Effects of exercise on disablement process model outcomes in prostate cancer patients undergoing androgen deprivation therapy

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Background Androgen-deprivation therapy (ADT) results in adverse physiologic, metabolic, and functional side effects that may accelerate functional limitations in patients with prostate cancer (PC). Although exercise improves muscular strength and functional performance, the extent to which exercise yields similar improvements in other disablement process outcomes in men on ADT has yet to be systematically evaluated.

Objective To explore whether exercise results in comparable improvements in physiologic and structural body system impairment, functional limitation (relating to basic physical or mental actions), and physical disability domain outcomes identified in the Disablement Process Model (DPM) in PC patients who are receiving ADT.

Methods Data from studies of exercise interventions in men on ADT were extracted on impairment, functional limitation, and physical disability domain outcomes. The average of weighted, bias-corrected effect sizes were calculated for each outcome and compared across domains. A total of 9 studies (6 randomized controlled trials, 3 uncontrolled trials) conducted with 684 PC patients met the inclusion criteria.

Results Exercise yielded heterogeneous effect-size improvements in physical impairments, ranging from large improvements in muscular strength (*d* = .74; 95% CI, .14-1.47) and endurance (*d* = 2.64; 95% CI, 1.08-2.84), to small improvements in body composition measures (*d* = .12; 95% CI, -.52-.68).

Conclusions Whereas exercise resulted in meaningful effect-size improvements in functional limitation domain outcomes (*d* = .39; 95% CI, -.42-1.01), findings from the 4 studies that assessed a physical disability, domain outcomes revealed only small improvements (*d* = .10; 95% CI, -.44-.43) in these outcomes. Collectively, exercise consistently results in meaningful improvements in physical impairments and functional limitations in basic physical tasks. However, to date, few studies have evaluated the effects of exercise on physical disability domain outcomes, and the results suggest that the effects of exercise on physical disability measures are of a smaller magnitude relative to those observed for impairment and functional limitation domain outcomes.

Prostate cancer (PC) affects about a quarter of a million men each year and is the second leading cause of cancer mortality in the US.[1] Androgen-deprivation therapy (ADT) is the foundation of treatment for men with metastatic PC and is now commonly incorporated into multimodality curative treatment (with radiotherapy and/or surgery) of localized or locally advanced PC.[2,3] However, it has become increasingly evident that men who undergo prolonged ADT endure significant and protracted adverse effects as a "trade-off" for more effective cancer control and increased longevity. In recent years, mounting evidence has demonstrated that the catabolic and metabolic effects of ADT result in serious morbidity, including loss of lean muscle mass, increased fat mass (eg, sarcopenic obesity), reduced muscle strength, and lower bone mineral density.[4-11]

More than 70% of PC patients in the United States are aged 60 years or older.[1] Epidemiological evidence has demonstrated that nearly half of all adults aged 65 years or older exhibit meaningful functional limitations, and 20% report difficulty with basic activities of daily living.[12] Consequently, the adverse effects accompanying ADT place older men who are undergoing ADT at increased risk for frailty and functional limitations.[6,7] As prolonged administration of ADT becomes increasingly com-

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mon in the treatment of metastatic and localized PC, many men will cope with lasting treatment-related side effects that could meaningfully compromise their physical function and accelerate progression toward physical disability and loss of independence.[4,9,13-17] Given the critical role of ADT in the treatment of PC, there is now a vital need to identify feasible, efficacious interventions for reducing the risk of functional decline in men undergoing prolonged exposure to androgen suppression. In this regard, there is now strong evidence that exercise is a promising lifestyle intervention that can offset, or even reverse, many of the adverse effects of ADT. Indeed, exercise interventions consistently yield significant, clinically meaningful improvements in muscular strength, fatigue, physical function, and quality of life in PC patients on ADT.[18-20] These findings provide support for the use of exercise as an adjuvant treatment during ADT and reinforce proposals that exercise be included as part of the standard of care treatment for PC patients.[21]

Although emerging evidence has established that exercise is a valuable behavioral intervention for men undergoing ADT,[19] the pathways through which exercise may improve functional limitations or prevent physical disability remain poorly delineated. The Disablement Process Model (DPM), originally introduced by Nagi[22] and subsequently expanded by Verbrugge and Jette,[23] is a well-established theoretical framework that has frequently been applied in research that addresses the effects of exercise on the disablement process in aging populations.[24-28] The DPM proposes that outcomes from 4 interrelated domains (active pathology, impairments, functional limitations, and physical disability) comprise the primary pathway involved in functional decline and progression toward physical disability. Within the DPM, *active pathology* is defined as the interruption of normal cellular processes based on degenerative disease processes or injury and trauma. *Impairments* are abnormalities or dysfunction in basic physiologic and structural body systems, whereas *functional limitations* are restrictions in ability to perform basic physical or mental actions. *Disability* is defined as the expression of physical or mental functional limitations in a social context resulting in difficulty in the performance of activities of daily living and personal/social role behaviors. The DPM domains are proposed to be interrelated in that active pathology results in impairments, impairments lead to functional limitations, and functional limitations facilitate the progression and/or onset of disability.

Although the DPM has been widely used as a framework for evaluating studies of the functional benefits of exercise for older adults,[24-28] it has yet to be systematically applied to PC patients. Nonetheless, it provides a strong conceptual framework for explaining both the adverse physiologic and functional effects of ADT (Figure 1) and the potential benefits of exercise in attenuating, or reversing, functional limitations, and physical disability in PC patients undergoing ADT. Specifically, the active pathology of PC and subsequent reduction of testosterone to castrate levels accompanying the administration of ADT result in declines in muscular strength, lean body mass, and bone mineral density as well as increases in fat mass and body fat percentage (eg, impairments). Impairments in muscular fitness and body composition lead to difficulty in the performance of basic physical tasks such as walking or climbing stairs (eg, functional limitations). In turn, limitations in the ability to complete these basic physical tasks lead to difficulty in the performance of activities of daily living and the personal/social role behaviors necessary to maintain independence (eg, physical disability). As depicted in Figure 1, given the adverse physiologic effects of ADT and the established physiologic adaptations accompanying exercise training, the focus of this review is on the effects of exercise on physical impairments, functional limitations in basic physical tasks, and physical disability.

From a conceptual standpoint in applying the DPM to PC patients, ADT-induced accumulation of physical impairments in fitness, body composition, and bone density can foster functional limitations in a patient's ability to perform basic physical tasks, which subsequently facilitates the onset and/or progression of physical disability. Thus, therapeutic interventions that produce improvements in relevant physiologically related impairment and functional limitation domain outcomes could have a meaningful impact in preventing and/or minimizing the risk of physical disability in men on ADT. There is clear support for the role of exercise as a biobehavioral determinant of the disablement process. Exercise interventions can minimize and/or reverse functional decline through its favorable effect upon impairment and functional limitation domain outcomes.[24,25] However, results from systematic reviews of the exercise-aging literature[26-28] reveal considerable variability in the magnitude of improvement in DPM domain outcomes accompanying exercise training. On the one hand, exercise consistently results in improvements in impairment (muscular strength, aerobic capacity) and functional limitation domain outcomes (eg, performance on walking, stair climbing, chair rise tasks). On the other hand, far fewer studies have investigated the effects of exercise on physical disability domain outcomes (eg, difficulty in the performance of activities of daily living and personal and/or social role behaviors), and results from the limited number of studies to explore this relationship suggest the improvements in physical disability-related outcomes are smaller than are those observed for impairment and functional limitation domain outcomes.

Collectively, these findings have led some to suggest that exercise is necessary, but not sufficient alone, to pre-

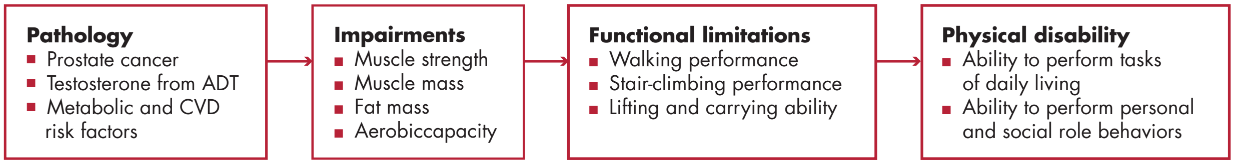

FIGURE 1 The disablement process model applied to prostate cancer patients undergoing androgen deprivation therapy

ADT, androgen-deprivation therapy; CVD, cardiovascular disease

vent physical disability among older adults.[25,28] It is important to recognize that the effects of exercise on functional limitations and physical disability becomes complicated by conceptual and measurement issues.

As noted by Keysor and Brembs, many self-report measures contain items reflecting both function and disability.[28] Furthermore, some researchers erroneously refer to functional limitations and physical disability synonymously and use the same objective tests (ie, 400-m walk, chair stand, etc) as assessments of both functional limitations and disability. Nonetheless, the DPM provides a conceptual framework that clearly differentiates these constructs and allows for the evaluation of the comparable effects of exercise on functional limitations and physical disability.

Despite growing evidence of the promise of exercise as a supportive care intervention for PC patients, the utility of exercise interventions for producing meaningful improvements in DPM outcomes in men undergoing prolonged ADT has yet to be systematically evaluated. Establishing the comparable efficacy of exercise for eliciting improvements in relevant impairment, functional limitation, and physical disability domain outcomes among men on ADT would yield important information guiding the design and delivery of exercise interventions targeting PC patients. Consequently, the primary purpose of this systematic review is to explore if exercise yields comparable improvements in impairment, functional limitation, and physical disability domain outcomes of the DPM in PC patients undergoing ADT.

Methods

Study selection and data abstraction

Studies included in the systematic review were obtained through computer and manual searches following the Preferred Reporting Items for Systematic Reviews (PRISMA).[29] We conducted an original search in May 2012 of titles and abstracts in the PubMed, MEDLINE. Psychinfo, Sport Discus, and Web of Science databases. We conducted this search again in December 2013, during a revision of the manuscript, to ensure inclusion of any additional articles that were published in the interim. Searches were conducted of English language articles that addressed human participants only. Search terms including exercise (aerobic exercise, physical activity, resistance exercise, strength training, weight training, and rehabilitation), ADT, and prostate cancer were entered in different combinations. Consistent with PRISMA guidelines,[29] the flow diagram in Figure 2 summarizes the results of the computerized database search. Manual searches were also conducted using the reference lists of other narrative and meta-analytic reviews of the exercise–cancer literature[30-33]

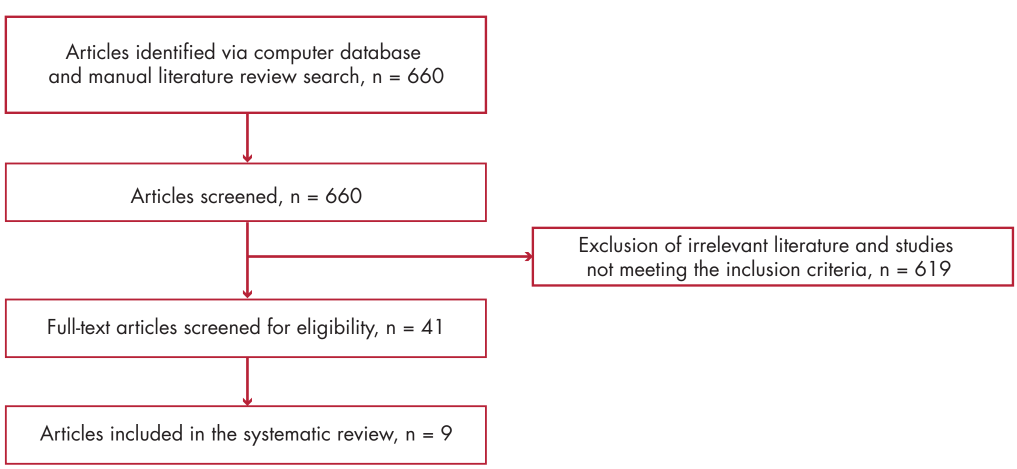

FIGURE 2 PRISMA study search flow diagram

as well as the reference lists of each study included in the present review.

Data extraction was performed by 2 reviewers (BCF, ARL) and any instance of disagreement about a study's inclusion or exclusion criteria was resolved by consensus of all the authors. To be included in the present review, studies had to have:

- Targeted a sample of men with histologically defined diagnosis of PC currently undergoing ADT. Studies that combined men diagnosed with PC together with patients and/or survivors of other types of cancer were excluded.
- Assessed the effects of an exercise intervention on more than 1 outcome that could be classified into the impairment, functional limitation, or physical disability domains of the DPM.[22] For the purposes of this review, we have defined exercise as planned, structured, and repetitive physical activity participation to improve or maintain one or more components of physical fitness. Studies of the efficacy of pelvic floor exercises to address incontinence were excluded because that type of activity was not consistent with our operational definition of exercise. In addition, to isolate the independent effects of exercise, studies that combined exercise with other interventions were excluded from the review.
- Provided adequate statistical information to calculate effect sizes.

Data synthesis

Results from the studies that have been included in the present review have been synthesized using qualitative summary and quantitative effect size calculation. Qualitative synthesis was conducted through a narrative review of each study's design, resistance exercise (RE) intervention characteristics, and primary outcome findings. Quantitative synthesis was conducted by calculating weighted, bias corrected (Hedges) Cohen's *d* effect sizes[34] and 95% confidence intervals (CIs) using an effect size an confidence interval calculator.[35,36] Given the limited number of studies that have evaluated the effect of exercise on DMP outcomes, the lack of large scale randomized, controlled trials and the considerable variability in the exercise interventions implemented, we believed that a meta-analysis of these findings would be premature at this time. However, given that the objective of the present review was to explore whether or not exercise results in comparable improvements in DPM outcomes, it is also critical to the interpretation of the extant findings to provide an estimate of the magnitude of the exercise effect across DPM domains. Consequently, the average of the bias-corrected, weighted effect sizes were calculated and compared across DPM domains." Cohen's *d* effect sizes are classified as: small = 0.20; moderate = 0.50; and large = 0.80. Because many studies in this review were uncontrolled trials that did not include a control or comparison group in the experimental design, we focused on the magnitude of pre- to post-intervention change in the outcomes that were observed after the exercise intervention. It should be noted that negative effect size values can reflect favorable changes in select outcomes (eg, declines in ratings of fatigue or decreases in duration needed to complete timed functional performance tasks). However, the sign of effect sizes was set so that only positive values indicate improvement in that respective outcome. Thus, positive effect size values indicate that exercise resulted in improvement in an outcome, whereas negative effect sizes reflect unfavorable changes in an outcome. The weighted, bias-corrected effect sizes and CI for the effect size are provided for each DPM outcome that was included in the reviewed studies.

Methodological quality assessment

The methodological quality of each study was assessed by 2 independent reviewers (BCF, ARL) using 7 quality indicators from the Delphi Consensus Criteria List.[37] The following quality indicators were used to assess each study's methodology:

- Was randomization performed?
- Was treatment allocation concealed?
- Were groups similar at baseline on key outcome measures?
- Were participant eligibility criteria specified?
- Were outcome assessments obtained by blinded evaluators?
- Were descriptive statistics for primary outcome measures reported?
- Were intention to treat analysis conducted?

Each item was rated as Yes, No, or Don't Know, based on the methods reported in each study (Table 1). Given that there is presently no validated summary scoring system for the Delphi Criteria List, the percentages of the quality indicators met by the studies were tabulated and described to judge overall methodological quality of the studies. Comparisons of the percentages of quality indicators met between the randomized trials and nonrandomized trials were also evaluated.

Results

Study characteristics and DPM domain assessments

A total of 9 studies targeting 684 PC patients met the inclusion criteria. The mean age of study participants was 68 years (SD, 2.15). Sixty-seven percent of the studies were randomized controlled trials,[38-42] and 33% were uncontrolled trials.[43-45] In regard to the type of exercise intervention, 3 studies examined resistance exercise alone,[38,43,45] 1 examined aerobic exercise alone,[39] 3 examined combined resistance and aerobic exercise interventions,[40,42,44] and 2 compared resistance and aerobic exercise interventions.[41]

TABLE 1 Methodologic quality indicators from the Delphi Quality Assessment Criteria

Study	Randomized	Allocation concealed	Key outcomes similar at baseline	Eligibility criteria specified	Single blind	Key descriptive statistics provided	Intent-to-treat analysis
Segal[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Galvao[43]	No	na	na	Yes	No	Yes	Don't know
Taylor[39]	Yes	Yes	Yes	Yes	Don't know	Yes	Yes
Culos-Reed[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Segal[41]	No	na	na	Yes	No	Yes	Don't know
Hansen[45]	Yes	Yes	Yes	Yes	Don't know	Yes	Don't know
Galvao[40]	Yes	Don't know	Yes	Yes	Don't know	Yes	Yes
Cluos-Reed[44]	No	na	na	Yes	Yes	Yes	Don't know
Santa Mina[48]	Yes	No	Yes	Yes	No	Yes	Yes

na, not available

The average duration of the exercise interventions was 17.50 weeks (SD, 5.98) and 56% of the exercise interventions were supervised, 22% of the interventions involved primarily unsupervised, home-based exercise, and 22% involved a combination of supervised and unsupervised exercise (Table 2).

A summary of the impairment, functional limitation, and physical disability domain outcomes included in the 9 studies is summarized in Table 3. Seven of the 9 studies (78%) included assessments of impairment domain outcomes. Several different impairment domain outcomes were assessed, including muscular strength, muscular endurance, balance, aerobic capacity, body composition, and bone mineral density. Six of the 9 studies (67%) assessed functional limitation domain outcomes, including 6-min walk, 400-m walk, chair stand, timed up and go, and self-reported function (eg, Short Form 36-item physical function subscale). Conversely, 4 of 9 studies (44%) assessed a physical disability outcome. The only measure implemented in any of the studies that was categorized into the physical disability domain was the Functional Assessment of Cancer Therapy–Fatigue, which tapped the extent to which fatigue interfered with the performance of activities of daily living. Consistent with DPM domain outcomes assessments that were observed in systematic reviews of the exercise–aging literature, most of the exercise interventions in the present review included measures of impairment and functional limitation domain outcomes, whereas few studies have included assessments of physical disability domain outcomes.

Methodological quality assessment

Overall, the studies met 71% of the Delphi study quality indicators (range, 100%-29%) included in the methodological assessment. Of note is that 67% of the studies were randomized, 56% implemented intention-to-treat analysis, and 33% conducted blinded assessments of key outcomes. There were considerable differences between randomized and non-randomized studies in the number of quality indicators met. The 6 randomized studies met an average of 83% of the quality indicators whereas the 3 non-randomized studies met only 33% of the quality indicators considered in the present review.

Exercise interventions

A brief summary of the sample, assessments, and the effect sizes accompanying exercise-induced changes in the impairment, functional limitation, and physical disability domain outcomes in each study is provided in the following section of the review.

In a randomized controlled trial, Segal et al,[38] compared the effects of a 12-week, center-based, supervised resistance exercise intervention with those of a wait-list control group in a sample of 155 PC patients on ADT. The RE prescription consisted of 3 sessions a week in which participants completed 2 sets of 8-12 reps at 70%-80% of their one-repetition maximum (1RM). Assessments of impairment domain outcomes (eg, muscular endurance and body composition) and physical disability (FACT–F: interference in performing activities of daily living because of fatigue) were obtained at baseline and 12-week follow-up. No functional limitation domain outcomes were measured. RE resulted in significant increases in upper- and lower-body muscular endurance. However, information that was necessary to calculate effect sizes for improvements in muscular endurance was not provided. No significant changes in body composition were observed. Information to calculate the effect

TABLE 2 Study characteristics

Study	Design	Sample size	Exercise intervention				
			Mode	Load/volume/ intensity	Frequency	Duration, weeks	Supervised/ unsupervised
Segal[38]	RCT	155	RE	70%-80% 1RM 2 sets, 8-12 reps	3x a week	12	S
Galvao[43]	NR	10	RE	80% 1RM 2-4 sets, 6-12 reps	2x a week	20	S
Taylor[39]	RCT	134	AE	na	3-5x a week	26	S, U
Culos-Reed[42]	NR	31	AE, RE	na	3-5x a week	12	U
Segal[41]	RCT	121	AE, RE	60%-70% 1RM 2 sets, 8-12 reps 60%-75% VO2 peak	3x a week	24	S
Hansen[45]	NR	10	RE	RPE 9-13	3x a week	12	S
Galvao[40]	RCT	57	AE, RE	65%-80% HR 6-2 RM	2x a week	12	S
Cluos-Reed[44]	RCT	100	AE, RE	na	3-5x a week	16	S, U
Santa Mina[48]	RCT	66	AE, RE	60%-80% 1RM 60%-80% HRReserve 2-3 sets, 8-12 reps	3-5x a week	24	U

AE, aerobic exercise; HR, heart rate; HRReserve, heart rate reserve; na, data not available; NR, nonrandomized study; RCT, randomized controlled trial; RE, resistance exercise; RM, repitition maximum; RPE, rating of perceived exertion; S, supervised exercise; U, unsupervised exercise; VO2,aerobic capacity

sizes for body composition was also not available. However, RE was associated with a statistically significantly, yet small effect size reduction in the role of fatigue in interfering with activities of daily living (*d* = .11; 95% CI, -.41-.20).

Galvao and colleagues[43] conducted a single-arm, uncontrolled trial examining the effects of a center-based, supervised 20-week progressive resistance exercise intervention in a sample of 10 men undergoing ADT. The RE prescription consisted of 2 sessions a week in which participants completed 2-4 sets using loads corresponding to their 6RM-12RM. Assessments of multiple impairment (muscular strength, muscular endurance, balance, body composition, and bone mineral density) and functional limitation domain outcomes (6-min walk, 400-m walk, stair climb, and chair stand) were obtained at baseline and 20-week follow-up. No physical disability domain outcomes were measured. The resistance exercise intervention yielded improvements in the impairment domain outcomes of upper- (*d* = 1.84; 95% CI, .79-2.88) and lower-body muscular strength (*d* = 1.45; 95% CI, .46-2.43), upper- (*d* = 2.51; 95% CI, 1.34-3.64) and lower-body muscular endurance (*d* = 2.77; 95% CI, 1.55-4.00), and balance (*d* = .88; 95% CI, .04-1.88). Conversely, the RE intervention resulted in small effect size improvements in the impairment domain body composition outcomes of lean body mass (*d* = 0.03; 95% CI, -.84-.91), fat mass (*d* = 0.09; 95% CI, -.79-.97), body fat percentage (*d* = 0.01; 95% CI, -.86-.89), and bone mineral density (*d* = 0.08; 95% CI, -.96-.80). Resistance exercise also resulted in improvements in the functional limitation domain outcomes of 6-min walk (*d* = .55; 95% CI, -.34-1.45), 400-m walk (*d* = .78; 95% CI, -.13-1.69), stair climb (*d* = 0.21; 95% CI, -.67-1.08), and chair stand performance (*d* = 1.19; 95% CI, .24-2.14).

Taylor and colleagues[39] compared the effects of a 24-week lifestyle physical activity intervention with those of an educational support group and standard care control group in a sample of 134 PC patients on ADT. The physical activity intervention involved 6 months of weekly or biweekly group-based sessions designed to promote at least 30-min of daily, home-based moderate intensity physical activity. Promotion of home-based walking and purposeful, lifestyle activity were the primary goals of the intervention. Assessments of functional limitation domain outcomes (6-min walk performance and self-reported physical function) were obtained at baseline and 6- and 12-month follow-up. No impairment or physical disability domain outcomes were measured. Results revealed small nonsignificant changes in 6-min walk (6 months: *d* = 0.17; 95% CI, -.61-.27 and 12 months: *d* = 0.17; 95% CI, -.61-.27) and self-reported physical function (6 months: *d* = 0.09; 95% CI, -.34-.53 and 12 months *d* = 0.26; 95% CI, -.18-.70).

Culos-Reed and colleagues[44] conducted a single-arm, uncontrolled trial examining the effects of a 12-week, home-based exercise intervention in a sample of 31 men undergoing

TABLE 3 Disablement process model domain outcomes assessed and effect sizes (*d*) after the exercise interventions

	Domain					
	Impairment		Functional limitations		Physical disability	
Study	**Measure**	***d***	**Measure**	***d***	**Measure**	***d***
Segal[38]	Muscular strength		na	–	FACT-F	.11
	Chest press	NR				
	Leg extension	NR				
	Body composition					
	Lean body mass	NR				
	Fat mass	NR				
Galvao[43]	Muscular strength		Chair stand	1.19	na	–
	Upper body	1.84	6-min walk	.55		
	Lower body	1.45	Stair climb	.21		
	Muscular endurance		400-m walk	.78.		
	Upper body	2.51				
	Lower body	2.77				
	Body composition					
	Lean body mass	.03				
	Fat mass	.09				
	Body fat %	.01				
	BMD	.08				
	Balance (SOT)	.88				
Taylor[39]	na	–	6-min walk		na	–
			6 mo	.17		
			12 mo	.17		
			SF-36			
			6 mo	.09		
			12 mo	.26		
Culos-Reed[42]	na	–	6-min walk	.54	na	–
			SF-36	.11		
Segal[41]	RE intervention		na	–	FACT-F	
	Muscular strengt				3 mo	.16
	Chest press	.89			6 mo	.26
	Leg extension	.74				
	Aerobic fitness					
	VO2 maximum	.13				
	Body composition	.06				
	Body fat %					
						.11
	AE intervention	.12			FACT-F	.01
	Muscular strength	.04			3 mo	
	Chest press				6 mo	
	Leg extension	.03				
	Aerobic fitness					
	VO2 maximum	.20				
	Body composition					
	Body fat %					
Hansen[45]	Muscular strength		6-min walk	.37	FACT-F	.12
	Leg extension	.51	Timed up and go	.39		
	Body composition					
	Muscle volume	.10				

Continued on next page

ADT. The exercise intervention involved walking, light resistance band training, and flexibility exercises performed 3-5 times a week. Assessments of functional limitation domain outcomes (6-min walk performance and self-reported physical function) were obtained at baseline and 12-week follow-up. No impairment or physical disability

TABLE 3 *continued*

Study	Impairment Measure	d	Functional limitations Measure	d	Physical disability Measure	d
Galvao[40]	Muscular strength		Chair stand	.49	na	–
	Chest press	.34	6-min walk	.65		
	Seated row	.68	400-m walk	.34		
	Leg press	.74	SF-36	.07		
	Leg extension	.78				
	Body composition					
	Lean body mass	.10				
	Fat mass	.03				
	Body fat %	.07				
	Balance (SOT)	.37				
Cluos-Reed[44]	Body composition		6-min walk	.13	na	–
	Neck circumference	.15				
	Waist circumference	.08				
Santa Mina[48]	AE intervention		na	–	FACT-F	
	Body fat %				3 mo	.07
	3 mo	.33			6 mo	.02
	6 mo	.29			12 mo	.02
	12 mo	.28				
	Grip strength					
	3 mo	.02				
	6 mo	.04				
	12 mo	.07				
	RE intervention					
	Body fat %		na	–	FACT-F	
	3 mo	.12			3 mo	.05
	6 mo	.14			3 mo 6 mo?	.20
	12 mo	.28			3 mo 12 mo?	.02
	Grip strength					
	3 mo	-.17				
	6 mo	-.07				
	12 mo	-.11				

AE, aerobic exercise; FACT-F, Functional Assessment of Cancer Therapy–Prostate; na, not applicable – no assessments from that domain were obtained in the study; NR, data necessary to calculate the effect size were not provided; RE, resistance exercise; SF-36 = Short Form 36-item Physical Function Subscale; SOT, Sensory Organization Test; VO2, aerobic capacity

domain outcomes were measured. Findings demonstrated that the exercise intervention resulted in significant improvement in 6-min walk performance (*d* = 0.54; 95% CI, -.03-1.04). However, only a small change in self-reported physical function (*d* = 0.11; 95% CI, -.38-.61) was observed.

Galvao et al[40] conducted a randomized controlled trial comparing the effects of a center-based, supervised 12-week aerobic and resistance exercise intervention with those of a usual care control group in a sample of 57 men undergoing ADT. The RE prescription consisted of 2 sets per exercise at loads corresponding to their 6-12 RM, and the aerobic exercise prescription involved 15-20 min of exercise training at 65%-80% of one's heart rate maximum (HRMax). Assessments of multiple impairment (muscular strength, muscular endurance, balance, and body composition) and functional limitation domain outcomes (6-m walk, 400-m walk, chair stand, and self-reported physical function) were obtained at baseline and 20-week follow-up. No physical disability domain outcomes were measured. Findings revealed significant improvements in impairment domain outcomes of upper body muscular strength (chest press: *d* = 0.34; 95% CI, .19-.85 and seated row: *d* = 0.68; 95% CI, .15-1.21), lower body muscular strength (leg press: *d* = 0.74; 95% CI, .21-1.27 and leg extension: *d* = 0.78; 95% CI, .25-1.32), upper body muscular endurance (*d* = 1.09; 95% CI, .54-1.65), and lower body muscular endurance (*d* = 1.49; 95% CI, .91-2.07). Exercise also elicited improvement in balance (*d* = 0.37; 95% CI, .15-.88). In contrast to these outcomes, the exercise intervention produced small effect size changes in body composition measures of lean body mass (*d* = 0.10; 95% CI, -.61-.41), fat mass (*d* = 0.03; 95% CI, -.48-.55), or body fat percentage (*d* = 0.07; 95% CI, -.45-.58). With regard to functional limitation domain outcomes, the exercise intervention yielded improvements in chair stand (*d* = 0.49; 95% CI, -.03-1.01), 6-m walk (*d* = 0.65; 95% CI, .13-1.18), and 400-m walk (*d* = 0.34; 95% CI, -.18-.86) performance. However, a negligible change in self-reported physical function (*d* = 0.07; 95% CI, -.59-.44) was observed after exercise.

Galvao and colleagues[46] also conducted an ancillary analysis of findings from their aforementioned trial[40] to explore the effects of acute versus prolonged (chronic) exposure to ADT on the benefits of exercise training in the study. The effects of exercise in 16 men with an acute exposure to ADT of less than 6 months and 34 men with chronic exposure of greater than 6 months were compared. With regard to DPM outcomes, descriptive statistics of this ancillary analysis were only provided for body composition measures (impairment domain). Results revealed that the exercise intervention yielded small effect size improvements in body composition measures of lean body mass (*d* = 0.09; 95% CI, -.60-.43), appendicular skeletal muscle mass (*d* = 0.14; 95% CI, -.65-.38), and body fat percentage (*d* = 0.08; 95% CI, -.65-.38) for men with acute ADT exposure. In men undergoing chronic exposure to ADT, exercise produced similar effect size improvements in lean body mass (*d* = 0.11; 95% CI, -.62-41), appendicular skeletal muscle mass (*d* = 0.15; 95% CI, -.66-.37) but also a small effect size increase in body fat percentage (*d* = 0.16; 95% CI, -.35-.68). Collectively, these findings suggest that exercise resulted in similar, small effect size improvements in body composition measures for men undergoing acute or chronic ADT.

Segal and colleagues[41] conducted a randomized controlled trial comparing the effects of 24-week, center-based, supervised resistance exercise, aerobic exercise, and usual care interventions in a sample of 121 PC patients receiving radiation therapy and ADT (about 60% of the sample). The RE prescription consisted of 3 sessions a week in which participants completed 2 sets of 8-12 reps at 60%-70% of their 1RM. The aerobic exercise prescription involved 15-45 min of progressive exercise training at 60%-75% peak aerobic capacity (VO2peak). Assessments of impairment domain outcomes (muscular strength, aerobic capacity, and body composition) were obtained at 6-month follow-up. Assessment of a physical disability domain outcome (FACT-F: interference in performing activities of daily living due to fatigue) was obtained at baseline and 3- and 6-month follow-ups. No functional limitation domain outcomes were measured. The resistance exercise intervention produced increases in upper- body (*d* = 0.89; 95% CI, .43-1.35) and lower-body (*d* = 0.74; 95% CI, .28-1.19) muscular strength. However, resistance exercise resulted in small effect size improvements in aerobic capacity (*d* = 0.13; 95% CI, -.57-.31), body fat percentage (*d* = 0.06; 95% CI, -.38-.50), or physical disability (3 months: *d* = 0.17; 95% CI, -.27-.61 and 6 months: *d* = 0.26; 95% CI, -.18-.70). The aerobic exercise intervention also resulted in small effect size changes in upper-body strength (*d* = 0.12; 95% CI, -.56-.32), lower-body strength (*d* = 0.04; 95% CI, -.48-.40), aerobic capacity (*d* = 0.03; 95% CI, -.47-.41), body fat percentage (*d* = 0.20; 95% CI, -.64-.24), and physical disability (3 months: *d* = 0.11; 95% CI, -.33-.55 and 6 months: *d* = 0.01; 95% CI, -.45-.43). In an ancillary analysis of this trial, Alberga and colleagues[47] examined the role of age and presence or absence of ADT as moderators of the effects of the exercise intervention. Findings revealed that resistance exercise yielded comparable improvements in relevant DPM outcomes. Consequently, preliminary evidence suggests that the benefits of resistance exercise for PC patients are not attenuated by age or administration of ADT.

Hansen and colleagues[45] conducted a single-arm, uncontrolled trial examining the effects of a center-based, supervised 12-week eccentric resistance exercise intervention in a sample of 10 men on (n = 5) or off (n = 5) ADT. The exercise prescription consisted of 15 min of eccentric recumbent ergometry completed at an rating of perceived exertion (RPE) of 9-13. Assessments of impairment (muscular strength and muscle volume), functional limitation (6-min walk and timed up and go performance), and physical disability (FACT-F: interference in performing activities of daily living due to fatigue) domain outcomes were obtained at baseline and 12-week follow-up. The resistance exercise intervention resulted in meaningful improvements in muscular strength (*d* = 0.51; 95% CI, -1.77-.75), 6-min walk performance (*d* = 0.37; 95% CI, -1.62-.88), and timed up and go performance (*d* = 0.39; 95% CI, -.86-1.64). However, small effect size improvements in muscle volume (*d* = 0.10; 95% CI, -1.34-1.14) and physical disability (*d* = 0.12; 95% CI, -1.36-1.12) were observed following resistance exercise.

Culos-Reed and colleagues[42] conducted a randomized controlled trial in which they compared the effects of a 16-week home-based exercise intervention and a wait-list control group in a sample of 100 men undergoing ADT. The exercise prescription consisted of 3-5 days a week of home-based exercises using a resistance band and moderate intensity walking. Assessments of impairment (body composition) and functional limitation (6-min walk performance) domain outcomes were obtained at baseline and 16-week follow-up. No physical disability domain outcomes were measured. The home-based exercise intervention resulted in small effect size improvements in body composition (neck circumference: *d* = 0.15; 95% CI, -.29-.59 and waist circumference: *d* = 0.08; 95% CI, -.36-.52) and 6-min walk performance (*d* = 0.13; 95% CI, -.59-.33).

Santa Mina and colleagues[48] conducted a randomized controlled trial comparing the effects of 24-week, home-based, resistance and aerobic exercise interventions in a sample of 66 PC survivors. The RE prescription consisted of 3-5 sessions a week in which participants completed 2-3 sets of

8-12 reps at 60%-80% of their 1RM using resistance bands. The aerobic exercise prescription involved 3-5 sessions a week of 30 min of exercise training at 60%-80% heart rate reserve. Assessments of impairment (body fat percentage, grip strength) and physical disability (FACT-F: interference in performing activities of daily living due to fatigue) domain outcomes were obtained at baseline, 3-, 6-, and 12-month follow-up assessments. No functional limitation domain outcomes were measured. The home-based aerobic exercise intervention resulted in small effect size improvements in the impairment domain outcomes of body fat percentage (3 months: d = 0.33; 95% CI, -.16-.83; 6 months: d = 0.29; 95% CI, -.21-.78; 12 months: d = 0.28; 95% CI, -.21-.71) and grip strength (3 months: d = 0.02; 95% CI, -.51-.47; 6 months: d = 0.04; 95% CI, -.53-.45; 12 months: d = 0.07; 95% CI, -.56-.42). The aerobic exercise intervention also yielded small effect size improvements in the FACT-F (3 months: d = 0.07; 95% CI, -.42-.56; 6 months: d = 0.02; 95% CI, -.51-.47; 12 months: d = 0.02; 95% CI, -.51-.47). The resistance exercise intervention also resulted in small effect size improvements in body fat percentage (3 months: d = 0.12; 95% CI, -.36-.60; 6 months: d = 0.14; 95% CI, -.34-.62; 12 months: d = 0.28; 95% CI, -.20-.76) and small effect size decreases in grip strength (3 months: d = -0.17; 95% CI, -.65-.31; 6 months: d = -0.07; 95% CI, -.55-.40; 12 months: d = -0.11; 95% CI, -.58-.37). Similar to the aerobic exercise intervention, resistance exercise resulted in small effect size improvements in the FACT-F (3 months: d = 0.05; 95% CI, -.53-.42; 6 months: d = 0.20; 95% CI, -.28-.67; 12 months: d = 0.02; 95% CI, -.46-.49).

Overall exercise intervention effects on DPM domain outcomes

Findings from the studies included in the present review suggest that exercise interventions result in meaningful improvements in DPM domain outcomes among PC patients undergoing ADT. However, the magnitude of the improvement accompanying exercise varied considerably across the DPM domains. For example, exercise yielded large average effect size increases in impairment domain outcomes of muscular strength (d = .74; 95% CI, .14-1.47) and muscular endurance (d = 2.64; 95% CI, 1.08-2.84), moderate improvement in balance (d = 0.63; 95% CI, .10-1.38), and small improvements in aerobic capacity (d = 0.08; 95% CI, -.52-.36) and bone mineral density (d = 0.08; 95% CI, -.96-.80). Exercise also resulted in small effect size improvements in measures of body composition including lean body mass (d = 0.08; -.93-.82), fat mass (d = 0.06; 95% CI, -.64-.76), and body fat percentage (d = 0.17; 95% CI, -.40-.63). Exercise also elicited moderate improvements (d = 0.39; 95% CI, -.42-1.01) in functional limitation domain outcomes. It should be noted that exercise-induced improvements in functional limitation domain outcomes were more pronounced for performance measures of physical function (d = 0.46) relative to self-reported measures of physical function (d = 0.13). Finally, exercise resulted in smaller effect size improvements in the lone physical disability measure, FACT-F: interference in performing activities of daily living due to fatigue (d = 0.10; 95% CI, -.64-.76) relative to those observed for impairment or functional limitation domain outcomes.

Discussion

The purpose of this review was to conduct one of the first evaluations of efficacy of exercise interventions for eliciting comparable improvements in impairment, functional limitation, and physical disability domain outcomes identified within a DPM framework[22] among PC patients undergoing ADT. Findings from the present review demonstrate that exercise interventions consistently result in significant, clinically meaningful improvements in select impairment (muscular fitness, balance) and functional limitation (functional performance) domain outcomes. The observed improvements in fitness and functional outcomes are consistent with findings of the recent reviews of the exercise–cancer literature, including the ACSM expert panel documenting the strong evidence supporting the benefits of exercise for PC patients and survivors.[18-20] Collectively, these findings underscore the meaningful benefits of exercise for PC patients and provide additional support for the position that exercise should be integrated as part of the standard of care treatment for PC patients undergoing ADT. However, in contrast to the results for impairment and function limitation domains, few of the exercise intervention studies included assessments of physical disability domain outcomes and results of studies including such measures yielded smaller effect size improvements for physical disability-related outcomes relative to either impairment or functional limitation domain outcomes. These findings are also consistent with results of contemporary reviews of the exercise-aging and exercise–arthritis literature[26-28] and extend these results, for the first time, to PC patients undergoing ADT.

Preserving and/or improving fitness and functional performance are key considerations in the treatment of PC patients on ADT.[6,7,49] Assessment batteries in exercise intervention studies reflect recognition of the importance of these outcomes as measures of impairments in muscular fitness and performance measures of functional limitations were assessed in 75% of the studies reviewed and assessments of impairments in body composition were included in 63% of studies. However, only 4 of 9 (44%) of the reviewed exercise intervention studies assessed outcomes that were categorized as representing the physical disability domain. Perhaps of even greater importance, no study incorporated assessments of outcomes from each of the domains comprising the DPM.[22] Given the DPM provides a conceptual framework that has been shown to explain meaningful variability in the effects of exercise on functional outcomes in older adults,[25] it is reasonable to suggest that using the DPM to aid in guiding assessment approaches in future exercise intervention trials targeting PC patients undergoing ADT may help delineate the complex processes involved in preventing functional limitations and progress toward physical disability through exercise interventions.

There are methodological considerations that may in part explain why the effects of exercise on physical disability domain outcomes were modest when compared with the observed improvements in impairment and functional limitation domain outcomes. First, the only physical disability domain outcome assessed in any of the studies was the extent to which fatigue interfered with the performance of activities of daily living obtained with the FACT-F. It is important to recognize that the FACT-F is primarily a measure of cancer-related fatigue, not a scale specifically designed to tap into the complex, multidimensional aspects that comprise physical disability. Although we chose to categorize it as a physical disability domain outcome based on the scale's focus on interference with the performance of activities of daily living, we recognize this is not a comprehensive measure of physical disability and nor would all researchers categorize the FACT-F as an index of physical disability. Consequently, this measure may not be particularly sensitive to change with exercise interventions. It is also possible that exercise may result in improvements in other aspects of physical disability that are not adequately captured by measures focusing only on the role of fatigue in the performance of common daily tasks. It important to also recognize that one's baseline level of disability and functioning influences the likelihood of observing exercise-induced improvements in these outcomes. Specifically, it is well documented that those exhibiting greater levels of dysfunction and/or disability at baseline demonstrate the greatest postexercise improvements in these outcomes. Given that none of the trials targeting PC patients on ADT specifically recruited men with established difficulty performing activities of daily living, it is possible that these samples' baseline disability status may have been sufficiently favorable to limit the amount of improvement that could be observed after exercise. Collectively, these findings underscore the importance of including more comprehensive assessments of physical disability domain outcomes in future exercise intervention trials targeting PC patients on ADT.

Conceptually, some have interpreted the difference in the magnitude of the effects of exercise on DPM domain outcomes observed in older adults to indicate that although exercise is necessary, it is insufficient alone to improve and/or prevent disability.[26-28] Given the limited number of studies that have assessed the effects of exercise on physical disability outcomes in PC patients together with the narrow scope of these measures (ie, the focus on the extent to which fatigue interferes with activities of daily living), we suggest that the results of our present review demonstrate that the effect of exercise on physical disability domain outcomes has yet to be systematically evaluated among PC patients. Consequently, it premature to conclude this assertion appropriately applies to men undergoing ADT. Nonetheless, the smaller effects of exercise observed for disability domain outcomes does suggest this contention warrants consideration and further inquiry in future exercise intervention trials targeting PC patients on androgen suppression therapy.

In this regard, it is possible that modification of traditional exercise interventions could help patients apply fitness and functional benefits gained from exercise to facilitate improvements in physical disability outcomes.[26] Recent evidence from exercise intervention trials in older adults demonstrated that combining exercise with a cognitive behavioral counseling component designed to help motivate participants to reengage in the performance of challenging activities of daily living was superior to exercise alone for improving functional limitations and self-reported physical disability.[25,50,51] In light of these promising findings, it is reasonable to suggest that implementing multicomponent interventions that help participants to actively link and transfer exercise-induced improvements in impairment and functional limitation domain outcomes to the performance of activities of daily living may be one strategy for augmenting the beneficial effects of exercise on physical disability domain outcomes. Additional research examining both the efficacy of exercise alone for improving physical disability outcomes in PC patients burdened with difficulty in completing activities of daily living and systematic inquiry of the benefits of multicomponent intervention approaches is required to determine the usefulness of integrating these interventions in the treatment of men on ADT.

Another particularly relevant finding from the present review is that exercise was associated with small effect size improvements in various indices of body composition. Interventions that produce favorable changes in body composition are of considerable value to men on ADT and the potential benefit of exercise for offsetting and/or reversing the unfavorable changes in body composition that accompany androgen suppression is one aspect that contributes to the increased interest in implementing exercise in the treatment of PC patients on ADT. The small average effect sizes accompanying improvements in lean body mass, fat mass, and body fat percentage observed after exercise in this review may raise concerns for some researchers and/or clinicians regarding the body composition-related benefits of exercise for men on ADT. Nonetheless, there are several considerations in interpreting these findings that clearly underscore the value of exercise interventions for the preservation of lean body mass and favorable body composition among PC patients undergoing ADT. For example, results from a recent meta-analytic review revealed that prolonged ADT is associated with an average increase of 7.7% in body fat percentage and a 2.2% decrease in lean body mass.[52] Findings from the present review demonstrate that men who received exercise therapy interventions did not experience this unfavorable shift in body composition accompanying ADT and actually exhibited small improvements in these outcomes. Thus, although exercise may not have produced dramatic improvements in body composition, it does seem to have a meaningful protective effect by attenuating the adverse changes in body composition that are reliably documented with ADT. It should also be acknowledged that several studies included in the present review implemented exercise interventions that were likely of insufficient intensity and/or duration to produce significant, clinically meaningful improvements in body composition outcomes. It is noteworthy that Galvao and colleagues[40] observed an increase of nearly 2 kg of lean body mass after 12 weeks of one of the most intensive exercise interventions to date conducted in men on ADT. Although this change in lean body mass is characterized by a small effect size, it is highly relevant clinically, particularly because it was achieved after only 12 weeks of exercise training. We contend that these findings reinforce the considerable value of exercise in attenuating or reversing the adverse effects of ADT on body composition in PC patients. It is possible that longer duration and more intensive exercise interventions may yield superior improvements in DPM outcomes than documented in the present review. In light of the established benefits of exercise in studies so far, future inquiry exploring the feasibility and efficacy of implementing longer duration, more intensive exercise interventions in PC patients undergoing ADT is warranted.

It is also reasonable to contend that complementing exercise interventions with concomitant dietary modification could augment the beneficial effect on body composition outcomes in men on ADT. It has been well established that combining exercise and dietary intervention approaches is superior to the implementation of either intervention alone in producing clinically meaningful change in body weight and body composition.[53-56] Accordingly, combining exercise and dietary interventions could yield synergistic benefits for preserving or enhancing body composition outcomes among men on ADT. The therapeutic efficacy of a combined lifestyle intervention approach promoting exercise and dietary modification for men on ADT warrants future inquiry.

Based on the modest percentage of quality indicators met across all studies (66%) observed in the Delphi List methodological assessment,[37] quality of the exercise intervention studies in PC patients on ADT conducted to date could be reasonably classified as moderate to weak. However, given the relatively limited amount of research conducted in this area, the lower overall quality ratings for the total group of studies is not particularly surprising. Pilot and/or feasibility studies that are conducted in the early stages of systematic inquiry in a new field would not be expected to as methodologically rigorous as later stage investigations. For example, the 3 nonrandomized studies, which could be characterized as pilot and/or feasibility studies, met only 34% of the quality indicators. Conversely, the 5 randomized trials satisfied 86% of the quality indicators. The formative nature of the research objectives of select studies included in the present review could have an impact on the effort to evaluate the methodological quality of the overall research area and this must be carefully considered when interpreting this assessment. Therefore, although tabulation of the quality indicators suggests that study quality was quite variable across studies, we would characterize the methodological quality of the randomized trials examining exercise as a supportive care intervention for men on androgen-deprivation therapy as strong. Provided that findings from these studies yielded favorable improvements in variety of disablement process domain outcomes, exercise represents a promising supportive care intervention that can elicit significant improvement in variety of relevant DPM outcomes for men on ADT. It should also be recognized that although the Delphi criteria provide one approach to assessing methodologic quality, some researchers may prefer alternative assessments that provide a more quantitative evaluation (eg, the Pedro rating scale). As the number of large-scale randomized exercise intervention trials targeting DPM outcomes in prostate cancer patients increases, implementing different approaches to assessing the quality of the research in this area of inquiry could prove particularly informative.

Limitations and recommendations

Findings from this systematic review suggest that exercise interventions consistently result in moderate to large effect size improvements in muscular fitness and functional performance measures and may attenuate adverse effects of ADT on body composition outcomes. The observed improvements are clinically meaningful and reinforce growing recognition of the value of implementing exercise as an adjuvant behavioral intervention in the treatment of PC patient undergoing ADT. However, few of the studies assessed physical disability domain outcomes and those that did demonstrated that exercise resulted in smaller effect size improvements (d = .10) in measures of physical disability (eg, performance of activities of daily living and socially defined roles) relative to the observed improvements in impairment and functional limitation domain outcomes. Consequently, findings from this review underscore the value of promoting regular exercise participation in men undergoing ADT. However, provided that 3 of the 9 studies employed nonrandomized designs with relatively small sample sizes,[36,40,41] the magnitude of the effect of exercise on the DPM outcomes should be interpreted cautiously. Nonetheless, although the present results are promising, given the relatively limited number of exercise intervention studies targeting PC patients to date, there is much left to be determined with regard to establishing how to optimize the therapeutic efficacy of exercise for PC patients on ADT.

Given that preserving strength, favorable body composition, and functional capacity are key concerns in the treatment of men on ADT, it is critical to apply conceptual models of the disablement process to guide the intervention design and selection of outcomes assessments in future exercise interventions targeting this population. Given the dearth of studies that assessed disability-related outcomes, it is of particular importance to further explore the effects of exercise on each of the domains that comprise the primary pathway to functional decline in the DPM. Accordingly, we recommend that future exercise intervention trials incorporate concomitant assessments of relevant outcomes from each of the impairment, functional limitation, and physical disability domains of the DPM. This assessment approach will allow investigators to begin delineating the pathways through which exercise may improve and/or attenuate functional limitations and physical disability. This strategy could also advance knowledge of how to more effectively personalize exercise interventions to target patients' most pressing deficits in disablement process outcomes.

Recent evidence suggests that multicomponent behavioral interventions may be particularly effective in minimizing or preventing functional limitations and physical disability in frail, older adults.[28,57] In support of this position, results from several recent randomized controlled trials in older adults with chronic disease demonstrate the efficacy of combined lifestyle exercise and dietary interventions in improving functional, disease risk, and quality of life outcomes that are relevant to PC patients undergoing prolonged ADT.[53,54,58,59] Ornish and colleagues have also shown that modification of exercise and dietary behaviors can significantly improve biomarkers of PC progression in men with localized, low-grade PC, with normal hormone status.[60,61] A recent pilot study by Nobes and colleagues,[62] also demonstrated that combination of exercise, a low-glycemic diet, and metformin resulted in significant improvements in body composition, blood pressure, and body mass index in men on ADT. Although those findings suggest comprehensive lifestyle interventions are promising approaches for PC patients, the efficacy of lifestyle interventions integrating both exercise and dietary modification have yet to be systematically evaluated in men undergoing prolonged ADT. Given the potential value of this approach for improving body composition and function, future inquiry addressing the synergistic effects of exercise and dietary interventions in PC patients on ADT is warranted.

Long-term adherence is widely recognized to be a critical determinant of the functional and quality of life benefits that accompany exercise in older adults with chronic disease.[25,54,58,59] However, no studies to date have examined the extent to which the beneficial effects of exercise are sustained following the cessation of structured exercise interventions in PC patients. Although the adherence rates observed in the present review were promising, it should be recognized this rate reflected exercise session attendance alone, which is a relatively simplistic index of adherence that does not directly address the participants' compliance with all facets of the exercise prescription (eg, intensity, duration, volume, time, etc). Determining the role of adherence to all aspects of the exercise prescription in producing lasting improvement in relevant disablement and chronic disease outcomes would be integral in defining the amount of exercise participation that yields therapeutic benefits in men on ADT. Subsequent studies testing the efficacy of theory-based behavioral intervention approaches for promoting exercise adherence could also have a meaningful impact on the design and delivery of exercise interventions for PC patients. Integrating cognitive behavioral counseling to help sedentary individuals develop the self-regulatory skills necessary for successful adoption and maintenance of regular exercise has been shown to increase adherence to and the therapeutic efficacy of exercise interventions among older adults with chronic disease.[51,53,54,58,59,63,64] Using this approach as part of a multicomponent intervention strategy could augment the benefits of exercise therapy for men on ADT.

There are several limitations to the present review. The relatively small number of studies addressing exercise interventions in men on ADT limits what can be concluded about the effects of exercise on the DPM outcomes. First, our approach to quantitatively comparing the effects of exercise across DPM domains involved calculating the average of the bias-corrected, weighted effect sizes. We recognize that this is not as robust an approach for correcting bias as standard meta-analytic procedures. Nonetheless, we believe our approach represents an important initial step in synthesizing the effects of exercise on DPM outcomes in PC patients. Once sufficient numbers of studies are available, future reviews that use standardized meta-analytic procedures will allow for a more comprehensive assessment of the magnitude of the effects of exercise across the DPM domains. A related limitation is that only 6 of the 9 studies included in the review were randomized controlled trials. Thus, the extent to which the effects of exercise observed in the uncontrolled trials were due, in part, to behavioral artifacts or selection bias cannot be determined or discounted at the present time. A related limitation is the dearth of randomized controlled trials led us to focus our review on effect sizes accompanying pre- to postintervention changes in outcomes after exercise. Therefore, knowledge of the magnitude of the benefit of exercise above that observed with usual care approaches to treatment remains unclear and warrants further inquiry.

Physical disability domain outcomes were assessed in only 3 of the 9 studies in this review. In addition, the only measure categorized into the physical disability domain focused only on the extent to which fatigue interfered with the performance of activities of daily living. These assessment considerations limit what can be concluded about the effects of exercise on physical disability domain outcomes in PC patients on ADT. Keysor and Brembs[28] also point out that many self-report measures of physical function and disability have items representing both domains. Given the importance of distinguishing the effects of exercise on the various disablement domains, we urge investigators to include valid, reliable, multidimensional measures of physical disability in future intervention trials targeting men on ADT.

Finally, we also recognize that some disability researchers espouse use of the World Health Organization's International Classification of Functioning model[65] over the DPM which was the conceptual framework used to organize the outcomes examined in the present review. Although there are unquestionable merits to alternative models, we and others[24-28] propose the DPM has value for examining the benefits of exercise for offsetting functional decline and this model may be of particular utility for investigations of the efficacy of exercise therapy in PC patients on ADT. Thus, although there is no consensus on the most appropriate disablement process model, it is unquestionably prudent to recommend that conceptual frameworks such as the DPM and the international classification of functioning be implemented to guide the design and delivery of future exercise interventions targeting men on ADT.

Conclusion

In summary, this is one of the first systematic reviews examining if exercise yields comparable improvements in impairment, functional limitation, and physical disability domain outcomes of the DPM.[22] Findings suggest that exercise consistently elicits meaningful improvements in strength and functional task performance and attenuates the deleterious effect of ADT on body fat percentage, lean body mass, and fat mass. These improvements reinforce the considerable benefits of exercise on key clinical outcomes for PC patients. Thus, the primary clinical implication of this review is that it provides additional evidence supporting the value of incorporating exercise as an adjuvant behavioral intervention in the treatment of PC patients undergoing ADT. However, despite these favorable findings, results of this systematic review also reveal that few studies have investigated the effect of exercise on physical disability domain outcomes. These limited findings demonstrated that exercise resulted in small effect size improvements in one aspect of physical disability, the extent to which fatigue interfered with the performance of activities of daily living. However, given the narrow focus of physical disability-related outcomes included in these studies, the small effect of exercise observed in this review must be interpreted cautiously and future investigations assessing the effects of exercise on more comprehensive assessments of physical disability are required to adequately assess the potential benefit of exercise on physical disability outcomes. Taken collectively, a primary research implication of this review is that future exercise intervention trials should be designed to incorporate valid, reliable measures of outcomes from each DPM domain. Such trials would delineate the extent to which improvements in impairment and functional limitation domain outcomes facilitate benefits for the performance of activities of daily living will expand current knowledge of how to optimize the value of exercise in the treatment of PC patients undergoing ADT.

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