Study protocol and statistical analysis plan

Official study title: Effect of combined training on quality of life, functional capacity, cardiovascular function, and body composition in prostate cancer patients undergoing androgen suppression therapy: a randomized controlled clinical trial.

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Introduction

In men, prostate cancer (PC) is the most prevalent cancer in Brazil, after non-melanoma skin cancer. One of the main forms of treatment is androgen suppression therapy (AST). Despite its effectiveness in controlling tumor growth, AST causes adverse effects such as erectile dysfunction, fatigue, decreased muscle mass, increased body fat percentage, decreased functional capacity, decreased muscle strength, and increased cardiovascular events due to a drastic decrease in testosterone and dihydrotestosterone. This scenario negatively impacts quality of life. Physical exercise can mitigate these effects; however, in Brazil, only one study evaluating the effect of physical exercise in these patients has been found to date. OBJECTIVE: To evaluate the effect of supervised physical exercise on quality of life components, functional capacity, cardiovascular parameters, handgrip strength, and physical activity level in men with PC undergoing AST.

Study Design

A randomized controlled clinical trial will be conducted in patients with CP in TSA, allocated to an intervention group (IG) and a control group (CG). Data collection and the physical exercise intervention will be carried out at the Rehabilitation Center of the Sports Center (CDS) of the Federal University of Santa Catarina (UFSC). The IG will perform combined training, involving muscle strength and aerobic capacity during 12 weeks, with 60-minute sessions, three times a week. Outcomes will be assessed before and after the intervention, including quality of life (SF-36, EORTC QLQ-BR30, and EORTC QLQ-PR25 questionnaires), functional capacity (maximal treadmill test, 6-minute walk test, timed-up-and-go test, 30-second sit-to-stand test and handgrip strength), cardiovascular parameters (clinical and ambulatory systolic and diastolic blood pressure, resting heart rate, heart rate variability, flow-mediated dilation, arterial stiffness, and carotid intima-media thickness (IMT) measurement), body composition, and physical activity level. Possible adverse events will be recorded weekly.

Inclusion Criteria

The inclusion criteria stipulate that participants must have prostate cancer in stages I to III, duly certified by a physician in their medical record, be undergoing androgen suppression therapy, be 40 to 75 years old, and have a medical certificate authorizing the intervention and the performance of the tests. Furthermore, they must not have participated in research or any type of systematic intervention involving physical exercise four months prior to the start of the study, must reside in the Greater Florianópolis-SC region, and must sign the Informed Consent Form.

Exclusion Criteria

Participants will be excluded if they do not meet the inclusion criteria or if they present any health condition that prevents participation in the exercise program.

Procedures

Medical History

Participants will answer a questionnaire about sociodemographic data (age, marital status, education, occupation, etc.), clinical data (tobacco use, alcohol use, illnesses, medications, balance, dizziness), as well as specific information about prostate

cancer (diagnosis, treatments, surgeries, recurrence, initiation and type of hormone therapy).

Anthropometry

Body mass measurements (Marte® PP 180 scale, 100 g precision) and height (AlturaExata® stadiometer, 1 mm precision) will be collected. BMI (kg/m²) will be calculated from these data, also analyzed by percentile, according to the cut-off points of the Ministry of Health.

Functional Capacity Measurements

Agility/Dynamic Balance: Timed Up and Go (TUG) test at habitual and maximum speed, in addition to adapted versions with dual tasks (TUG with animals and TUG from the previous month).

Lower Limb Strength: 30-second sit-to-stand test in a standardized chair, arms crossed over the chest, counting complete repetitions.

Handgrip Strength: Assessed with a Jamar hydraulic dynamometer, in a seated position with elbows at 90°. Three attempts per side, with a 60-second interval; the best value was used.

Cardiorespiratory Fitness: Incremental treadmill test (LAEF/UFSC), with warm-up and incremental incline until voluntary exhaustion. Respiratory variables (VE, VO_2, HR, RPE, blood lactate) will be monitored during the test. Capillary blood samples from the earlobe will be collected at each stage and after completion.

VO_2max and iVO_2max: Determined by the highest average VO_2 in 20 seconds and the corresponding incline. Exhaustion criteria include HR >90% of predicted, RPE >18, RER >1.1, and absence of a significant increase in VO_2. First Lactate Threshold (LL1): Obtained from the lactate curve as a function of inclination, with capillary blood samples analyzed using a lactometer.

Randomization and Allocation

Eligible patients will be randomly assigned to an intervention group (supervised combined training) or a control group, in 1:1 blocks, using a sequence generated by the randomizer.com software. Allocation will be confidential and hidden from evaluators to reduce bias.

Control Procedure

The supervised combined training will attend Sports Center (CDS) of the Federal University of Santa Catarina (UFSC). They will begin with aerobic exercise on a treadmill, performed in interval format, three times a week, on non-consecutive days. Each session will have a warm-up and cool-down of five minutes of walking at 4 km/h, without incline. The intensity will be prescribed based on 40% of the difference between the first lactate threshold (LL1) and iVO_2max (Δ40%), adjusted by 10% due to the characteristics of the population. Previous studies have shown that intensities slightly below physiological thresholds favor greater session duration, and the maximum lactate steady state is adopted. In the first week, the stability of lactate concentrations ([Lac]) will be verified through blood samples at the end of each repetition; if there is no stability, the incline will be reduced by 1% and reassessed in subsequent sessions. Training will be

continuously monitored by heart rate and subjective perception of effort (Borg scale 6–20). Progression will occur by increasing the treadmill incline (1% every two weeks) or by modifying the effort/rest ratio.

Strength training will include the major muscle groups, with progression of volume and intensity throughout the program. This progression will be based on repetition zones, reducing the number of repetitions and increasing the overload, with intensity control by the number of repetitions in reserve (3–4 RIR), ensuring adequate stimulus and safety in execution.

Statistical Analysis Plan

Continuous variables will be tested for normality and homogeneity (Shapiro-Wilk and Levene tests) and presented as mean ± standard deviation or median and interquartile range; categorical variables will be presented as absolute and relative frequencies. For comparisons between groups, independent t-tests or equivalent non-parametric tests and Fisher's exact test will be used. Outcomes will be presented as mean and standard error and analyzed using Generalized Estimating Equations (GEE), with Bonferroni post-hoc test, considering group and time as factors. Analyses will follow intention-to-treat and per-protocol methods (≥70% of sessions in the intervention group and attendance at assessments in the control group). Missing data will be imputed by maximum likelihood. The significance level adopted will be 0.05 and effect sizes calculated according to Morris (small, medium, large). Analyses will be performed using SPSS 22.0.

Ethical Considerations

The study was approved by the Ethics Committee of the Federal University of Santa Catarina (CAAE: 95978626.5.0000.0121).

Expected Results

Based on the assessed outcomes, participants in the intervention group are expected to show significant improvements in quality of life, with gains in physical, emotional, and social aspects. Advances in functional capacity are also expected, evidenced by better performance in mobility tests, greater distance covered in the six-minute walk, and an increase in the number of repetitions in the sit-to-stand test. Flexibility and balance should progressively improve, with greater range of motion and postural stability even under more challenging conditions.

In the strength component, an increase lower limb strength and handgrip strength is expected, reflecting greater functional autonomy. Regarding cardiorespiratory fitness, an increase in VO_2max and greater tolerance to exertion are expected, with stable lactate concentrations at submaximal intensities. Cardiovascular parameters should show improvement, including reduced blood pressure, greater heart rate variability, increased flow-mediated dilation, and decreased arterial stiffness and carotid intima-media thickness.

Regarding body composition, a reduction in body fat percentage and preservation or increase in muscle mass are expected. The level of physical activity should increase, with a reduction in sedentary behavior. Finally, a low occurrence of adverse events is anticipated, confirming the safety and feasibility of the supervised intervention.