Impact of Physical Exercise Program Interventions on Erectile Function and Cardiovascular Health in Males with Prostate Cancer

Eric Chung1,2,3, Handoo Rhee2
1AndroUrology Centre, Brisbane, QLD and Sydney, NSW, Australia, 2Department of Urology, Princess Alexandra Hospital, University of Queensland, Brisbane, QLD, Australia, 3Department of Urology, Macquarie University Hospital, Sydney, NSW, Australia

Prostate cancer (PC) and its associated treatments can cause significant cardiovascular and sexual dysfunctions. While structured exercise interventions can induce positive outcomes in males with PC, there are limited data on its effects on cardiovascular health, erectile function, or the combination of these outcomes. It has been proposed that positive changes in biomarkers of cardiovascular health through physical exercise programs, can result in cardiovascular remodelling and improve penile haemodynamic and erectile function recovery in those with metabolic syndrome and/or cardiovascular diseases, although the data is accruing in males who are diagnosed and/or treated for PC. While the results of this review article support structured physical exercise interventions to effectively prevent and mitigate the development of both sexual and cardiovascular dysfunctions in males with PC, appropriate caution should be maintained and future clinical research should focus on the development of standardised and evidence-based exercise guidelines in the setting of PC survivorship.

Keywords: Cardiovascular system; Erectile dysfunction; Exercise; Prostate cancer; Treatment outcomes

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Prostate cancer (PC) is a common malignancy and its associated treatments often result in various complications including male sexual dysfunction [1,2]. Similar to the higher incidence of PC with age, older males are more likely to report erectile dysfunction (ED) too [1,3]. There is a strong association between ED and cardiovascular disease (CVD) [4,5] since they share similar risk factors and pathophysiologic mechanisms [6,7]. The use of androgen deprivation therapy (ADT) in males with PC has been shown to increase subsequent risk of CVD due to adverse changes in body composition, metabolic profile, vascular hemodynamic, and biomarkers [6,7].

Published literature shows that a significant proportion of males with PC on active surveillance have ED [2] whilst those undergoing active PC treatment invariably have a higher rate of male sexual dysfunction [2,8]. Furthermore, there is a higher rate of cardiovascular-related morbidity and mortality in males who receive ADT [9]. Some of the proposed pathophysiologic mechanisms for ED relating to various PC treatments include neurovascular injury, inflammatory changes,
damage to surrounding structures, corporal hypoxia, and penile fibrosis, the adverse impact from urinary or bowel complications, as well as alterations in metabolic profile, psychosocial and relationship dynamics [8].

Penile rehabilitation is accepted as the standard of care in males following radical prostatectomy [10,11] and there is growing evidence to advocate its role in males receiving radiation therapy and ADT too [12]. While established pharmacotherapy for penile rehabilitation can be effective in restoring erectile function (EF), they may not affect underlying endothelial dysfunction which is thought to be the underlying basis for ED. Several publications have highlighted the role of lifestyle interventions and modification of these metabolic factors could improve CVD and alleviate ED [13-16]. In general, aerobic exercise involves endurance-type exercise for a sustained period and increases physical endurance and cardiac health; while anaerobic exercise consists of short, intensive levels of physical activity that improves muscle mass and strength [17,18]. There is some evidence that these physical activity interventions can improve sexual function in the cancer population [16,17] although its effects on cardiovascular health, EF, or the combination of these outcomes are uncertain in PC males [18,19]. The following review article examines the current understanding of the role of physical exercise program interventions on EF recovery and cardiovascular remodelling in males with PC.

**METHODS AND MATERIALS**

This review included research on ED and physical exercises in males with PC. Original articles, narrative reviews, systematic review and meta-analysis was undertaken on PUBMED search up to December 2020 based on the following keywords namely “erectile dysfunction”, “structured exercise program”, “cardiovascular”, “biomarkers”, and “prostate cancer”. This paper is not designed to provide systematic review or meta-analysis on this subject, nor offer a detailed description of each structured physical exercise program interventions in PC management.

**CLINICAL EVIDENCE ON CARDIOVASCULAR REMODELLING AND ERECTILE FUNCTION RECOVERY FOLLOWING PHYSICAL EXERCISE PROGRAM INTERVENTIONS (TABLE 1)**

While the positive impact of physical activity on cardiometabolic modifications [20,21] and EF [16,22] are well established, there are limited well-designed clinical trials are analysing the effects of structured exercise interventional programs on sexual function in PC populations whether it is pre-treatment or following radical prostatectomy, radiation therapy, or ADT [23-25]. It has been proposed that changes in biomarkers of cardiovascular health through physical exercise programs can improve penile haemodynamic and alleviate sexual dysfunction [26]. A recent systematic review [16] highlighted that a supervised exercise training with moderate-to-vigorous exercise intensity may be effective in improving EF in clinical populations such as those with metabolic syndrome and/or CVDs, although this did not include PC males.

Published literature in this field that evaluates the relationship between physical activity and sexual function in males with PC have reported mixed findings. Among males who had completed active treatment (surgery, or surgery and radiation therapy), no significant between-group differences were observed for sexual function for either the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its PC-specific module (EORTC QLQ-PR25) (-5.8, p=0.412) or the International Index of Erectile Function (IIEF)-5 scores (-2.8, p=0.431) at 15 months despite low-to-moderate intensity supervised aerobic and resistance exercise training [27]. Both the exercise and control groups experienced a significant improvement in sexual function as assessed by the EORTC QLQ-PR25 (+9.8, p=0.008 and +15.6, p=0.008, respectively), but not in the IIEF-5 (both p>0.05).

Preoperative exercise program on sexual function did not significantly improve EF in males who underwent radical prostatectomy at 6 months [28]. The same group [29] did not observe any acute effect of exercise on the cortical silent period on neuroimaging study that reflects self-reported vigour and positive mood. In a non-linear aerobic training study in males following radical
| Study (reference) | Type of prostate cancer treatment | Type of physical exercise program | Study design | Erectile function outcome | Cardiovascular parameters |
|-------------------|----------------------------------|-----------------------------------|--------------|--------------------------|--------------------------|
| Zoft et al [27]   | Post-radical prostatectomy       | Multi-modal intensity exercise     | 15-month program; randomised trial with 56 males received exercise and 29 males in control group | Improved IIEF-5 (p=0.008) | Improved VO2 peak (p=0.018) |
| Mina et al [28]   | Pre-radical prostatectomy        | Physical activity guidelines per American College of Sports Medicine | Non-blinded (retrospective); 234 males met vs. 275 not met guideline | Improved erectile function (p=0.049) | Not reported |
| Jones et al [30]  | Post-radical prostatectomy       | Aerobic exercise                  | Randomised trial, 25 males in each group | Improved IIEF-5 (p=0.406) | Improved VO2 peak (p=0.017) and FMD (p=0.07) |
| Dahn et al [31]   | Radiation                        | Normal physical activity          | 11 males non-randomised | Improved IIEF-5 (better for EBRT than brachytherapy) | No data |
| Ben-Josef et al [32] | Radiation                      | Twice-weekly yoga class           | Randomised trial, 22 received yoga and 28 in control group | Improved IIEF-5 (p=0.033) | No data |
| Dieperink et al [33] | Radiation and androgen deprivation therapy | Pelvic floor exercise            | Randomised trial, 79 received physical therapist and 82 in control group | Improved sexual function | Improved SF-12 physical component summary (p=0.002) |
| Cormie et al [34] | Androgen deprivation therapy     | Aerobic and resistance exercise   | Randomised trial, 29 in active group and 28 in control group | Improved sexual activity (p=0.045) | No data |
| Cormie et al [35] | Androgen deprivation therapy     | Aerobic and resistance exercise   | Randomised trial, 32 in active group and 31 in control group | Improved sexual function (p=0.028) | Improved VO2 peak (p=0.004), muscular strength (ps≤0.026), and total cholesterol: high-density lipoprotein:cholesterol ratio (p=0.028) |
| Pernar et al [36] | Newly diagnosed prostate cancer  | Walking exercise                  | Randomised trial, 21 in walking group and 20 in control group | Improved high-density lipoprotein (p=0.04), low-density lipoprotein (p=0.08), and systolic blood pressure (p=0.18). | |

IIEF: International Index of Erectile Function, VO2 peak: peak oxygen uptake, FMD: brachial artery flow-mediated dilation, EBRT: external beam radiation therapy, SF-12: quality-of-life Short-form-12 questionnaire.
prostatectomy, Jones et al [30] reported that the prevalence of ED (IIEF score ≤21) decreased by 20% in the aerobic training group with significant between-group differences were observed for changes in brachial artery flow-mediated dilation and peak oxygen uptake (VO₂peak), favouring aerobic training, although there were no group differences in other markers of cardiovascular risk profile or patient-reported outcomes.

For males who received radiation therapy, Dahn et al [31] observed males who maintained habitual physical activity levels were more likely to respond to erectile drugs, and those who had external beam radiation therapy for PC fared better than males who receive brachytherapy or combination treatments. Similarly, Ben-Josef et al [32] showed that a twice-weekly yoga class was associated with a significant reduction in pre-existing and radiation therapy-related sexual dysfunction in males who had external beam radiation therapy. On the other hand, a home-based 20-week pamphlet-based pelvic floor strengthening and resistance training intervention in males who had completed radiation therapy four weeks before study randomisation, did not result in any significant improvement on sexual function, as assessed by the Expanded Prostate Cancer Index Composite (EPIC)-26 scores (p=0.117) [33].

In the group of males on ADT who underwent a 12-week twice-weekly supervised moderate-to-vigorous intensity aerobic and resistance exercise intervention, combined with home-based aerobic exercise training, Cormie et al [34] found the exercise group maintained good sexual activity scores, especially on sexual libido pre- to post-intervention, whereas control group participants experienced a worsening in sexual activity over the same study period. Non-linear exercise program involving aerobic and resistance exercise when initiating ADT has been shown to significantly reduce treatment toxicity while improving social functioning and mental health [35]. Sexual activity did decrease in both groups, but to a lesser extent in the exercise group. Blood pressure parameters were maintained in the exercise group, while the control group did experience a significant increase in diastolic blood pressure.

A more sedentary exercise program by Pernar et al [36] also did not show significant between-group improvements in blood pressure parameters or sexual function (based on a visual analogue scale with the associated question ‘Do you have problems with your sex life?’). Interestingly, this study observed a non-significant within-group reduction in sexual function in the walking group (+25.8%) and non-significant within-group improvement in the usual care group (-28.6%) which may be explained in part by the self-reported level of social support provided to participants by their partners. Perceptions of both partner support and patient self-confidence in performing sexual activities may support the explanation for the above-mentioned clinical finding. Couple-based approaches with the involvement of the partner in exercise programs engage males and females as equal to improve their own and their partner’s physical health and allow for relationship-focus strategies [37-39]. This in turns may improve physical intimacy and other relational outcomes. Integration of pharmacotherapy and couple-based psychotherapy with structured exercise programs has been shown to enhance sexual outcomes too [40].

Collectively, the above-mentioned articles suggest that structured physical exercise interventions have a positive effect on cardiovascular health and can be effective in promoting improvements in sexual function in males with PC. Whether it is supervised higher-intensity aerobic exercise or more casual physical activity, the beneficial changes in sexual health outcomes should encourage adoption of these exercise interventions as a standard of care in PC survivorship. Nonetheless, it should be acknowledged that male sexual dysfunction in males with PC is a complex interplay of various factors beyond just penile erection and cardiovascular dysfunction [8]. Alterations in urinary and bowel functions, coupled with changes in psychosocial and relationship dynamics can affect sexual function in males following PC treatment [2].

Further clinical trials should explore various exercise interventions of differing durations, intensities and frequencies to identify the optimal exercise ‘dose’ for maximum positive effects on cardiovascular remodelling and sexual health in PC populations. The adoption of consistent, formal standards for methods and data reporting in exercise testing is needed to ensure high-quality research in the field of clinical oncology. The engagement of highly-trained allied health professionals with appropriate qualifications in sexual health and rehabilitation [41] are required to personalise these physical interventions for optimal clinical outcomes. Additional studies incorporating more novel biomark-
ers of CVD coupled with more objective evaluations of sexual function including use of penile colour Duplex ultrasonography or cortical neuroimaging study [42] should be conducted to further delineate the effects of physical activity on CVD risk remodelling and recovery of sexual function in this population.

CONCLUSIONS

Treatments for PC can cause significant cardiovascular and sexual dysfunctions. Physical exercise program interventions have a positive impact on cardiovascular remodelling and sexual function in men, and PC survivors should be encouraged to be physically active. While the results of this review article support structured physical exercise interventions to effectively prevent and mitigate the development of both sexual and cardiovascular dysfunctions in PC patients, appropriate caution should be exercised due to significant heterogeneity in exercise intervention designs and studied PC groups within the included articles. Further research is needed to develop standardised and evidence-based exercise guidelines to optimise the prevention and mitigation of cardiovascular and sexual dysfunctions in the setting of PC survivorship.

ACKNOWLEDGEMENTS

Professor Chung is the Chair of the Prostate Cancer Survivorship Committee on Sexual Health, Function and Rehabilitation for the International Consultation and Sexual Medicine. He has received the Princess Alexandra Hospital Research Foundation Grant on the role of structured exercise programs in improving cardio-vascular health and erectile function in males with prostate cancer.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: EC. Data curation: EC, HR. Formal analysis: EC, HR. Methodology: EC, HR. Supervision: EC. Writing – original draft: EC. Writing – review & editing: EC, HR.

REFERENCES

1. Negoita S, Feuer EJ, Mariotto A, Cronin KA, Petkov VI, Hussey SK, et al. Annual report to the nation on the status of cancer, part II: recent changes in prostate cancer trends and disease characteristics. Cancer 2018;124:2801-14.
2. Chung E, Brock G. Sexual rehabilitation and cancer survivorship: a state of art review of current literature and management strategies in male sexual dysfunction among prostate cancer survivors. J Sex Med 2013;10 Suppl 1:102-11.
3. McKinlay JB. The worldwide prevalence and epidemiology of erectile dysfunction. Int J Impot Res 2000;12 Suppl 4:S6-11.
4. Thompson IM, Tangen CM, Goodman PJ, Probstfield JL, Moinpour CM, Coltman CA. Erectile dysfunction and subsequent cardiovascular disease. JAMA 2005;294:2996-3002.
5. Gandaglia G, Briganti A, Jackson G, Klomer RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol 2014;65:968-78.
6. Corona G, Rastrelli G, Isidori AM, Pivonello R, Bettocchi C, Reisman Y, et al. Erectile dysfunction and cardiovascular risk: a review of current findings. Expert Rev Cardiovasc Ther 2020;18:155-64.
7. Gacci M, Eardley I, Giuliano F, Hatzichristou D, Kaplan SA, Maggi M, et al. Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 2011;60:809-25.
8. Chung E. Management of treatment-related sexual complications in cancer care: evidence for erectile function recovery and penile rehabilitation after radical prostatectomy in prostate cancer survivorship. Expert Rev Qual Life Cancer Care 2017;2:279-86.
9. Zhao J, Zhu S, Sun L, Meng F, Zhao L, Zhao Y, et al. Androgen deprivation therapy for prostate cancer is associated with cardiovascular morbidity and mortality: a meta-analysis of population-based observational studies. PLoS One 2014;9:e107516.
10. Chung E, Gillman M. Prostate cancer survivorship: a review of erectile dysfunction and penile rehabilitation after prostate cancer therapy. Med J Aust 2014;200:582-5.
11. Feng D, Tang C, Liu S, Yang Y, Han P, Wei W. Current management strategy of treating patients with erectile dysfunction after radical prostatectomy: a systematic review and meta-analysis. Int J Impot Res 2020. doi: 10.1038/s41443-020-00364-w [Epub].
12. Doherty W, Bridge P. A systematic review of the role of penile rehabilitation in prostate cancer patients receiving radiotherapy and androgen deprivation therapy. J Med Imaging Radiat
Sci 2019;50:171-8.
13. Kaya-Sezginer E, Gur S. The inflammation network in the pathogenesis of erectile dysfunction: attractive potential therapeutic targets. Curr Pharm Des 2020;26:3955-72.
14. Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 2012;87:766-78.
15. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med 2011;171:1797-803.
16. Gerbild H, Larsen CM, Graugaard C, Areskoug Josefsson K. Physical activity to improve erectile function: a systematic review of intervention studies. Sex Med 2018;6:75-89.
17. Campos C, Sotomayor P, Jerez D, González J, Schmidt CB, Schmidt K, et al. Exercise and prostate cancer: from basic science to clinical applications. Prostate 2018;78:639-45.
18. Baumann FT, Zopf EM, Bloch W. Clinical exercise interventions in prostate cancer patients--a systematic review of randomized controlled trials. Support Care Cancer 2012;20:221-33.
19. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al. Exercise for men with prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;69:693-703.
20. Lin X, Zhang X, Guo J, Roberts CK, McKenzie S, Wu WC, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2015;4:e002014.
21. Artero EG, Lee DC, Lavie CJ, España-Romero V, Sui X, Church TS, et al. Effects of muscular strength on cardiovascular risk factors and prognosis. J Cardiopulm Rehabil Prev 2012;32:351-8.
22. Vear NK, Coombes JS, Bailey TG, Skinner TL. The interplay between vascular function and sexual health in prostate cancer: the potential benefits of exercise training. Med Sci (Basel) 2020;8:11.
23. Owen PJ, Daly RM, Livingston PM, Fraser SF. Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: an update. Prostate Cancer Prostatic Dis 2017;20:137-45.
24. Kiwata JL, Dorff TB, Schroeder ET, Gross ME, Dieli-Conwright CM. A review of clinical effects associated with metabolic syndrome and exercise in prostate cancer patients. Prostate Cancer Prostatic Dis 2016;19:323-32.
25. Wittmann D, Mehta A, Northouse L, Dunn R, Braun T, Duby A, et al. TrueNTH sexual recovery study protocol: a multi-institutional collaborative approach to developing and testing a web-based intervention for couples coping with the side-effects of prostate cancer treatment in a randomized controlled trial. BMC Cancer 2017;17:664.
26. Silva AB, Sousa N, Azevedo LF, Martins C. Physical activity and exercise for erectile dysfunction: systematic review and meta-analysis. Br J Sports Med 2017;51:1419-24.
27. Zopf EM, Bloch W, Machtens S, Zumbé J, Rübben H, Marschner S, et al. Effects of a 15-month supervised exercise program on physical and psychological outcomes in prostate cancer patients following prostatectomy: the ProRehab study. Integr Cancer Ther 2015;14:409-18.
28. Santa Mina D, Guglietti CL, Alibhai SM, Matthew AG, Kalnin R, Ahmad N, et al. The effect of meeting physical activity guidelines for cancer survivors on quality of life following radical prostatectomy for prostate cancer. J Cancer Surviv 2014;8:190-8.
29. Santa Mina D, Guglietti CL, de Jesus DR, Azargive S, Matthew AG, Alibhai SM, et al. The acute effects of exercise on cortical excitation and psychosocial outcomes in men treated for prostate cancer: a randomized controlled trial. Front Aging Neurosci 2014;6:332.
30. Jones LW, Hornsby WE, Freedland SJ, Lane A, West MJ, Moul JW, et al. Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer. Eur Urol 2014;65:852-5.
31. Dahn JR, Penedo FJ, Molton I, Lopez L, Schneiderman N, Antoni MH. Physical activity and sexual functioning after radiotherapy for prostate cancer: beneficial effects for patients undergoing external beam radiotherapy. Urology 2005;65:953-8.
32. Ben-Josef AM, Chen J, Wileyto P, Doucette A, Bekelman J, Christodoulou J, et al. Effect of Eischens yoga during radiation therapy on prostate cancer patient symptoms and quality of life: a randomized phase II trial. Int J Radiat Oncol Biol Phys 2017;98:1036-44.
33. Dieperink KB, Johansen C, Hansen S, Wagner L, Andersen KK, Minet LR, et al. The effects of multidisciplinary rehabilitation: RePCa-a randomised study among primary prostate cancer patients. Br J Cancer 2013;109:3005-13.
34. Cormie P, Newton RU, Taaffe DR, Spry N, Joseph D, Akhll Hamid M, et al. Exercise maintains sexual activity in men undergoing androgen suppression for prostate cancer: a randomized controlled trial. Prostate Cancer Prostatic Dis 2013;16:170-5.
35. Cormie P, Galvão DA, Spry N, Joseph D, Chee R, Taaffe DR, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int 2015;115:256-66.
36. Pernar CH, Fall K, Rider JR, Markt SC, Adami HO, Andersson SO, et al. A walking intervention among men with prostate cancer: a pilot study. Clin Genitourin Cancer 2017;15:e1021-8.
37. Lyons KS, Winters-Stone KM, Bennett JA, Beer TM. The effects of partnered exercise on physical intimacy in couples coping with prostate cancer. Health Psychol 2016;35:509-13.
38. Chambers SK, Schover L, Halford K, Clutton S, Ferguson M, Gordon L, et al. ProsCan for couples: randomised controlled trial of a couples-based sexuality intervention for men with localised prostate cancer who receive radical prostatectomy. BMC Cancer 2008;8:226.
39. Winters-Stone KM, Lyons KS, Dobek J, Dieckmann NF, Bennett JA, Nail L, et al. Benefits of partnered strength training for prostate cancer survivors and spouses: results from a randomised controlled trial of the Exercising Together project. J Cancer Surviv 2016;10:633-44.
40. Cormie P, Chambers SK, Newton RU, Gardiner RA, Spry N, Taaffe DR, et al. Improving sexual health in men with prostate cancer: randomised controlled trial of exercise and psychosexual therapies. BMC Cancer 2014;14:199.
41. Areskoug-Josefsson K, Gard G. Physiotherapy as a promoter of sexual health. Physiother Theory Pract 2015;31:390-5.
42. Chung E. Contemporary and novel imaging studies for the evaluation of erectile dysfunction. Med Sci (Basel) 2019;7:87.