, we'd ask them to share photographs taken by patients of their penile curvature with an erection. We would also perform a physical exam palpating for plaque with the penis on stretch. Patients who were not achieving

rigid erections were not explicitly excluded from this study but if they did not have demonstrable curvature and a palpable plaque, they were not diagnosed with peyronie's disease. We understand that this could be a limitation to the study, and therefore, we have added now added this as a limitation.

**Changes in the text:** See lines 185-189.

**Comment 6:** Lines 109-130 of the discussion fit better in the introduction.

**Reply 6:** Thank you for this suggestion. We also agree that moving the two paragraphs to introduction may be a better fit.

**Changes in the text:** See lines 64-81.

**Comment 7:** Control appropriate referencing (page 4, line 94)

**Reply 7:** Thank you for brining up to our attention. We have now addressed this.

**Changes in the text:** Please see line 114.

### **Reviewer C**

This study has investigated the incidence of PD in post prostatectomy patients who used penile rehabilitation.

[Major concerns]

1. A major weakness of this study is that it did not include patients who did not receive PR.
2. How was PD diagnosed?
  - Did you perform physical examination and ultrasound or only pictures taken by the patient?

[Minor concerns]

1. The title is a bit awkward. Edit stylishly.
2. Were there any differences in age, BMI, race, baseline IIEF (or EHS) and type of PR between PD (n=17) group and no PD group (n=564)?

**Comment 7:** How was PD diagnosed? Did you perform physical examination and ultrasound or only pictures taken by the patient?

**Reply 7:** Thank you for the question. At our clinic, PD is diagnosed based on clinical history and examination. If patient provided history of bending of the penis, or penile pain without sexual activity, then we inquired about signs and symptoms of peyronie's disease. When patients felt comfortable, we'd ask them to share photographs taken by patients of their penile curvature with an erection. We would also perform a physical exam palpating for plaque with the penis on stretch. If a patient had history consistent with peyronie's disease and a palpable plaque, then they received a diagnosis just as we would diagnoses any patient presenting to our clinic with chief complaint of penile curvature. Ultrasound is reserved only for patients that go on to receive treatment for their PD.

**Changes in the text:** N/A

**Comment 8:** The title is a bit awkward. Edit stylishly.

**Reply 8:** Thank you for the feedback. We have changed the title to: “Potential primary prevention of Peyronie’s disease post prostatectomy? Retrospective analysis of peri-operative multi-modal penile rehabilitation.”

**Changes in the text:** See above.

**Comment 9:** Were there any differences in age, BMI, race, baseline IIEF (or EHS) and type of PR between PD (n=17) group and no PD group (n=564)?

**Reply 9:** Thank you for this question. IIEF and type of PR was not evaluated for this short report. We also did not collect BMI. However, there were no statistical differences in age, race, and ethnicity among the two mentioned groups.

**Changes in the text:** N/A

#### **Reviewer D**

The authors report a lower incidence of Peyronie's disease in a relatively large number of patients undergoing penile rehabilitation after total prostatectomy, compared with previous cohorts.

As the authors also stated in their limitation, the group that did not undergo penile rehabilitation at their institution should be considered a control. The incidence of Peyronie's disease is likely to vary widely by cohort. We would very much like to await such a report from the authors' institution.

**Comment 10:** We would very much like to await such a report from the authors' institution.

**Reply 10:** Thank you for your comments. We are considering a more long-term controlled trial at our institution to help us find some additional answers, and we are also excited for the results. At this time we are unable to provide a control cohort because these are patients who had follow-up outside of our institution and therefore did not establish care with the sexual health team to initiate penile rehabilitation.

**Changes in the text:** N/A

#### **Reviewer E**

The authors present a retrospective study determining the incidence of Peyronie’s disease (PD) in post-radical prostatectomy patients that undergo penile rehabilitation (PR). They find an incidence rate of 2.9%, which is lower than a published study from 2010 (Tal et al) which found that 7.6% of patients observed to have PD one year after prostatectomy. However, their comparison to the study by Tal et al is flawed. The study by Tal et al found that white race (vs non-white, 18% vs. 7%,  $P < 0.001$ ) was predictive of PD development after RP. In the study by Tal et al 83% of the 1000 patients were

white, whereas in the present studies 67% of the 581 patients were white- which would skew the incidence of PD to a lower value. In addition, Tal et al did not consider PR as a factor in their study population.

As stated by the authors, there are no direct control or comparison groups for this study and therefore they cannot make any causation claims between PR and the incidence of PD. Without the control group they cannot make any conclusion as to the significance of the decrease in percentage of PD following RP compared to prior studies, or even if it is different to the incidence of PD in the general population.

The reference list is not numbered.

In the previous Tal et al studies over time there is an increase in the number of patients that develop PD over time (i.e. 7.6% of patients after prostatectomy were found to have PD at 1 year, 13.7% at 2 years, and 15.9% at 3 years). Do the authors see a similar time dependent progression in the incidence of PD undergoing PR?

**Comment 11:** However, their comparison to the study by Tal et al is flawed. The study by Tal et al found that white race (vs non-white, 18% vs. 7%,  $P < 0.001$ ) was predictive of PD development after RP. In the study by Tal et al 83% of the 1000 patients were white, whereas in the present studies 67% of the 581 patients were white- which would skew the incidence of PD to a lower value. In addition, Tal et al did not consider PR as a factor in their study population.

**Reply 11:** Thank you for this feedback. We strongly agree with you that comparing this study with Tal et al would not be accurate. Our intention was not to compare this study. Tal et al was one of the first studies to study and report on PD after radical prostatectomy. In this study, we add to the literature by suggesting that the rates of PD among patients radical prostatectomy are lower than suggested by Tal among patients that have undergone penile rehabilitation. At this stage, without a controlled study, we cannot make any conclusions. We hope that our study paves the way for future studies to evaluate the effect of penile rehabilitation on the molecular and pathological level on PD.

**Changes in the text:** N/A

**Comment 12:** The reference list is not numbered.

**Reply 12:** Thank you for pointing this out. We have now addressed this.

**Changes in the text:** Please see the updated references page.

**Comment 13:** In the previous Tal et al studies over time there is an increase in the number of patients that develop PD over time (i.e. 7.6% of patients after prostatectomy were found to have PD at 1 year, 13.7% at 2 years, and 15.9% at 3 years). Do the authors see a similar time dependent progression in the incidence of PD undergoing PR?

**Reply 13:** The median follow up for patients who developed PD in our study was approximately 3 years. Among the 17 patients that developed PD, 2 were diagnosed

within 12 months, 5 were diagnosed in the second year post-op, and the remaining 10 patients were diagnosed after 24 months post-op. We have added this information in our results.

**Changes in the text:** Please see lines 129-132.

## **Reviewer F**

A Retrospective Review" provides valuable insights into the incidence of Peyronie's disease (PD) among prostate cancer patients who underwent penile rehabilitation after radical prostatectomy. The study is well-conducted, and the results are presented clearly. However, there are a few areas that require attention and clarification before the manuscript can be considered for publication. The following comments and suggestions are provided to improve the manuscript:

1. Introduction: a. The introduction effectively highlights the importance of PD and its association with radical prostatectomy. However, it would be beneficial to provide a brief overview of the challenges and impact of PD on patients' quality of life, in addition to the existing information on erectile dysfunction.

2. Methods: a. Provide more details regarding the selection criteria for patients included in the study. How were patients selected for penile rehabilitation? Were there any specific criteria for recommending or excluding patients from the rehabilitation program? b. Clarify whether the rehabilitation program was standardized for all patients or if there were variations in the treatment protocol based on individual patient characteristics. c. Specify the follow-up duration for patients included in the analysis. d. It would be helpful to mention the statistical methods used for the analysis, including the calculation of descriptive statistics and the one-sample t-test.

3. Results: a. Provide more information about the characteristics of the patients who developed PD, such as age, time since surgery, and pre-operative erectile function. This additional information would enhance the understanding of the study findings. b. Consider presenting the descriptive statistics, including means and standard deviations, for variables such as age, time since surgery, and erectile function, in addition to Table 1. c. When reporting statistical significance, provide the exact p-values (e.g.,  $p=0.07$ ) rather than stating  $p>0.05$ .

4. Discussion: a. Expand the discussion on the potential mechanisms linking radical prostatectomy to the development of PD. Include a more comprehensive review of the literature on this topic and discuss the proposed hypotheses in more detail. b. Address the limitations mentioned in the manuscript more explicitly, and discuss their potential impact on the interpretation of the results. c. Provide a clearer statement regarding the novelty of the study. While the study is the first to investigate the prevalence of PD in a population using a post-prostatectomy penile rehabilitation protocol, it is important to highlight this novelty in a more explicit manner.

5. Conclusion: a. The conclusion should summarize the key findings of the study and their potential implications for clinical practice. Consider highlighting the need for further research to confirm the potential benefits of penile rehabilitation in reducing the

incidence of PD among post-prostatectomy patients.

6. General: a. Ensure consistent use of abbreviations throughout the manuscript. For example, if "penile rehabilitation" is abbreviated as "PR," use this abbreviation consistently. b. Proofread the manuscript for grammatical errors and typos. There are a few instances where the sentences could be rephrased for clarity.

Once these revisions and clarifications are made, the manuscript will be more comprehensive and ready for publication. The study provides valuable insights into the incidence of PD in post-prostatectomy patients undergoing penile rehabilitation, and the results have the potential to impact clinical practice and guide future research in this field.

**Comment 14:** However, it would be beneficial to provide a brief overview of the challenges and impact of PD on patients' quality of life, in addition to the existing information on erectile dysfunction.

**Reply 14:** Thank you for this useful comment. We agree that adding information on the severe impact of PD on quality of life adds to the importance of our findings. We have added some information on this.

**Changes in the text:** See lines 77-81.

**Comment 15:** a. Provide more details regarding the selection criteria for patients included in the study. How were patients selected for penile rehabilitation? Were there any specific criteria for recommending or excluding patients from the rehabilitation program? b. Clarify whether the rehabilitation program was standardized for all patients or if there were variations in the treatment protocol based on individual patient characteristics

**Reply 15:** Thank you for this question. At our institution, every patient that undergoes radical prostatectomy will be referred to Mens Clinic to initiate penile rehabilitation. Rehabilitation is standardized for all patients per discussed in our methodology. We have emphasized this more in the Methods section. Importantly, this is why we do not have a control group as mentioned in response to reviewer D above. One limitation of institution's location in a major metropolitan area is that there are two additional large academic center and many other hospitals – therefore, patients who did not continue follow-up at UCLA where penile rehabilitation is the standard, returned to their “home” urologists or institutions and we do not have access to follow-up data. We are discussing methods to try to build on our current data set either through future prospective studies or using survey methodology to capture data from patients outside our institution.

**Changes in the text:** Please see lines 100 – 116; lines 177-178, and lines 183 to 185.

**Comment 16:** Specify the follow-up duration for patients included in the analysis.

**Reply 16:** Table 1 includes the follow-up duration for all patients included as well as those that developed PD. The median follow up for all patients was 643 days, and the median follow up for patients that developed PD was 1168 days.

**Changes in the text:** Please see Table 1.

**Comment 17:** It would be helpful to mention the statistical methods used for the analysis, including the calculation of descriptive statistics and the one-sample t-test.

**Reply 17:** Thank you for this comment. This has been mentioned in the last paragraph of the Methods section.

**Changes in the text:** Please see lines 119-121.

**Comment 18:** Results: a. Provide more information about the characteristics of the patients who developed PD, such as age, time since surgery, and pre-operative erectile function. This additional information would enhance the understanding of the study findings. b. Consider presenting the descriptive statistics, including means and standard deviations, for variables such as age, time since surgery, and erectile function, in addition to Table 1. c. When reporting statistical significance, provide the exact p-values (e.g.,  $p=0.07$ ) rather than stating  $p>0.05$ .

**Reply 18:** We appreciate this feedback. We have added the average age of patients that developed PD in the results section. The time since surgery for diagnosis has been documented in Table 1. Unfortunately pre-operative erectile function is hard to obtain as we offer patients to fill out standardized tools but they prefer to speak to their clinicians, and this variable was not included in the chart review of our patients. Statistics and p-values have been mentioned in Table 1 and results section.

**Changes in the text:** Please see lines 123-132 and Table 1.

**Comment 19:** a. Expand the discussion on the potential mechanisms linking radical prostatectomy to the development of PD. Include a more comprehensive review of the literature on this topic and discuss the proposed hypotheses in more detail.

**Reply 19:** Thank you for this suggestion. We have included some information on this in lines 73-77. Unfortunately the literature on possible causes behind prostatectomy and PD is quite sparse. We have emphasized this in the Discussions.

**Changes in the text:** Please see lines 157 – 160.

**Comment 20:** b. Address the limitations mentioned in the manuscript more explicitly, and discuss their potential impact on the interpretation of the results.

**Reply 20:** Thank you for this suggestion. We have included some information in the limitations section on their impact on the interpretations of the results. We have also added additional points per previous reviewers comments.

**Changes in the text:** Please see lines 185-189.

**Comment 21:** Provide a clearer statement regarding the novelty of the study. While the study is the first to investigate the prevalence of PD in a population using a post-prostatectomy penile rehabilitation protocol, it is important to highlight this novelty in a more explicit manner.

**Reply 21:** We appreciate this feedback. We have made the novelty more explicit in the Introduction, and again in the Conclusion paragraphs.

**Changes in the text:** Please see lines 91-92, and 202-209.



**Comment 22:** Conclusion: a. The conclusion should summarize the key findings of the study and their potential implications for clinical practice. Consider highlighting the need for further research to confirm the potential benefits of penile rehabilitation in reducing the incidence of PD among post-prostatectomy patients.

**Reply 22:** We have written a Conclusion paragraph that includes the points mentioned in this comment.

**Changes in the text:** Please see lines 202-209.

**Comment 23:** General: a. Ensure consistent use of abbreviations throughout the manuscript. For example, if "penile rehabilitation" is abbreviated as "PR," use this abbreviation consistently. b. Proofread the manuscript for grammatical errors and typos. There are a few instances where the sentences could be rephrased for clarity.

**Reply 23:** Thank you for this suggestion. We have addressed your comments throughout the manuscript. We hope that the new revisions have fixed the aforementioned issues.

**Changes in the text:** Please see revisions throughout the manuscript.