Lifestyle & Behavioral Change Interventions among Prostate Cancer Men on Androgen Deprivation Therapy: Protocol for A Systematic Review.

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Protocol

**Keywords:** Prostate cancer, ADT, Lifestyle medicine, oncology, Androgen deprivation therapy, sports medicine, culinary medicine, metabolic syndrome, behavioral medicine.

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Abstract

Background: Androgen deprivation therapy (ADT) is one of the main treatment modalities for men with prostate cancer. It is known to relieve symptoms in patients with metastatic prostate cancer and might have a survival benefit in some patients. Despite the potential benefits associated with its use, ADT can cause a multitude of side effects that adversely affect quality of life. We will be discussing the potential benefits of lifestyle modifications including smoking cessation, moderating alcohol and caffeine consumption, vitamin D and calcium supplementation, and regular incorporation of weight bearing or resistance exercises, nutritional and dietary modifications and the role of food supplementation. We will also investigate the role and efficacy of Social Cognitive Theory in empowering and motivating patients to promote adherence to those lifestyle modifications.

Methods: A literature search was conducted on PubMed, Scopus and the Cochrane Library a total of 2455 publications was found. The search was made to include lifestyle interventions among prostate cancer patients on androgen deprivation therapy.

Conclusions: The review will investigate if there is benefit in implementing lifestyle interventions as smoking cessation, moderating alcohol, food supplementation, phyto-nutrients supplementation and regular weight bearing or resistance exercises to mitigate side effects of androgen deprivation therapy. We will also investigate behavioral interventions using social cognitive theory to maintain adherence to those lifestyle modifications using patient education.

Systematic review registration: It was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 28/4/2020 and was last updated on 2/2/2020 (registration number 167663).

Introduction

6. Rationale

Androgen deprivation therapy (ADT) is one of the main treatment modalities for men with prostate cancer. It is known to relieve symptoms in patients with metastatic prostate cancer and might have a survival benefit in some patients. Despite the potential benefits associated with its use, ADT can cause a multitude of side effects that adversely affect quality of life and may require therapy modification, presenting challenges for the clinician in charge of treatment.

The side effects of ADT for prostate cancer includes fatigue[3], osteoporosis and bone fractures[4], vasomotor symptoms[5], sexual dysfunction[6], body composition and metabolism associated with potential cardiovascular adverse effects[4]. Moreover just as challenging is the psychosocial adverse effects like increased incidence of depression[7] and anxiety[8], a bad sense of perceived body image due to gynecomastia [4]. Decreased penile and testicular size[9].
We will be discussing the potential benefits of lifestyle modifications including smoking cessation, moderating alcohol and caffeine consumption, vitamin D and calcium supplementation, and regular incorporation of weight bearing or resistance exercises, nutritional and dietary modifications and the role of food supplementation. We will also investigate the role and efficacy of Social Cognitive Theory in empowering and motivating patients to promote adherence to those lifestyle modifications.

7. Objectives:

The ultimate aim would be to incorporate all the mentioned elements in an integrative approach before, during and after ADT so as to improve the patient's quality of life, survival, and to even investigate the biochemical response if existent of those approaches.

Methods

8. Eligibility Criteria:

Inclusion criteria:

a. Study Designs:

RCTs, observational and pilot studies of relevance.

b. Participants:

We will include adult males irrespective to their racial background who are diagnosed with prostate cancer and who are on ADT.

c. Interventions:

Lifestyle modifications as smoking cessation, moderating alcohol, food supplementation, phyto-nutrients supplementation and regular weight bearing or resistance exercises.

Behavioral interventions using social cognitive theory to maintain adherence to those lifestyle modifications using patient education.

d. Outcome:

Improvement in patient’s reported quality of life measures and improvement in biochemical response

e. Setting:

No restriction on Setting

f. Language:
Will include studies in English.

**Exclusion criteria:**

**a. Study Designs:**

Cross-sectional, case series and case reports will be excluded. Studies not performed on humans.

**b. Participants:**

Participants age less than 18 will be excluded as well as patients not on ADT. Any other oncologic disease will excluded.

**c. Interventions:**

Surgical and interventional radiology to mitigate side effects of ADT

**e. Language:**

Studies not written in English.

9. **Information Sources:**

PubMed: 618(a): 4 files; 207(b): 2 files

Scopus: 890(a): 1 file; 401(b): 1 file

Cochrane Library: 254(a): 3 files; 85(b): 3 files

10. **Search strategy:**

Search Strategy: All searches completed on November 15, 2019

**PubMed:** both search strategies may be copied and pasted into the main PubMed search box. Files are .nbib file extension

P1 AND P2 AND I=618

((((prostate cancer OR prostatic cancer OR prostatic neoplasm OR prostatic neoplasms OR prostatic carcinoma OR "Prostatic Neoplasms"[Mesh]))) AND ((androgen deprivation therapy OR adt OR androgen-deprivation OR androgen deprivation OR androgen ablative therapy OR androgen blockade OR anti-androgens OR antiandrogens OR bicalutamide OR nilutamide OR flutamide OR "Flutamide"[Mesh] OR luteinising hormone-releasing hormone agonists OR luteinizing hormone-releasing hormone agonists OR Lhrh agonist OR leuprolerin OR "Leuprolide"[Mesh] OR goserelin OR "Goserelin"[Mesh] OR triptorelin OR "Triptorelin Pamoate"[Mesh] OR luteinising hormone-releasing hormone antagonists OR LHRH antagonists OR cyproterone OR "Cyproterone"[Mesh] OR degarelix OR abarelix OR abiraterone OR...
"Abiraterone Acetate"[Mesh] OR androgen-receptor inhibitor OR enzalutamide OR "Androgen Antagonists" [Mesh] OR "Androgen Receptor Antagonists"[Mesh] OR gonadotropin releasing hormone receptor antagonist)) AND ((lifestyle behavior OR lifestyle modification OR lifestyle OR "life style" OR life-style OR "Life Style"[Mesh] OR exercise OR "Exercise"[Mesh] OR resistance training OR "Resistance Training"[Mesh] OR smoking cessation OR "Smoking Cessation"[Mesh] OR diet OR "Healthy Diet"[Mesh] OR dietary OR nutrition OR caloric restriction OR "Caloric Restriction"[Mesh]))

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((((prostate cancer OR prostatic cancer OR prostatic neoplasm OR prostatic neoplasms OR prostatic carcinoma OR "Prostatic Neoplasms"[Mesh]))) AND ((androgen deprivation therapy OR adt OR androgen-deprivation OR androgen deprivation OR androgen ablative therapy OR androgen blockade OR anti-androgens OR antiandrogens OR bicalutamide OR nilutamide OR flutamide OR "Flutamide"[Mesh] OR luteinising hormone-releasing hormone agonists OR luteinizing hormone-releasing hormone agonists OR Lhrh agonist OR leuprolrelin OR "Leuprolide"[Mesh] OR goserelin OR "Goserelin"[Mesh] OR triptorelin OR "Triptorelin Pamoate"[Mesh] OR luteinising hormone-releasing hormone antagonists OR LHRH antagonists OR cypromerone OR "Cypromerone"[Mesh] OR degarelix OR abarelix OR abiraterone OR "Abiraterone Acetate"[Mesh] OR androgen-receptor inhibitor OR enzalutamide OR "Androgen Antagonists"[Mesh] OR "Androgen Receptor Antagonists"[Mesh] OR gonadotropin releasing hormone receptor antagonist)) AND ((lifestyle behavior OR lifestyle modification OR lifestyle OR "life style" OR life-style OR "Life Style"[Mesh] OR exercise OR "Exercise"[Mesh] OR resistance training OR "Resistance Training"[Mesh] OR smoking cessation OR "Smoking Cessation"[Mesh] OR diet OR "Healthy Diet"[Mesh] OR dietary OR nutrition OR caloric restriction OR "Caloric Restriction"[Mesh]))

P1 AND P2 AND I=890

( TITLE-ABS-KEY ( prostate AND cancer ) OR TITLE-ABS-KEY ( prostatic AND cancer ) OR TITLE-ABS-KEY ( prostatic AND neoplasm ) OR TITLE-ABS-KEY ( prostatic AND neoplasms ) OR TITLE-ABS-KEY ( prostatic AND carcinoma ) ) AND ( TITLE-ABS-KEY ( androgen AND deprivation AND therapy ) OR TITLE-ABS-KEY ( adt ) OR TITLE-ABS-KEY ( androgen-deprivation ) OR TITLE-ABS-KEY ( androgen AND deprivation ) OR TITLE-ABS-KEY ( androgen AND ablative AND therapy ) OR TITLE-ABS-KEY ( androgen AND blockade ) OR TITLE-ABS-KEY ( anti-androgens ) OR TITLE-ABS-KEY ( antiandrogens ) OR TITLE-ABS-KEY ( bicalutamide ) OR TITLE-ABS-KEY ( nilutamide ) OR TITLE-ABS-KEY ( flutamide ) OR TITLE-ABS-KEY ( luteinising AND hormone-releasing AND hormone AND agonists ) OR TITLE-ABS-KEY ( luteinizing AND hormone-releasing AND hormone AND agonists ) OR TITLE-ABS-KEY ( hrrh AND agonist ) OR TITLE-ABS-KEY ( leuprolrelin ) OR TITLE-ABS-KEY ( leuprolide ) OR TITLE-ABS-KEY ( goserelin ) OR
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( TITLE-ABS-KEY ( prostate AND cancer ) OR TITLE-ABS-KEY ( prostatic AND cancer ) OR TITLE-ABS-KEY ( prostatic AND neoplasm ) OR TITLE-ABS-KEY ( prostatic AND neoplasms ) OR TITLE-ABS-KEY ( prostatic AND carcinoma ) ) AND ( TITLE-ABS-KEY ( androgen AND deprivation AND therapy ) OR TITLE-ABS-KEY ( adt ) OR TITLE-ABS-KEY ( androgen-deprivation ) OR TITLE-ABS-KEY ( androgen AND deprivation ) OR TITLE-ABS-KEY ( androgen AND ablative AND therapy ) OR TITLE-ABS-KEY ( androgen AND blockade ) OR TITLE-ABS-KEY ( anti-androgens ) OR TITLE-ABS-KEY ( antiandrogens ) OR TITLE-ABS-KEY ( bicalutamide ) OR TITLE-ABS-KEY ( nilutamide ) OR TITLE-ABS-KEY ( flutamide ) OR TITLE-ABS-KEY ( luteinising AND hormone-releasing AND hormone AND agonists ) OR TITLE-ABS-KEY ( luteinizing AND hormone-releasing AND hormone AND agonists ) OR TITLE-ABS-KEY ( hrr AND agonist ) OR TITLE-ABS-KEY ( leuprolrelin ) OR TITLE-ABS-KEY ( leuprolide ) OR TITLE-ABS-KEY ( goserelin ) OR TITLE-ABS-KEY ( triptorelin ) OR TITLE-ABS-KEY ( luteinising AND hormone-releasing AND hormone AND antagonists ) OR TITLE-ABS-KEY ( lhrr AND antagonists ) OR TITLE-ABS-KEY ( cyproterone ) OR TITLE-ABS-KEY ( degarelix ) OR TITLE-ABS-KEY ( abarelix ) OR TITLE-ABS-KEY ( abiraterone ) OR TITLE-ABS-KEY ( androgen-receptor AND inhibitor ) OR TITLE-ABS-KEY ( enzalutamide ) OR TITLE-ABS-KEY ( androgen AND antagonists ) OR TITLE-ABS-KEY ( gonadotropin AND releasing AND hormone AND receptor AND antagonist ) ) AND ( TITLE-ABS-KEY ( lifestyle AND behavior ) OR ( lifestyle AND modification ) OR TITLE-ABS-KEY ( lifestyle ) OR TITLE-ABS-KEY ( "life style" ) OR TITLE-ABS-KEY ( exercise ) OR TITLE-ABS-KEY ( resistance AND training ) OR TITLE-ABS-KEY ( smoking AND cessation ) OR TITLE-ABS-KEY ( diet ) OR TITLE-ABS-KEY ( dietary ) OR TITLE-ABS-KEY ( nutrition ) OR TITLE-ABS-KEY ( caloric AND restriction ) ) AND ( TITLE-ABS-KEY ( osteoporosis ) OR TITLE-ABS-KEY ( bone AND mineral AND density ) OR TITLE-ABS-KEY ( bone AND density ) OR TITLE-ABS-KEY ( bone AND fractures ) OR TITLE-ABS-KEY ( bone AND metabolism ) OR TITLE-ABS-KEY ( bone AND fractures ) OR TITLE-ABS-KEY ( cardiovascular AND diseases ) OR TITLE-ABS-KEY ( diabetes ) OR TITLE-ABS-KEY ( diabetes AND mellitus ) )

Cochrane Library: to reproduce search strategy, please refer to the following four parts, copy and paste each part individually on its dedicated search line in the Search Manager mode, then combine parts: P1 AND P2 AND I; P1 AND P2 AND I AND O.
Files are RIS.

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osteoporosis OR [mh "Osteoporosis"] OR bmd OR bone mineral density OR bone density OR [mh "Bone Density"] OR bone fractures OR bone metabolism OR [mh "Fractures, Bone"] OR cardiovascular diseases OR diabetes OR diabetes mellitus OR [mh "Diabetes Mellitus"]

11a. Study records:

Literature search results will be uploaded to Covidence Software, an Internet based software that facilitates collaboration among reviewers during the study selection process. Screening will be based upon inclusion and exclusion criteria and will be done by two authors for verification.

11b. Selection process:

The authors will screen the titles and abstracts produced by the search against the inclusion and exclusion criteria. Afterwards full text articles will be downloaded using Mendeley web importer, for data extraction Covidence will be used, with further refinement and detail of inclusion and exclusion criteria to align with the study goals mentioned above. If conflict arises, two authors will then screen the full text reports and decide whether these meet the inclusion criteria. We will resolve conflict through discussion. We will record the reasons for excluding trials. Neither of the review authors will be blind to the journal titles or to the study authors or institutions.

11c. Data collection process:
Will be done through Covidence, standardized forms will be designed and then implemented into Covidence. Reviewers will extract data and in duplicate from each eligible study. Data extracted will include demographic data, methodology, intervention details, and all reported patient-important outcomes. Data extracted will be exported then by Covidence to an automated Excel spreadsheet. Reviewers will resolve conflict by discussion. We will contact study authors for further clarifications if needed.

12. Data Items

We will extract data as first author and year of publication from the studies, study design (pilot, RCT), recruitment and number of patients enrolled, patient characteristics as age, race. Disease characters as cancer stage, time on ADT. Targeted outcomes and the means to measure them. Intervention components and mode of delivery, length and follow-ups, behavioral change theory or techniques. Retention percentile, results, limitations. Where information of the above mentioned items are missing, we will contact the corresponding author of the study to request the missing information.

13. Primary outcomes

Will be the patients responding to intervention to one or more of the following problems.

a. Fatigue: measurement of visual analog scale [VAS] or Brief Fatigue Inventory as well as the capability to perform activities of daily living for
b. Osteoporosis: bone mineral density (BMD) measurements of the hip, a dual-energy x-ray absorptiometry (DXA) T-score ≤-2.5 is consistent with osteoporosis.
c. Vasomotor symptoms: The number and intensity of hot flashes.
d. Sexual dysfunction: evaluated through AUA and IIEF scores, NPT scores.
e. Body composition and metabolism: Percent Body fat and lean body mass. Assessment of diabetic profile through A1C levels and glycosylated albumin.
f. Cardiovascular adverse effects: Tracked through improvement in lipid profile.
g. Depression and anxiety: patient reported improvement in symptoms.
h. Exercise capacity: walking range distance, number and power of reps as reported by trainers.
i. Biochemical response: PSA levels.

14. Risk of bias

The quality assessment in a systematic review will be evaluated for quality of the finally included studies (individually) by assessing bias. For randomized controlled trials Cochrane Risk of Bias will be incorporated. We will assess the risk of bias for the following domains: selection (random sequence generation; allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome), attrition (incomplete outcome data), reporting (selective reporting), and other unclear bias. Each assessment will be given an ID, two reviewers will be performing the assessments
independently in duplicate. A summary and risk of bias graph will be made plus study-by-study domain level and overall risk of bias judgements. This will be followed by a discrepancy check between two. For observational studies we will assess for the following domains: selection (random sequence generation; allocation concealment), performance (blinding of participants and personnel), detection (blinding of outcome), attrition (incomplete outcome data), reporting (selective reporting), and other unclear bias.

15. **Data synthesis.**

A systematic narrative synthesis will be provided with information given in text and tables to review and explain the characteristics and outcomes of the included studies. The narrative synthesis will explore the relationship and findings both within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination. Given the multitude of outcome measures of this review, we will resort to a qualitative (narrative) synthesis to summarize the data from different studies. Data will be arranged in order to aid with the identification of subgroups. Variables for sub-group analysis will include types of intervention, sample size, ethnicity and age. This will be done within the boundaries of inclusion and exclusion criteria and will be framed with reference to the strength and quality of the evidence. Findings of included reviews will be narratively described including explanation of the treatment measure and its efficacy and if applicable comparisons of interventions. We will try to answer the following questions

1. Does the intervention work? (within the primary outcomes we have mentioned before in part 13 of this protocol)
2. Does it work better than the current standard of care?
3. Was it integrated in current practice and how to do so if this is the case?
4. What was the overall result after integration?

We will resort to retain studies of any level risk of bias in our analyses if the need presents in order to answer some of the key questions and actually provide information of a critical outcome. Results will be reported for randomized controlled trials, and then supplement the results with information drawn from non-randomized trials.

16. **Meta-bias**

Publication bias will be assessed by searching the PROSPERO database for relevant reviews that have been registered but not published we might resort to graphical methods (such as funnel plots. For reporting bias. For studies published after July 1st 2005, we will screen the Clinical Trial Register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialssearch).

17. **Confidence in cumulative estimate**
The quality of evidence for all outcomes will be adjudicated using the Grading of Recommendations Assessment, Development and Evaluation working group methodology. Considering the domains of risk of bias, consistency, directness, precision, and publication bias. Quality will be adjudicated as high, moderate, low, or very low.

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