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Protocol for a feasibility and early efficacy study of the Comprehensive Lifestyle Improvement Program for Prostate Cancer-2 (CLIPP2)

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ABSTRACT

Background: Although androgen deprivation therapy (ADT) for prostate cancer demonstrates improved overall and disease-free survival, it is associated with adverse effects such as obesity and metabolic syndrome that increase risk of cardiometabolic disease and diabetes type 2. ADT also leads to fatigue, depression and erectile dysfunction, which reduce quality of life (QoL). Lifestyle modification has shown promise in reducing obesity, metabolic syndrome and diabetes type 2 in other disease types. However, there is a paucity of data regarding the utility of lifestyle modification in men receiving ADT for prostate cancer.
Methods: The primary aim of the Comprehensive Lifestyle Improvement Program for Prostate Cancer-2 (CLIPP2) is to test the feasibility of conducting a 24-week lifestyle modification intervention in men on ADT for prostate cancer. Additionally, it will also determine the effect of this intervention on weight loss, cardiometabolic markers (secondary aim and markers of interest: serum glucose, insulin resistance, hemoglobin A1C and lipid panel), and QoL (tertiary aim). The intervention will be delivered weekly via telephone for the first 10 weeks and bi-weekly for the remaining 14 weeks. Questionnaires and serum samples will be collected at baseline, week 12, and week 24. Anthropometric measurements will be collected at baseline, week 6, week 12, week 18 and week 24.
Results: We hypothesize that the CLIPP2 intervention will produce a 7% weight loss that will result in improved markers associated with cardiometabolic disease and type 2 diabetes in the study population.
Conclusion: Results will provide insight into the role of lifestyle modification in addressing ADT adverse effects as well as provide preliminary data to inform the development of future lifestyle interventions in this area.
Trial registration: NCT04228055 Clinicaltrials. gov.

1. Background

Prostate cancer is the most common cancer diagnosis and the second most common cause of cancer attributable to death among U.S. men [1]. Since prostate cancer is an androgen driven disease, reducing circulating androgens through androgen deprivation therapy (ADT) is an important modality for treating prostate cancer. ADT is associated with adverse effects such as insulin resistance, obesity, and metabolic syndrome [2–4], which increase the individual's risk of diabetes type 2 and cardiovascular disease [5], the most common cause of death in this population [6]. Other adverse effects of ADT include quality of life (QoL) altering symptoms such as erectile dysfunction, decreased libido, hot flashes and fatigue [7–9].

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Lifestyle modification, through changes in nutrition, physical activity and other supportive behaviors, have been shown to reduce insulin resistance, metabolic syndrome and obesity, as well as improve QoL in other disease types [10,11]. Hence, we hypothesize that lifestyle modification could be effective in addressing obesity and metabolic syndrome in men on ADT for prostate cancer. Major components of lifestyle modification, such as nutrition, physical activity, stress management, and sleep optimization, have been shown to individually benefit men on ADT for prostate cancer. Freedland et al. tested the effect of low carbohydrate diet (LCD) on metabolic adverse effects in men on ADT for prostate cancer in a clinical trial. In this trial (Carbohydrate and Prostate Study 1 (CAPS1)), LCD plus a walking intervention was compared to a control group consisting of usual diet and exercise in men on ADT for prostate cancer [12]. Results demonstrated that LCD plus walking reduced insulin resistance by 4%, whereas in the control group, insulin resistance increased by 36% ($p = 0.13$). Furthermore, LCD plus walking demonstrated improvement in weight (weight loss of 10.6 kg, $p < 0.001$) and components of metabolic syndrome (high-density lipoprotein (increased by 27%, $p = 0.003$) and triglycerides (decreased by 37%, $p = -0.036$)) [12]. A review by Yunfeng et al. investigates the role of exercise on addressing adverse effects associated with ADT using data from 15 studies and 1135 individuals [13]. They conclude that exercise is associated with improved exercise tolerance, fatigue, weight, and sexual function in men on ADT for prostate cancer. There was no difference between aerobic and resistance training. Similarly, review by Teleni et al. also concluded that physical activity enhances health and disease-specific QoL [14]. Although sleep disturbance and stress are frequently associated with ADT, very few studies have investigated the impact of targeted interventions to address them, and those that have, noted positive impact on metabolic health and QoL [15,16].

Despite each of the above components having an effect on improving metabolic health and QoL in men on ADT for prostate cancer, to date, the combined effect of all components has not been investigated. The Comprehensive Lifestyle Improvement Program for Prostate Cancer-2 (CLIPP2) has been designed to address this deficiency by taking a comprehensive approach to lifestyle modification. This includes low carbohydrate diet, aerobic physical activity, sleep optimization, and stress management. CLIPP2 will provide a robust multi-behavioral approach customized for men on ADT for prostate cancer and build on lessons learned from our prior study in this population [17].

2. Methods

2.1. Study design

CLIPP2 is a single-arm, open-label, clinical trial designed to address the following specific aims: 1) To demonstrate the feasibility of conducting a 24-week lifestyle modification intervention in men on ADT for prostate cancer. 2) To demonstrate the effects of a 24-week lifestyle modification intervention on metabolic indices (serum glucose, insulin resistance, hemoglobin A1C, and lipid panel). 3) To demonstrate the effects of a 24-week lifestyle modification intervention on QoL. Regulatory approval for this project has been obtained from the University of Arizona (UArizona) Institutional Review Board (IRB) and its affiliated hospital system – Banner University Medical Center as well as the Banner MD Anderson Cancer Center IRB. The UArizona is the IRB of record.

2.2. Recruitment

Thirty-six participants will be recruited from the University of Arizona Cancer Center in Tucson, the surrounding community, and Banner MD Anderson Cancer Center (Gilbert, AZ). Potential participants will be informed of the study via their physicians. If participants express interest, their information will be shared with the Clinical Research Associate (CRA), who will determine eligibility. Participants recruited through the community will be instructed to call the CRA directly for timely screening. After eligibility has been ascertained, the CRA will obtain informed consent and answer any questions participants may have concerning the study.

2.3. Eligibility

Participants must meet the following criteria. *Inclusion criteria*: 1) men diagnosed with prostate cancer (Stage I to III) who have been treated with ADT within the last five years, 2) Men 40–80 years of age, 3) willing to participate in the lifestyle modification intervention and all assessments and measurements, 4) English speaking, 5) if participating in any other clinical trial, subjects will have a 30-day washout period before they can become eligible for this trial, 6) Body Mass Index (BMI) more than 25 kg/m^2.

2.3.1. Exclusion criteria

1) Men currently participating in any other clinical trials, 2) men with a life expectancy less than 12 months, 3) Stage IV prostate cancer, 4) inability to walk two city blocks, 5) diagnosed with digestive diseases (inflammatory bowel disease, irritable bowel syndrome, diverticulitis, chronic constipation) preventing major dietary changes, 6) individuals unable to fully comprehend the informed consent or other procedural requirements, and 7) participants already following a diet plan (such as a low calorie program, low carbohydrate diet, ketogenic diet, vegan diet or vegetarian diet), 8) participants already following an intensive exercise program equal to or exceeding 75 min of vigorous or 150 min of moderate intensity weekly physical activity will be excluded from the study.

2.4. Informed consent

The investigational nature and objectives of the trial, the procedures and interventions involved and their attendant risks and discomforts, and the potential alternative therapies, risks and obligations, will be carefully explained to each participant; then, a signed consent, approved by the University of Arizona's Human's Subjects' Protection Program Review Board, will be obtained. Documentation of informed consent will be maintained in each participant's research file and a copy will be shared with the participant.

2.5. Study procedure

This is a single-arm, open-label, clinical trial with a pre-post study design. Participants will be scheduled for a baseline visit after informed consent is obtained. During this visit, anthropometric measurements, questionnaire data, biological samples (blood), and body composition data will be collected. Participants will be provided with a fitness tracking device (e.g., FitBit Charge 3) that will provide the study team with physical activity and sleep data. Participants can keep the fitness tracker for personal use after the study is completed. The intervention will be delivered by a trained health coach weekly for the first 10 weeks and bi-weekly for the remaining 14 weeks via telephone. Questionnaires and serum samples will be collected at baseline, week 12, and week 24. Anthropometric measurements will be collected at baseline, week 6, week 12, week 18 and week 24.

2.6. Intervention

The CLIPP2 intervention has been modeled after the Diabetes Prevention Program (DPP) and adapted for men with prostate cancer. The DPP was a randomized clinical trial that investigated a multicomponent lifestyle modification intervention as compared to metformin or placebo to prevent type 2 diabetes in a high risk population

[11]. Results demonstrated that after an average follow-up period of 2.8 years, the incidence of diabetes was 11.0, 7.8, and 4.8 cases per 100 person years in the placebo, metformin, and the lifestyle modification arms, respectively [11]. These results were maintained 10 years after the primary intervention [18]. As in DPP, the CLIPP2 intervention will help participants 1) achieve 7% weight loss from their starting weight and 2) achieve and maintain 150 min of moderate-intensity physical activity weekly. Also, as in DPP, CLIPP2 curriculum will cover topics such as behavioral modification of diet, aerobic physical activity, and stress management, as well as supportive strategies designed to help the participants achieve these goals [11]. The fundamental components of the intervention are based on social cognitive theory, the theory of planned behavior, and the transtheoretical model [19].

For the purpose of CLIPP2, the DPP curriculum has been adapted for prostate cancer survivors by using language and references that are pertinent to this population. Additionally, CLIPP2 will modify the dietary intervention by introducing a low carbohydrate diet in place of the original DPP low fat diet intervention. Participants will be provided telephone-based health coaching, educational handouts, and meal plans to support reductions in their net carbohydrate intake (net = total carbohydrates – fiber) to <50 g of carbohydrates per day. The principal investigator has extensive experience using LCD to address obesity and metabolic syndrome in cancer and non-cancer patients. This approach has been demonstrated to be clinically useful in both settings. Topics covered during the weekly sessions are listed in Fig. 1. Sessions pertaining to sleep and stress management were strengthened and customized to this population. The curriculum will be taught by a health coach experienced in delivering the DPP curriculum and trained by a DPP principal investigator and master trainer, who is also a co-author of this paper. Participants will be requested to measure their blood ketone levels using a finger stick ketone machine to determine if they are in ketosis. Participants unable or unwilling to conduct finger sticks will have the option of self-reporting weekly ketone levels using urine ketone strips.

2.7. Outcome measures

2.7.1. Feasibility measures

Since the primary aim of this study is to determine feasibility of conducting this 24-week lifestyle modification intervention, outcome measures for this aim will be recruitment and retention rates and protocol adherence by the participants. The recruitment goal is set at 36 participants over a 6-month period with both the retention and the adherence goals set at 80% participants. Specifically, if 80% of participants complete the 24-week trial period, the retention goal will be met. If 80% of participants reduce their carbohydrate intake to less than 50 net carbohydrates per day, they will be considered adherent to the protocol.

2.7.2. Efficacy measures

For aim 2, anthropometric measurements (height in inches, weight in pounds, waist and hip circumference in inches) and blood pressure (systolic and diastolic mm of hg) will be carried out by trained study personnel using established protocols at baseline, week 6, week 12, week 18 and week 24. This will ensure consistency between measurements. Whole blood and serum will be collected at baseline, 12 and 24 weeks using standard phlebotomy techniques. 2 ml of whole blood will be aliquoted for hemoglobin A1C, fasting insulin, lipid panel and comprehensive metabolic panel (CMP) measurement. The remaining sample will be centrifuged to separate plasma and serum and aliquoted into 1 ml samples and stored at −80 °C. Two milliliters of serum will be sent to Clinical Laboratory Improvement Amendment (CLIA) certified clinical laboratory to assess markers of efficacy (hemoglobin A1C, lipid panel, fasting insulin, and CMP). The remaining samples will be stored in −80° freezer for future research. Insulin resistance will be calculated using HOMA-IR formula, which is fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5. Participants will use a point-of-care finger (POC) stick device to report ketone levels weekly. Participants unable or unwilling to conduct POC finger sticks will have the option of self-reporting weekly ketone levels using urine ketone strips. For aim 3, QoL will be determined using standardized validated questionnaires. The Patient Reported Outcomes Measurement Information System (PROMIS) Global Physical and Mental Health Scale will be used to determine the overall QoL, whereas the Expanded Prostate Cancer Index Composite Short Form (EPIC-26) will be used to assess disease-specific QoL.

Session	Session Title	Session	Session Title
1	Welcome to CLIPP	9	Problem Solving
2	Be a Carb Detective	10	Four Keys to Healthy Eating Out
3	Eating Fewer Carbs	11	Talk Back to Negative Thoughts
4	Healthy Eating	12	The Slippery Slope of Lifestyle Change
5	Move Those Muscles	13	Jump Start Your Activity Plan
6	Being Active – A Way of Life	14	Make Social Cues Work *for* You
7	Tip the Carb Balance	15	You Can Manage Stress
8	Take Charge of What's Around You	16	Ways to Stay Motivated

Fig. 1. Intervention sessions.

2.7.3. Ancillary measures

Ancillary measures will be used for correlative analyses and to guide future research. These will consist of FitBit activity measures, Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality, and the Arizona Food Frequency Questionnaire (AzFFQ) standardized instrument to assess food consumption patterns averaged across the group over time. Questionnaires will be collected at baseline, week 12, and week 24 and stored for future analyses. Body composition analysis will be conducted at baseline and week 24 using a bioelectrical impedance analysis (BIA) machine. Serum collected at baseline, week 12, and week 24 will be processed for markers of inflammation (Interleukin-6, Interleukin 1-beta, Interleukin-8, stromal cell derived factor 1-alpha & basic fibroblast growth factor) and angiogenesis (vascular endothelial growth factor & plasma placental growth factor) using the Enzyme Linked Immunosorbent Assay (ELISA). Kits will be purchased from Meso Scale Discovery (Gaithersburg, MD) and R&D systems (Minneapolis, MN). Prior literature demonstrates changes in these markers due to ADT [1]. ELISA will be run through the University of Arizona Cancer Center Analytical Chemistry Shared Resource under the supervision of study co-author and co-director of the shared service, Dr. Sherry Chow. Samples will be analyzed in duplicate. Samples collected from each participant will be analyzed together in the same batch. In addition, quality control samples will be analyzed along with the authentic samples in each batch of analysis. Exit surveys will be conducted at the end of the study, or earlier if the participant withdraws early. These qualitative and quantitative surveys will help measure participant satisfaction. Survey results will be helpful in planning the next phases of this project.

2.8. Statistical considerations

2.8.1. Statistical analysis

The primary aim of this study is to determine feasibility of conducting a lifestyle modification intervention in a population of men with prostate cancer who have been exposed to ADT within the past five years. Feasibility will be determined by calculating the study's initiation, retention, and adherence rates. The study initiation rate will be calculated by dividing the total number of participants enrolled in the study by the total number of subjects screened for the study. Retention rate will be calculated by dividing the total number of participants in the study at weeks 12 and 24 by the total number of participants enrolled for the study. Adherence rate will be calculated by determining the proportion of participants able to reduce their carbohydrate intake to less than 50 net carbohydrates in a day. The overall adherence and retention rates and the associated 95% CIs will be reported at 12 and 24

weeks. The study will aim to achieve retention and adherence rates above 80%.

The secondary aim of this project is to detect the effects of lifestyle modification on cardio-metabolic risk factors. Baseline characteristics will be described using mean and standard deviation for continuous variables and frequency as well as the associated proportions for categorical variables. Each outcome for the secondary and tertiary aims will be measured at three time points (baseline, 12 weeks and 24 weeks). For each outcome, two-sided 95% confidence intervals will be constructed for changes from baseline at both 12 and 24 weeks. In addition, a linear, mixed-effects model will be fitted to explore the trajectory of changes overtime. If necessary, baseline values of the marker of interest, age, race, serum PSA, and Gleason score will be adjusted for the mixed effects models. The changes in each of the outcomes over time will allow us to evaluate whether lifestyle modifications can improve cardio-metabolic risk. Similar approach will be used to analyze data for aim 3 to understand the effect of lifestyle modifications on QoL. Analysis will be carried out using intent to treat (all participants) and modified intent to treat (restricting the analyses to participants who were adherent) approaches to determine if study adherence plays a role in mediating the relationship between lifestyle modifications and outcome variables.

2.8.2. Sample size and power

All 36 participants will be included in deriving adherence and retention rates. Those who drop out of the study will be considered to not be adherent to the protocol and not retained in the study. Based on a sample size of 36, the two-sided 95% confidence interval will not be wider than 0.342 for both adherence and retention rates at each follow-up visit. Only those participants who do not drop out from the study will be included in deriving changes from baseline for both secondary and tertiary aims. Our prior studies of lifestyle modification in this population report a study dropout rate of 10% [17]. We, therefore, conservatively assume a dropout rate of 15%, i.e. 30 participants with secondary and exploratory endpoints available. A sample size of 30 produces a power of 80% to detect a change of 0.47 standard deviations from baseline over two follow-up visits for each of the markers investigated in the secondary and tertiary aims assuming a within-subject correlation of 0.20 at a significance level of 5%. A within subject correlation of 0.20 based on a sample size of 30 and two follow-up visits indicates a variance inflation factor of 1.20 (i.e. 1 + 2–1)*0.20 and an effective sample size of 50 (i.e. 30*2/1.20).

3. Discussion

The Comprehensive Lifestyle Improvement Program for Prostate Cancer-2 (CLIPP2) is designed to investigate the feasibility and early efficacy of conducting a 24-week lifestyle modification intervention in men on ADT for prostate cancer. It will also provide data on the effects of this intervention on cardio-metabolic risk factors and QoL.

CLIPP2 builds on lessons learned from our prior study [17] which shows that, 1) participants prefer an intervention delivered remotely, rather than one in which they need to have in-person contact with the health coach; 2) instead of short reminder calls, participants prefer longer phone calls, providing them the opportunity to ask questions and problem solve if needed; 3) participants found some of the questionnaires confusing; 4) they also found having to log their food intake to be cumbersome and time consuming. In order to address these concerns, the following changes have been made to the CLIPP2 protocol: 1) the intervention will be delivered entirely remotely via telephone, eliminating the need for participants to meet the health coach in-person; this allows for better compliance and flexibility for participants. 2) Reminder phone calls have been replaced by 30-min phone calls to allow participants to ask questions and problem solve as needed. 3) Questionnaires have been streamlined by providing clear instructions to reduce confusion. 4) To reduce the burden on each participant, food logs will not be mandatory after week 8. However, because food logs are a valuable tool in understanding patient diet as well as problem solving, participants may be requested to re-start their food logs if their weight plateaus, for that may indicate a patient's progress is stagnating.

One limitation of this study is the lack of a control group. However, given that this is a feasibility study, this study's pre-post design is an appropriate study design. Using an intervention adapted from a standardized and successful program such as the DPP has several advantages (standardization, consistency, generalizability and reliability) as compared to the non-standardized intervention used in other studies. *Standardization* ensures that the same 16-session intervention is delivered to all individuals, and *Consistency* ensures that the intervention is delivered the same way for all participants and the cadence of intervention delivery is consistent for all participants. Even if the intervention is the same, but the delivery style changes, there may be differential impacts on participants. A single DPP trained health coach will deliver the intervention to all subjects to ensure consistency. DPP has been delivered and tested in various populations, which demonstrates its *Generalizability* among different populations. The above three concepts (standardization, consistency and generalizability) increase the *Reliability* of the results obtained as compared to other non-standardized intervention.

Results from the CLIPP2 study will inform researchers regarding the feasibility and utility of conducting a lifestyle modification intervention, consisting of a low carbohydrate diet and physical activity program, on metabolic indices and QoL. These results will provide strong preliminary data for the development of future randomized clinical trials in this population.

Declaration of competing interest

I wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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