

This is the accepted version of the publication Priya Kannan, Stanley J Winser, Lam Choi Ho, Leung C Hei, Lam C Kin, Garbien E Agnieszka and Leung HY Jeffrey, Effectiveness of physiotherapy interventions for improving erectile function and climacturia in men after prostatectomy: a systematic review and meta-analysis of randomized controlled trials, Clinical Rehabilitation (Journal Volume 33 and Issue 8) pp. 1298-1309. Copyright © 2019 (The Author(s)). DOI: 10.1177/0269215519840392

Effectiveness of physiotherapy interventions for improving erectile function and climacturia in men after prostatectomy: a systematic review and meta-analysis of randomised controlled trials

*Priya Kannan**, Stanley J. Winser, Lam Choi Ho, Leung C. Hei, Lam C. Kin, Garbien E. Agnieszka, Leung H.Y. Jeffrey

Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Hong Kong.

***Corresponding author:** ST532, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Hong Kong. Tel: +852 3400 3277; Fax: (852) 2330 8656.
Email: priya.kannan@polyu.edu.hk

Running title: Physiotherapy for sexual dysfunction after prostatectomy

Review registration: This systematic review is registered in the PROSPERO registry (CRD42017065255).

Word count

Abstract: 247

Text: 2687

No. of figures: 3

No. of tables: 2

Supplementary appendix: 2

Abstract

Objective: To determine the effectiveness of physiotherapy interventions for post-prostatectomy erectile dysfunction and climacturia.

Data Sources. Multiple databases were searched from database inception-February 2019.

Review methods: Randomised controlled trials comparing physiotherapy interventions to control were included.

Results: The search yielded 127 potentially relevant articles; seven met the inclusion criteria and were included in the review. Meta-analysis of two studies revealed a statistically significant effect of pelvic floor muscle training (PFMT) plus biofeedback compared to the no treatment control group for erectile function at the 12-month follow-up period (risk ratio (RR) 3.65 [95% confidence interval (CI) 1.02 to 13.05]; $P = 0.05$). Data from one small study ($n=31$) identified a greater number of men reporting improved climacturia in the PFMT plus electrical stimulation group compared to the no treatment control group; and the overall effect was significant (RR 15.60 [95% CI 0.95 to 254.91; $P = 0.05$). Meta-analyses of two studies found no statistically significant differences between groups receiving PFMT and no treatment control for erectile function or climacturia at long-term follow-up.

Conclusions. PFMT augmented with biofeedback improves erectile function after prostatectomy. Data from a single study found PFMT combined with electrical stimulation to be beneficial for post-prostatectomy climacturia. However, electrical stimulation is recommended for terminally ill people only. The effect of PFMT alone on post-prostatectomy erectile dysfunction and climacturia remains inconclusive. However, this is likely to be affected by the

participant adherence and physiotherapy supervision. High-quality trials providing intensive supervision and due consideration of adherence factors are recommended.

Introduction

The second most common cancer among men is prostate cancer.¹ Incidence of prostate cancer increases rapidly after the age of 50 years.² Radical prostatectomy is a surgical procedure to remove the prostate gland and the surrounding tissues. Radical prostatectomy is associated with erectile dysfunction (inability to obtain and maintain adequate erection for sexual intercourse) and climacturia (urine leakage during ejaculation)³. Recovery of erectile function following prostatectomy ranges from 12-24 months.^{4,5} Lack of active intervention in the recovery period results in flaccidity, and prolonged flaccid state is reported to cause irreversible damage to the cavernous tissue.⁵ Post-prostatectomy urinary incontinence has been associated with development of climacturia^{3,6-8} and urinary incontinence following prostatectomy has been identified as a potential predictor of climacturia in several studies.^{3,6,8}

In men, the pelvic floor muscles that are active during sexual intercourse for penile erection and ejaculation are the ischiocavernosus and the bulbospongiosus^{9,10}; atrophy of ischiocavernosus muscle partly contributes to erectile dysfunction.¹⁰ Conservative therapies that have been proposed for penile rehabilitation include pelvic floor muscle training, electrical stimulation, and biofeedback. However, the efficacy of these conservative therapies for sexual dysfunction following prostatectomy is not known.

To the best of our knowledge, there are no meta-analyses on the efficacy of physiotherapy interventions for erectile function and climacturia following prostatectomy. The efficacy of physiotherapy interventions for improving erectile dysfunction and climacturia is therefore not known. The objective of this review was to determine the effectiveness of

physiotherapy interventions in comparison to controls for improving erectile function and climacturia after radical prostatectomy or transurethral resection of tumor.

Methods

This systematic review was developed and is reported in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses guidelines.¹¹ An extensive Ovid Medline, EMBASE, Web of Science, EBSCO, PubMed, PEDro, and Scopus search was performed from database inception to February 2019, using the following search terms: *prostatectomy; sexual dysfunction; physiotherapy intervention; and randomised controlled trials*. Reference lists of relevant studies were hand searched for any other potentially relevant articles. No limits were placed on language or publication year. A detailed description of the search is provided in Supplementary Appendix 1. Study screening and selection were performed independently by two review authors. Conflicts were resolved by discussion between the review authors until consensus was reached. A third reviewer (PK) was consulted for unresolved conflicts.

Studies were eligible for inclusion if they (i) were randomised controlled trials, pilot randomised controlled trials, randomised crossover (if data available prior to crossover), cluster trials or unpublished work; (ii) compared physiotherapy interventions consisting of exercise and electrotherapy modalities such as electrical stimulation (a technique used to elicit a muscle contraction using electrical impulses) and biofeedback (instrument that allows detection of electrical signals from muscles and provides feedback reinforcing information via auditory or visual signals)¹² with either no treatment, sham, placebo, usual care, or active control; and (iii)

used self-reported recovery of climacturia or at least one of the following outcomes for erectile function: the international index of erectile function, self-reported erectile function, the sexual health inventory in men, or the quality of erection questionnaire. In urology, physiotherapy interventions including exercise (pelvic floor muscle training), biofeedback and electrical stimulation are provided by physiotherapists and other professionals such as physicians and nurses. Therefore, studies were not excluded on the basis of who delivered the intervention. Studies of quasi-experimental design were excluded. Studies comparing active interventions (electrical stimulation/biofeedback to sham electrical stimulation/biofeedback, and pelvic floor muscle training to electrical stimulation/biofeedback) were also excluded. For this review, we considered men who received only verbal/written instructions or lifestyle advice but no formal pelvic floor muscle training as no treatment controls.

The Physiotherapy Evidence Database (PEDro) scale¹³ and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool¹⁴ were used to rate the methodological quality and the quality of evidence respectively. Two reviewers performed the methodological quality assessment and compared their results with the quality scores reported on the PEDro website (<http://search.pedro.org.au/search>). Discrepancies between reviewer scores and scores reported on PEDro were resolved by discussion with the third reviewer (PK). Studies scoring ≥ 6 were considered high-quality and studies scoring ≤ 5 were considered low-quality.¹⁵

The quality of evidence (GRADE) was evaluated using GRADEpro software (version 3.6.1) (<http://tech.cochrane.org/revman/other-resources/gradepr/download>). The quality of

evidence was categorized as either “high,” “moderate,” “low,” or “very low”.¹⁶ The overall quality for an outcome measure was based on the lowest quality for the outcome.¹⁷ Studies were rated across outcome measures for risk of bias (such as lack of concealment of allocation, lost to follow-up > 15%)¹⁸, indirectness (use of surrogate outcome measures)¹⁹, imprecision (minimum or no overlap of confidence interval (CI) across studies)²⁰, inconsistency (evidence of clinical or statistical heterogeneity [$I > 50%$])²¹, and publication bias (industry sponsored).²² Given the nature of the intervention, studies were not downgraded for lack of participant blinding; however, studies were downgraded by one level for lack of either therapist or assessor blinding and by two levels for lack of therapist and assessor blinding.

Two independent reviewers extracted the following data from each included study: First author’s name and year of publication, study design, participant age (mean age and standard deviation or median and range), sample size per group, intervention and control, and results (n for dichotomous variable or mean and standard deviation data for continuous variable).

The meta-analysis was performed using RevMan 5.3 software. Separate meta-analyses were conducted for erectile function and climacturia. Studies reporting continuous data (mean and standard deviation) were pooled separately from studies reporting dichotomous (numbers and percentages) data. Studies comparing similar interventions (pelvic floor muscle training alone; pelvic floor muscle training alone plus ES or biofeedback) and assessment time-points (immediately after the intervention [usually 3 months] and final follow-up [usually 12-15 months]) were grouped together to obtain the pooled estimate of between-group differences. Treatment effect size and 95% CI were estimated for continuous data; whereas the risk ratio

(RR) and 95% CI were calculated for dichotomous data. Statistical heterogeneity was determined using the chi-square test. Weighted mean differences (WMD) were calculated to obtain the pooled estimate utilizing a fixed effects model for low heterogeneity ($I^2 < 50\%$) or random effects model for high heterogeneity ($I^2 > 50\%$).²³ Statistical significance was established as $P \leq 0.05$.

Results

The search yielded 127 potentially relevant articles. Of these, seven met the inclusion criteria and were included in the review (excluded studies and reasons for exclusion are summarized in Supplementary Appendix 2). The review process and the reasons for exclusion at each stage are summarized in Figure 1. Study characteristics are summarized in Table 1. Seven included studies provided data for 1622 participants aged 47-90 years. Of the seven included studies, only three²⁴⁻²⁶ made participants visualize the movement of their penis and testicles upon contraction of the pelvic floor muscles.

PEDro scores for included studies are reported in Table 1. The summary of findings generated by the GRADE profiler software is presented in Table 2. Methodological (PEDro) quality of included studies was low to high with mean PEDro score of 5.7 out of 10. Based on the GRADE assessment, the quality of evidence for both the outcome measures ranged from “very low” to “moderate”.

The GRADE quality of evidence for the comparison, pelvic floor muscle training plus ES versus no treatment contributed by two studies was “very low”. However, the PEDro quality for

these two studies was “low”. The discrepancy in the quality is due to one of the studies being downgraded for publication bias²⁷ in the GRADE system. Two^{25, 26} studies that obtained a “high” quality PEDro rating were rated as “moderate” in the GRADE system. One study that obtained a “low” quality PEDro rating was rated as “very low” in the GRADE system. These discrepancies in quality rating are because studies were downgraded for additional criteria such as publication bias, inconsistency, (methodological/clinical heterogeneity) and imprecision in the GRADE system but not in PEDro.

Pelvic floor muscle training plus electrical stimulation for erectile function and climacturia

Meta-analyses of two^{27, 28} methodologically low-quality, very low-grade studies with 98 participants found no statistically significant differences between groups receiving pelvic floor muscle training plus electrical stimulation and no treatment for erectile function (RR 1.45 [95% CI 0.87 to 2.41]; $p = 0.15$) at the 12-15 month follow-up (Fig. 2A). Data from one²⁸ small study ($n = 31$) of low methodological and grade quality identified a greater number of men reporting improved climacturia in the pelvic floor muscle training plus electrical stimulation group compared to the no treatment control group (6/14 vs. 0/16 in the control group); and the overall effect was significant (15.60 [95% CI 0.95 to 254.91; $p = 0.05$; Fig. 3A).

Pelvic floor muscle training plus biofeedback for erectile function

Meta-analyses of two^{24, 29} methodologically high-quality, very low-grade studies ($n = 122$) found no significant differences between groups receiving pelvic floor muscle training plus biofeedback and no treatment for erectile function at 3 months post-intervention (4.44 [95% CI 3.37 to 12.25]; $p = 0.26$; Fig. 2B). The pooled analysis of two studies^{29, 30}, one of high

methodological quality and the other of low-methodological quality revealed a significant effect of pelvic floor muscle training plus biofeedback compared to the no treatment control for erectile function at the 12-month follow-up period (RR 3.65 [95% CI 1.02 to 13.05]; $p = 0.05$; Fig. 2C).

Pelvic floor muscle training alone for erectile function and climacturia

Meta-analyses of two^{25, 26} methodologically high-quality, moderate-grade studies with 734 participants found no statistically significant differences between groups receiving pelvic floor muscle training and no treatment control for erectile function (RR 0.96 [95% CI 0.85 to 1.07]; $p = 0.44$; Fig. 2D) or climacturia (RR 1.01 [95% CI 0.96 to 1.07]; $p = 0.65$; Fig. 3B) at the 12-month follow-up.

Discussion

The pooled-analysis of high-quality, moderate grade studies^{25, 26} revealed a non-significant effect for pelvic floor muscle training alone on erectile function and climacturia. However, when pelvic floor muscle training was augmented with biofeedback, a greater number of men reported improved erectile function in the intervention group compared to the control group at 12 months follow-up (17% vs. 3% in the control group; Fig. 2C). Nevertheless, the overall effect was of marginal significance; these results are supported by two studies^{29, 30} of “high” quality and “very low” grade. Results at 3 months showed no significant effect of pelvic floor muscle training combined with biofeedback on erectile function. These findings indicate that men with post-prostatectomy erectile dysfunction might benefit from long term pelvic floor muscle training combined with biofeedback.

Less promising erectile function results supported by “low” methodological and “very low” grade evidence quality were obtained for pelvic floor muscle training supplemented with electrical stimulation compared to no treatment controls^{27, 28}. Although a greater number of men reported improved climacturia in the pelvic floor muscle training plus electrical stimulation group compared with the no treatment control group²⁸ (42.8% vs. 0% in the control group; Fig. 3B), the overall effect was of marginal significance. Regardless, the safety of administering electrical stimulation in the presence of cancer is still inconclusive.³¹ Numerous studies have identified disseminated tumor cells in blood and bone marrow of men with prostate cancer;³¹⁻³⁵ these cancer cells are reported to disseminate from the tumor early on.^{32, 36} Although there is no empirical evidence for the spread of malignant cells by electrical stimulation, the current recommendation is to apply electrical stimulation to improve muscle mass and strength in terminally ill patients only.³¹

Pelvic floor muscle training causes hypertrophy of pelvic floor muscles, increases muscle connective tissue strength, enhances awareness of muscles in the brain, and enables greater recruitment of active motor neurons.³⁷ However, success with pelvic floor muscle training is hampered by lack of adherence to training. Adherence to pelvic floor muscle training is influenced by patient and therapy related factors³⁸. Patient-related factors to non-adherence include (1) low level of motivation, (2) perception of minimal benefit, and (3) forgetting to do exercises³⁸. Therapy-related factors include (1) patient-therapist relationship (lack of connection and interaction with therapist), and (2) ineffective feedback of performance³⁸. Of the seven included studies, only two^{27, 29} tracked participant adherence with the exercises by making regular telephone calls to ensure they were performing exercises and to discuss barriers to

performing exercises. Future trials evaluating effectiveness of pelvic floor muscle training are recommended to (1) make use of technology (internet, mobile apps etc.) and educational approaches to improve adherence to pelvic floor muscle training³⁸; (2) use online electronic diaries instead of paper diaries (as patients who used electronic diaries are reported to be more compliant than those using paper diaries³⁹); (3) make frequent telephone calls to remind patients to do the exercises; (4) arrange frequent visits with the intervention provider; and (5) make frequent assessments to inform participants the outcomes of exercises.

Supervised pelvic floor muscle training for at least three months has been shown to produce better outcomes than unsupervised training.^{37, 40-42} However, only three of the included studies provided supervised training by a physiotherapist for three months.^{25, 26, 30} Future studies evaluating physiotherapy treatment effectiveness for the management of erectile dysfunction should provide adequate pelvic floor muscle training (for at least 3 months) by a trained physical therapist within the first few months post-operation.

The first step in pelvic floor muscle training is to identify and isolate the correct muscles;³⁷ contraction of the correct pelvic floor muscles leads to a scrotal lift and inward movement of the penis.²⁴ Visualization (with a mirror) is one way to ensure the correct muscles are contracting.^{24, 43} However, four²⁷⁻³⁰ of the seven studies did not report having evaluated participants ability to contract pelvic floor muscles or instructing men to visualize the movement of the penis. Men with erectile dysfunction are required to time a voluntary contraction of the pelvic floor muscles during sexual activity to maintain penile hardness sufficient for vaginal penetration.^{25, 44} Performing or timing a pelvic floor contraction during sexual activity is reported

to increase the intracavernosal pressure to establish rigidity of the tumescent penis.^{25, 44} However, only two studies^{25, 26} advised or taught men to perform voluntary contractions during sexual activity. Study protocols with inadequate supervision and advice could potentially lead to poor outcomes.

The comprehensive search strategy and use of psychometrically valid quality assessment tools are strengths of this review. Furthermore, language bias was eliminated by including studies published in all languages. The current systematic review has some limitations: (i) low quality and small sample size in included studies, (ii) low number of studies included in the meta-analysis, and (iii) some potentially relevant studies may have been missed either because of the search terms this review used or because they are indexed in databases not included in this review.

This systematic review found positive treatment effects for pelvic floor muscle training augmented with biofeedback for post-prostatectomy erectile dysfunction. However, these results need to be considered with caution because meta-analysis was conducted using small number of studies ($n = 2$) of low-high methodological quality, very-low-grade evidence. Data from one individual study found that pelvic floor muscle training augmented with electrical stimulation is beneficial for improving climacturia in men after prostatectomy. However, the safety of electrical stimulation for people with cancer remains uncertain. Phase 4 studies for identifying uncommon adverse effects are needed to test the safety of ES in the presence of malignancy. The value of pelvic floor muscle training alone and in combination with therapies such as biofeedback and electrical stimulation for the management of erectile dysfunction and

climacturia in men after prostatectomy remains uncertain. The evidence is limited, available evidence is of low quality. Therefore, rigorous, adequately powered, high-quality trials that comply with the Consolidated Standards of Reporting Trials (CONSORT) guidelines are required to produce a definitive answer. The effectiveness of pelvic floor muscle training and treatment success for improving erectile function in men cannot be investigated without due consideration of adherence factors. It is recommended that future studies evaluate strategies to increase adherence to a pelvic floor muscle training regimen. Future studies should include intensive supervision by a physiotherapist for at least 3 months, measures to evaluate the participants' ability to contract their pelvic floor muscles prior to exercise prescription and provide visual feedback for contraction instead of just verbal instructions.

Clinical messages

- Pelvic floor muscle training augmented with biofeedback improves erectile function in men after prostatectomy, but the evidence is limited.
- Data from an individual study found pelvic floor muscle training combined with electrical stimulation to be beneficial for improving post-prostatectomy climacturia. However, electrical stimulation is only recommended for terminally ill patients.

Declaration of conflict of interests: None declared.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: A meta-analysis. *JSM*. 2009;6(9):2538-46.
2. Bashir MN. Epidemiology of prostate cancer. *Asian Pac J Cancer Prev*. 2015;16(13):5137-41.
3. O'Neil BB, Presson A, Gannon J, Stephenson RA, Lowrance W, Dechet CB, et al. Climacturia after definitive treatment of prostate cancer. *J Urol*. 2014;191(1):159-63.
4. Bratu O, Oprea I, Marcu D, Spinu D, Niculae A, Geavlete B, et al. Erectile dysfunction post-radical prostatectomy—a challenge for both patient and physician. *J Med Life*. 2017;10(1):13-18.
5. Dall'Era JE, Mills JN, Koul HK, Meacham RB. Penile rehabilitation after radical prostatectomy: important therapy or wishful thinking? *Rev Uro*. 2006;8(4):209.
6. Capogrosso P, Ventimiglia E, Cazzaniga W, Montorsi F, Salonia A. Orgasmic dysfunction after radical prostatectomy. *World J Mens Health*. 2017;35(1):1-13.
7. Nilsson AE, Carlsson S, Johansson E, Jonsson MN, Adding C, Nyberg T, et al. Orgasm-associated urinary incontinence and sexual life after radical prostatectomy. *JSM*. 2011;8(9):2632-9.
8. Frey A, Sønksen J, Jakobsen H, Fode M. Prevalence and Predicting Factors for Commonly Neglected Sexual Side Effects to Radical Prostatectomies: Results from a Cross-Sectional Questionnaire-Based Study. *JSM*. 2014;11(9):2318-26.
9. Gratzke C, Angulo J, Chitale K, Dai Yt, Kim NN, Paick JS, et al. Anatomy, physiology, and pathophysiology of erectile dysfunction. *JSM*. 2010;7(1pt2):445-75.
10. Lavoisier P, Roy P, Dantony E, Watrelot A, Ruggeri J, Dumoulin S. Pelvic-floor muscle rehabilitation in erectile dysfunction and premature ejaculation. *Phys Ther*. 2014;94(12):1731-43.

11. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Me*. 2009;6(7):e1000097.
12. Watson T. Guidance for the clinical use of electrophysical agents. In *Electrotherapy: evidence-based practice*: Elsevier Health Sciences; 2008.
13. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phy Ther*. 2003;83(8):713-21.
14. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-94.
15. Maher CG. A systematic review of workplace interventions to prevent low back pain. *Aust J Physiother*. 2000;46(4):259-69.
16. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed)*. 2008;336(7650):924-6.
17. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ (Clinical research ed)*. 2004;328(7454):1490-94.
18. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407-15.
19. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol*. 2011;64(12):1303-10.

20. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol*. 2011;64(12):1283-93.
21. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol*. 2011;64(12):1294-302.
22. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol*. 2011;64(12):1277-82.
23. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1(2):97-111.
24. Dorey G, Speakman M, Feneley R, Swinkels A, Dunn C, Ewings P. Randomised controlled trial of pelvic floor muscle exercises and manometric biofeedback for erectile dysfunction. *Br J Gen Pract*. 2004;54(508):819-25.
25. Glazener C, Boachie C, Buckley B, Cochran C, Dorey G, Grant A, et al. Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. *The Lancet*. 2011a;378(9788):328-37.
26. Glazener C, Boachie C, Buckley B, Cochran C, Dorey G, Grant A, et al. Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. *Lancet*. 2011b;378(9788):328-37.

27. Fode M, Borre M, Ohl DA, Lichtbach J, Sønksen J. Penile vibratory stimulation in the recovery of urinary continence and erectile function after nerve-sparing radical prostatectomy: a randomized, controlled trial. *BJU Int.* 2014;114(1):111-7.
28. Geraerts I, Van Poppel H, Devoogdt N, De Groef A, Fieuws S, Van Kampen M. Pelvic floor muscle training for erectile dysfunction and climacturia 1 year after nerve sparing radical prostatectomy: a randomized controlled trial. *Int J Impot Res.* 2015;28(1):9-13.
29. Lin Y-H, Yu T-J, Lin VC-H, Wang H-P, Lu K. Effects of early pelvic-floor muscle exercise for sexual dysfunction in radical prostatectomy recipients. *Cancer Nursing.* 2012;35(2):106-14.
30. Prota C, Gomes C, Ribeiro L, de Bessa Jr J, Nakano E, Dall'Oglio M, et al. Early postoperative pelvic-floor biofeedback improves erectile function in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. *Int J Impot Res.* 2012;24(5):174-78.
31. Laakso E-L, Young C. Electrophysical agents (EPAs) for symptom control in cancer care—what is the evidence? *Phys Ther Rev.* 2010;15(4):334-43.
32. Morgan TM, Lange PH, Porter MP, Lin DW, Ellis WJ, Gallaher IS, et al. Disseminated tumor cells in prostate cancer patients after radical prostatectomy and without evidence of disease predicts biochemical recurrence. *Clin Cancer Res.* 2009;15(2):677-83.
33. Bianco Jr FJ, Wood Jr DP, de Oliveira JG, Nemeth JA, Beaman AA, Cher ML. Proliferation of prostate cancer cells in the bone marrow predicts recurrence in patients with localized prostate cancer. *Prostate.* 2001;49(4):235-42.
34. Ellis WJ, Pfitzenmaier J, Colli J, Arfman E, Lange PH, Vessella RL. Detection and isolation of prostate cancer cells from peripheral blood and bone marrow. *Urology.* 2003;61(2):277-81.
35. Morgan TM, Lange PH, Vessella RL. Detection and characterization of circulating and disseminated prostate cancer cells. *Front Biosci.* 2007;12:3000-9.

36. Klein CA, Blankenstein TJ, Schmidt-Kittler O, Petronio M, Polzer B, Stoecklein NH, et al. Genetic heterogeneity of single disseminated tumour cells in minimal residual cancer. *Lancet*. 2002;360(9334):683-9.
37. Felicíssimo MF, Carneiro MM, Saleme CS, Pinto RZ, da Fonseca AMRM, da Silva-Filho AL. Intensive supervised versus unsupervised pelvic floor muscle training for the treatment of stress urinary incontinence: a randomized comparative trial. *Int Urogynecol J*. 2010;21(7):835-40.
38. Frawley HC, McClurg D, Mahfooza A, Hay-Smith J, Dumoulin C. Health professionals' and patients' perspectives on pelvic floor muscle training adherence—2011 ICS State-of-the-Science Seminar research paper IV of IV. *Neurourol Urodynam*. 2015;34(7):632-9.
39. Marceau LD, Link C, Jamison RN, Carolan S. Electronic diaries as a tool to improve pain management: is there any evidence?: Blackwell Publishing Inc Malden, USA; 2007.
40. Zanetti MRD, Castro RdA, Rotta AL, Santos PDd, Sartori M, Girão MJBC. Impact of supervised physiotherapeutic pelvic floor exercises for treating female stress urinary incontinence. *Sao Paulo Med J*. 2007;125(5):265-9.
41. Konstantinidou E, Apostolidis A, Kondelidis N, Tsimtsiou Z, Hatzichristou D, Ioannides E. Short-term efficacy of group pelvic floor training under intensive supervision versus unsupervised home training for female stress urinary incontinence: A randomized pilot study. *Neurourol Urodyn*. 2007;26(4):486-91.
42. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev*. 2010;1(1). 42.

43. Dorey G, Glazener C, Buckley B, Cochran C, Moore K. Developing a pelvic floor muscle training regimen for use in a trial intervention. *Physiotherapy*. 2009;95(3):199-208.
44. Cohen D, Gonzalez J, Goldstein I. The role of pelvic floor muscles in male sexual dysfunction and pelvic pain. *Sex Med Reviews*. 2016;4(1):53-62.

Table 1. Characteristics and PEDro methodological quality scores of included studies (n = 7).

Study, PEDro quality, Language of publication	Participants		Intervention	Duration of intervention	EF, climacturia outcomes mean (SD)/ number
	Study design, age* (years), surgery	Number (Exp/Con)			
Dorey 2004 ²⁴ PEDro: 6/10 English	Randomised cross-over 59.5 (2.1) TURP	25/25	Exp: PFMT + BFB Con: No treatment for first 3-months. At 3-months, intervention similar to experimental group	30-minute sessions once a week for five weeks. No information about who provided treatment	<u>EF (3 months)</u> Exp: 17.2 (9.7) Con: 8.4 (7.3) Score: not reported <u>Climacturia</u> NE
Fode 2014 ²⁷ PEDro: 5/10 English	Parallel-group RCT Median (range) Exp: 62 (46-73) Con: 65 (49-76) RP	30/38	Exp: PFMT + PVS PVS: Amplitude: 2mm; frequency: 100Hz Duration: 10s of stimulation followed by a 10-s pause Con: One pre-operative session of PFMT	Daily stimulation for 6-weeks. No information about who provided treatment	<u>EF (3 months)</u> Exp: 5 Con: 4 <u>EF (12 months)</u> Exp: 16 Con: 12 Score ≥ 18 <u>Climacturia</u> NE
Lin 2012 ²⁹ PEDro: 6/10 English	Randomised cross-over 65.7 (6.12) RP	35/27	Exp: PFMT + BFB Con: No treatment for first three months. At 3-months, same treatment as for experimental group	Two one-to-one sessions. No information about who provided treatment	<u>EF (3 months)</u> Exp: 5.8 (2.3) Con: 5.0 (0.2) <u>EF (12 months)</u> Exp: 1 Con: 0 Score ≥ 18 <u>Climacturia</u> NE
Glazner 2011a ²⁵	Parallel-group RCT	EF: 189/190 Climacturia: 135/139	Exp: PFMT alone	Four one-to-one sessions of PFMT by a	<u>EF (12 months)</u> Exp: 84 Con: 85

PEDro: 7/10 English	62.4 (5.8) RP		Con: no treatment	physical therapist over a period of 3- months	Exp: 6.0 (3.3) Con: 6.5 (3.1) Score: NR. Study reports number of men not able to achieve any erection <u>Climacturia (12 months)</u> Exp: 109 Con: 109:
Glazner 2011b ²⁶ PEDro: 7/10 English	Parallel- group RCT 68.2 (7.7) TURP	EF: 177/178 Climaturia: 135/133	Exp: PFMT alone Con: No treatment	Four one-to- one sessions of PFMT by a physical therapist over a period of 3- months	<u>EF (12 months)</u> Exp: 125 Con: 135 Exp: 4.2 (3.7) Con: 4.6 (3.9) Score: NR. Study reports number of men not able to achieve any erection <u>Climacturia (12 months)</u> Exp: 132 Con: 130
Prota 2012 ³⁰ PEDro: 4/10 English	Parallel- group RCT 62.4 (6.4) RP	17/16	Exp: PFMT + BFB Con: No treatment	Once a week for 3-months by a physical therapist	<u>EF 6 months</u> Exp: 4 Con: 1 <u>EF 12 months</u> Exp: 8 Con: 2 Score \geq 20 <u>Climacturia</u> NE
Geraerts 2015 ²⁸ PEDro: 5/10	Parallel- group RCT 61.1 (5.8) RP	EF:14/16 Climaturia: 14/17	Exp: PFMT + ES ES: Frequency: 50 Hz; pulse duration: 600 μ s Con: No treatment for first	Once a week for 6-weeks followed by once every fortnight for another 6	<u>EF 15 months</u> Exp: 4 Con: 5 Exp: 11.1 (8.8) Con: 9.3 (7.1) Score \geq 18

English			15 months. At 15 months, similar treatment as for experimental group	weeks by therapist.	<u>Climacturia (15 months)</u> Exp: 6 Con: 0:
---------	--	--	--	---------------------	---

BFB = Biofeedback; Con = Control group; EF = Erectile Function; ES = Electrical Stimulation; Exp = Experimental group; NE = Not Evaluated; NR = Not Reported; PFMT = Pelvic Floor Muscle Training; PVS = Penile Vibratory Stimulator; RP = Radical Prostatectomy; TURP = Trans Urethral Resection of the Prostate.

*Age reported as mean and SD unless specified.

Table 2: Summary of findings (GRADE) for the effectiveness of interventions compared to no treatment control

PFMT alone					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE) [#]
	Assumed risk	Corresponding risk			
	Control	PFMT alone			
EF at 12-months	Study population		RR 0.96 (0.85 to 1.07)	734 (2 studies) ^{25, 26}	⊕⊕⊕⊖ Moderate ^a
	598 per 1000	574 per 1000 (508 to 640)			
	Moderate				
	603 per 1000	579 per 1000 (513 to 645)			
Climacturia at 12-months	Study population		RR 1.01 (0.96 to 1.07)	542 (2 studies) ^{25, 26}	⊕⊕⊕⊖ Moderate ^a
	879 per 1000	887 per 1000 (844 to 940)			
	Moderate				
	881 per 1000	890 per 1000 (846 to 943)			
PFMT plus ES					
Climacturia at 15-months	Control	PFMT plus ES	RR 15.6 (0.95 to 254.91)	31 (1 study) ²⁸	⊕⊕⊖⊖ Low ^{b,c,d}
	Study population				
	0 per 1000	0 per 1000 (0 to 0)			
	Moderate				
	0 per 1000	0 per 1000 (0 to 0)			
PFMT plus ES					
EF at 12-15 months	Control	PFMT plus ES	RR 1.45 (0.87 to 2.41)	98 (2 studies) ^{27, 28}	⊕⊖⊖⊖ Very low ^{d,e,f}
	Study population				
	315 per 1000	456 per 1000 (274 to 759)			
	Moderate				

	314 per 1000	455 per 1000 (273 to 757)			
PFMT plus BFB					
EF at 3-months		The mean of 3 months in the intervention groups was 4.44 higher (3.37 lower to 12.25 higher)		112 (2 studies) ^{24, 29}	⊕⊕⊕⊕ Very low ^{d,g,h}
PFMT plus BFB					
EF at 12-months	Control	PFMT plus BFB n,%			
	Study population		RR 3.65 (1.02 to 13.05)	105 (2 studies) ^{29, 30}	⊕⊕⊕⊕ Very low ^{d,i}
	38 per 1000	138 per 1000 (38 to 492)			
	Moderate				
63 per 1000	230 per 1000 (64 to 822)				

Note: BFB = Biofeedback; ES = Electrical Stimulation; EF = Erectile Function; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; PFMT = Pelvic Floor Muscle Training; RR = Risk Ratio.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

#GRADE Working Group grades of evidence

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change

the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aLack of therapist and assessor blinding in two^{25, 26} studies.

^bTherapist, assessor not blinded and lack of allocation concealment in one study²⁸.

^cInconsistency-Not applicable, single study.

^dVery wide CI.

^eTherapist and assessor not blinded in two studies^{27, 28}; dropout rate >15% in one study²⁷; and lack of allocation concealment in one study.²⁸

^fLikely to be industry sponsored.²⁷

^gTherapist and assessor not blinded in two studies.^{24, 29}

^hEvidence of heterogeneity ($I^2 > 50\%$) across studies.

ⁱLack of allocation concealment and dropout rate >15% in one study³⁰; Therapist and assessor not blinded in two studies.^{29, 30}

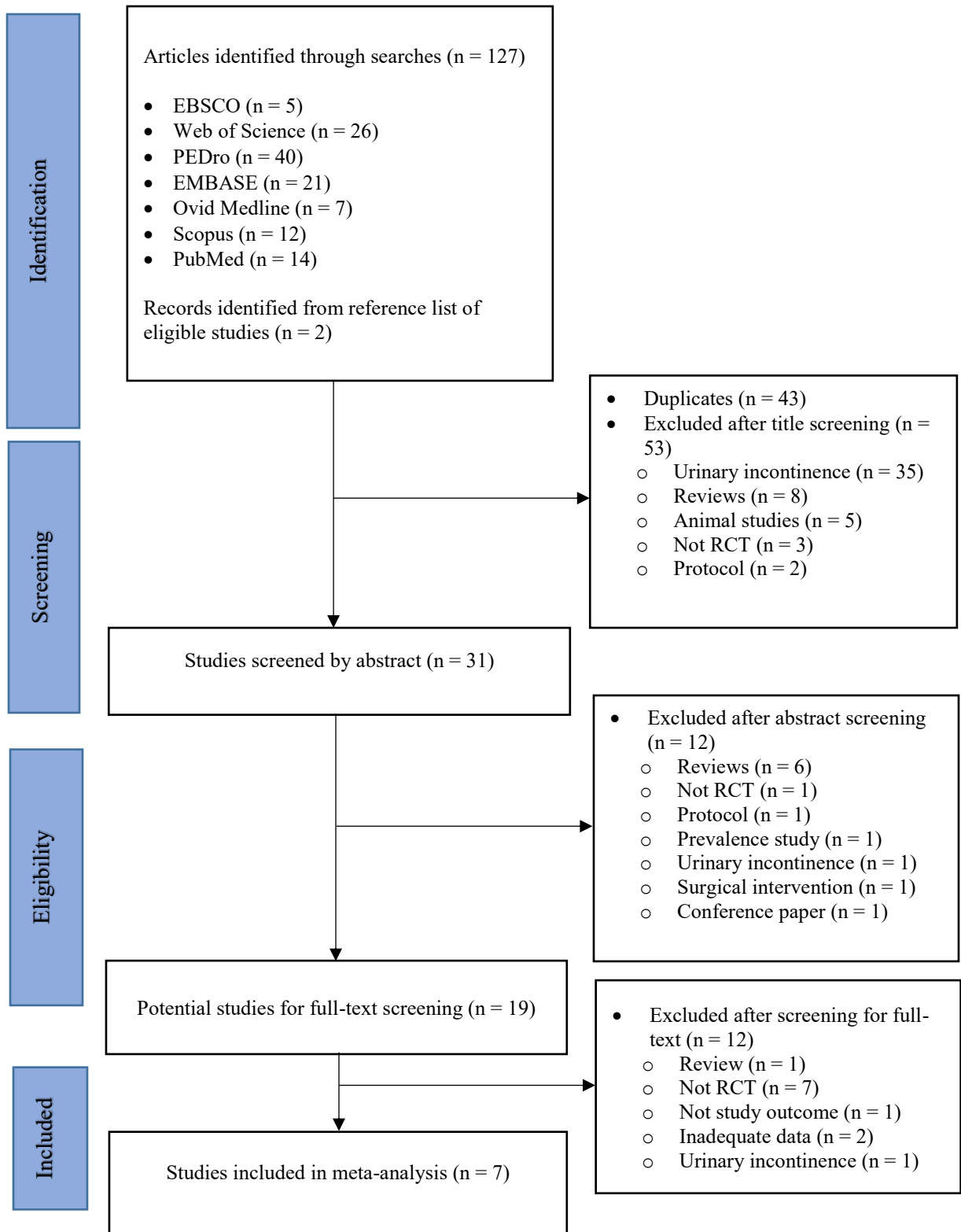
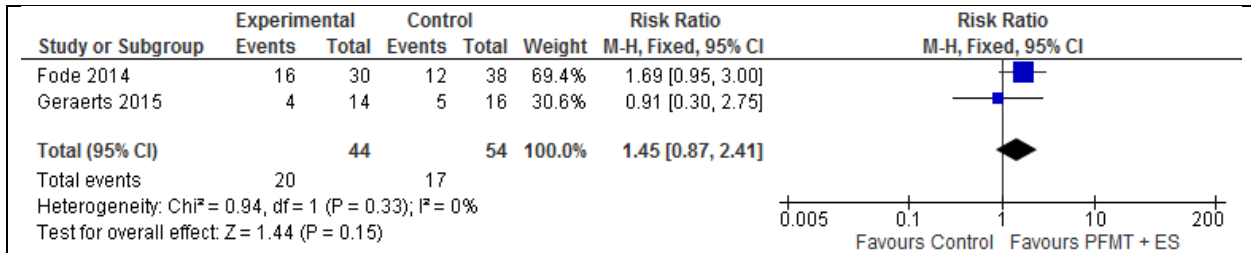
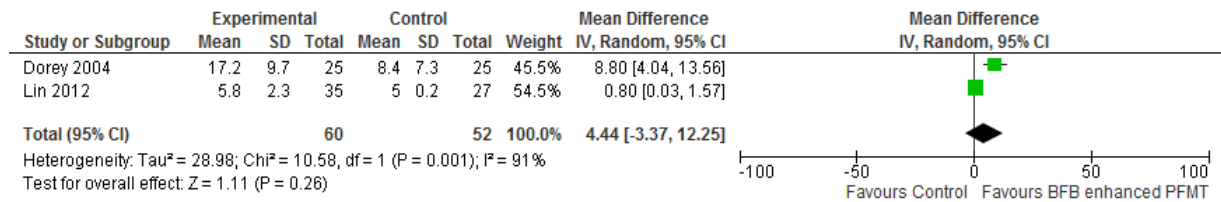


Figure 1. Flow diagram of searches and study selection.

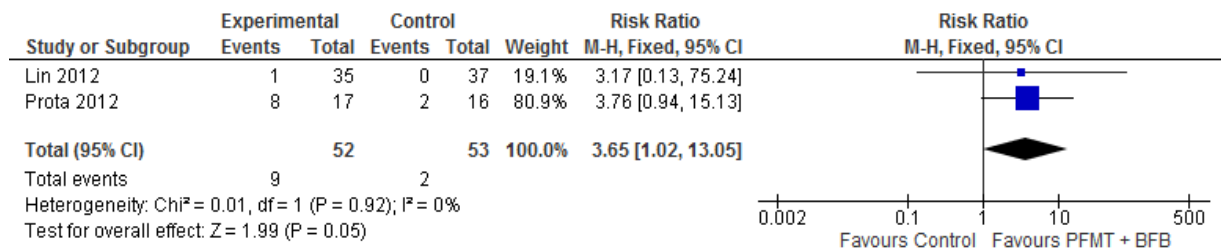
Figure 2. Treatment effectiveness for erectile dysfunction



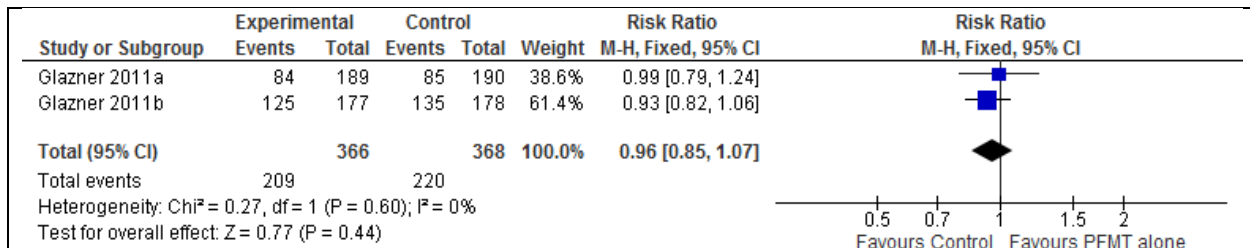
2A) PFMT plus ES for number of men reporting erectile function at 12-15 months follow-up



2B) PFMT plus BFB for erectile function at 3-months



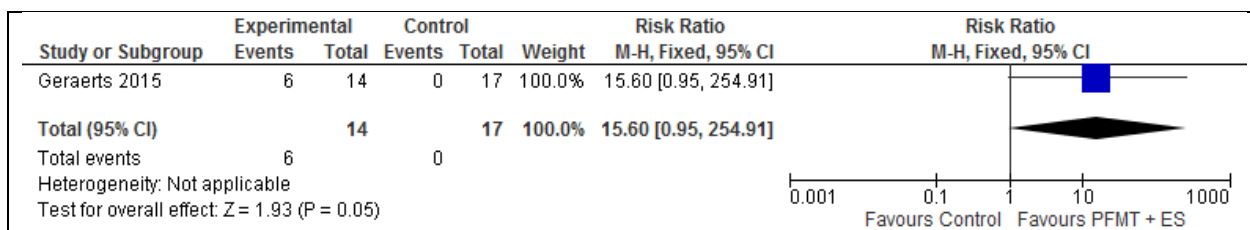
2C) PFMT plus BFB vs. no treatment control for number of men reporting erectile function at 3-months



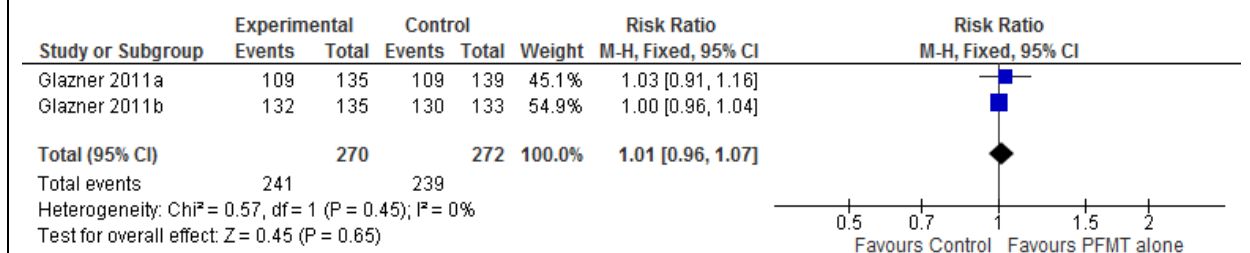
2D) PFMT vs no treatment for number of men reporting erectile function at 12-months follow-up

Note: BFB = Biofeedback; ES = Electrical Stimulation; PFMT = Pelvic Floor Muscle Training

Figure 3. Treatment effectiveness for Climacturia



3A) PFMT plus ES vs. no treatment for number of men reporting improved Climacturia at 15-months follow-up



3B) PFMT vs. no treatment for number of men reporting improved Climacturia at 12-months follow-up

Note: BFB = Biofeedback; ES = Electrical Stimulation; PFMT = Pelvic Floor Muscle Training

Supplementary Appendix 1: Search terms and search strategy

Subject areas	Search terms used
Prostatectomy AND	(prostatectomy) OR (radical prostatectomy) OR (transurethral resection of prostate) OR (prostatic Neoplasms) OR (prostatic hyperplasia) OR (prostate cancer) OR (prostate cancer surgery)
Sexual dysfunction AND	(sexual dysfunction) OR (erectile dysfunction) OR (penile erection) OR (climaturia)
Physiotherapy Interventions AND	(pelvic floor muscle exercise) OR (pelvic floor muscle strengthening) OR (pelvic floor muscle training) OR (electrical stimulation) OR (biofeedback) OR physiotherapy
Randomised Controlled Trial	(RCT) OR (random allocation) OR (randomised controlled tria*) OR (randomised controlled clinical trial)

Supplementary Appendix 2: Excluded studies and reasons for exclusion

1. Speakman M, 2004

Pelvic Floor Exercises for Treating Post-Micturition Dribble in Men With Erectile Dysfunction: A Randomised Controlled Trial.

Reason: Ineligible outcome measures.

2. Laurienzo CE 2018

Reason: Pelvic floor muscle training and electrical stimulation as rehabilitation after radical prostatectomy: a randomised controlled trial.

Reason: Data reported as median and range

3. Dorey G, 2005

Pelvic floor exercises for erectile dysfunction

Reason: Data reported as graphical format.

4. Van Kampen M, 2003

Treatment of erectile dysfunction by perineal exercise, electromyographic biofeedback, and electrical stimulation. *Physical therapy*. 2003 Jun 1;83(6):536-43.

Reason: Not RCT.

5. Lavoisier P, 2014

Pelvic-floor muscle rehabilitation in erectile dysfunction and premature ejaculation. *Physical therapy*. 2014 Dec 1;94(12):1731-43.

Reason: Not RCT.

6. Bocker B, 2002

Physikalische therapie der beckenbodeninsuffizienz (Physical therapy for pelvic floor insufficiency -- comparison of methods)

Reason: RCT evaluating Urinary incontinence.

7. Garcia M, 2015

Design and early clinical experience with a tactile feedback driven pelvic floor muscle training smartphone App.

Reason: Not RCT.

8. Reducing adverse effects of treatments for prostate cancer

Reason; Not RCT.

9. Karlsen, Randi V. 2017

Feasibility and acceptability of couple counselling and pelvic floor muscle training after operation for prostate cancer

Reason: Single-arm trial (no control group).

10. Meldrum, David R. 2014

Erectile Hydraulics: Maximizing Inflow While Minimizing Outflow

Reason: Review.

11. Sighinolfi, Maria Chiara, 2009

Potential Effectiveness of Pelvic Floor Rehabilitation Treatment for Prostatectomy Incontinence, Climacturia, and Erectile Dysfunction: A Case Series

Reason: Not RCT.

12. Geraerts, I. 2016

Pelvic floor muscle training for erectile dysfunction and climacturia 1 year after nerve sparing radical prostatectomy: a randomized controlled trial

Reason: Conference paper.

13. Goonewardene SS, 2018

A systematic review of PFE pre-prostatectomy.

Reason: Review.

14. Tafuri A, 2018

A pilot randomized trial of preoperative pelvic floor muscle exercise vs usual care to improve sexual function and health related quality of life after RARP: Preliminary disappointed results.

Reason: Conference paper.