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TITLE: Exercise to Counteract Loss of Bone and Muscle During Androgen Deprivation Therapy in Men with Prostate Cancer

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14. ABSTRACT

The original objective was to determine whether a 1-year intensive resistance exercise training (RT) program is more effective than a moderate-intensity walking program in ameliorating the effects on body composition of androgen deprivation therapy (ADT) in men with prostate cancer. It was postulated that: 1) RT will attenuate the declines in bone mineral density (BMD) and fat-free mass (FFM) to a greater extent than walking; and 2) both RT and walking will prevent an increase in fat mass. Primary outcomes are lumbar spine BMD and FFM. Secondary outcomes are: total body and hip BMD; fat mass; markers of bone turnover; serum sex hormones; physical functional performance; quality of life, and risk factors for cardiovascular disease (blood lipids, glucose tolerance, arterial stiffness). Because of the inability to enroll the projected number of participants, the study protocol was modified at the time of the 2006 annual IRB review to focus only on the intensive resistance training intervention.

15. SUBJECT TERMS

bone mineral density, osteoporosis, sarcopenia, bone turnover, resistance exercise training

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INTRODUCTION

The original aim of the study was to determine whether a 1-year intensive resistance exercise training (RT) program is more effective than a moderate-intensity walking program in ameliorating the effects on body composition of androgen deprivation therapy (ADT). It was postulated that, in men on ADT for the treatment of prostate cancer: 1) RT will attenuate the declines in bone mineral density (BMD) and fat-free mass (FFM) to a greater extent than walking; and 2) both RT and walking will prevent an increase in fat mass. It was proposed that a total of 40 men would be enrolled and randomized to either the RT or walking exercise programs. Primary outcomes are lumbar spine BMD and FFM**.** Secondary outcomes are: total body and hip BMD; fat mass; markers of bone turnover to determine whether changes in BMD are the result of changes in bone resorption and/or formation; serum sex hormones, including testosterone, estradiol, estrone, and sex hormone binding globulin; physical functional performance; and quality of life. Local project support enabled additional assessments of risk factors for cardiovascular disease, including blood lipid profile, oral glucose tolerance, and arterial stiffness. These procedures were not included in the original grant application, but were described in the revised protocol that was approved by the local IRB and the HSRRB. Because of the inability to enroll the projected number of participants, the study protocol was modified at the time of the 2006 annual IRB review to focus only on the intensive resistance training intervention.

BODY

The tasks in the Statement of Work are as follows:

Task 1: Preparation to initiate studies; months 1 – 3

- secure local IRB and HSRRB approval for study
- apply for research support from the General Clinical Research Center (GCRC)
- apply for research support from the Clinical Nutrition Research Unit (CNRU)
- prepare data forms
- prepare data base
- train research staff

Final approval of the protocol by the HSRRB was 8 August 2004. Thereafter, final approvals were obtained from the GCRC and CNRU for local project support. Recruiting efforts began in November 2004. The protocol was last approved by the local IRB on 17 June 2009.

Task 2: Subject recruitment; months 4-21

- enroll 2-3 subjects per month, total of 40 (20 with the change in study design)
- recruiting lectures at local prostate support group meetings
- meetings with private urology clinic staffs
- interactions with health reporters for local media
- place advertisements on newspaper and radio

Enrollment was below the projected level. Recruitment activities in the past two years focused on contacting urology and medical oncology clinics, both as a means of conserving resources for carrying out the intervention and because direct referral from health care colleagues in the university system was the primary source of volunteers.

Over the entire study, 140 men inquired about the study, 42 attended an orientation session, 39 provided informed consent, and 14 were enrolled in the study. Of the 14 enrolled, 10 completed final follow-up evaluations, and 4 dropped out of the study (time commitment, 1; progression of prostate cancer, 1; unknown, 2). Of the 25 men who provided informed consent but were not enrolled in the study: 12 dropped out for unknown or personal reasons (no response, 7; not enough time, 2; concern about blood draws, 1; refused to get follow-up evaluation for hypertension, 1; refused to get a bone scintigraphy, 1) and 13 did not qualify (started medications that influence bone metabolism, 4; unrepaired hernias, 2; positive bone scan, 1; renal disease, 1; exercising too much, 1; oxygen desaturation during ambulation, 1; unstable medical status, 3).

Task 3: Implement resistance exercise ~~and walking exercise~~ programs~~;~~ months 5 - 32

- maintain records of attendance, exercise performance
- routine maintenance of equipment
- track progress of individual participants

This task was completed, although not in the targeted number of volunteers.

Task 4: Data acquisition and management; months 4 – 32

- schedule all baseline and follow-up testing sessions for all participants
- review all data forms prior to computerization
- enter data into database
- perform routine quality control of database
- track blood samples stored for batch analyses of sex hormones and markers of bone turnover to be performed as participants complete the intervention

This task was not fully achieved. Because of the low subject accrual, serum assays have not yet been completed. These will be performed in the future (at the expense of the PI). See below for the tentative plan for publication of the data from the trial.

Task 5: Prepare schedule reports; months 1 to 36

- prepare required progress reports
- secure annual IRB (and HSRRB, if necessary) renewal of protocol
- file serious adverse event forms as necessary
- prepare abstracts for presentation

Annual IRB approval was obtained on 17 June 2009. No serious adverse events occurred. Because of the inability to recruit the targeted number of participants, the decision was made at the time of the 2006 IRB continuing review to focus the intervention only on the intensive resistance exercise intervention (i.e., discontinue randomization to the walking exercise group). Although this was not an ideal experimental design, the rationale was that it was better to increase the sample size in the resistance training group to demonstrate significant increases in bone and muscle mass in response to exercise (if they occur), than to distribute the limited number of subjects across two groups and have little chance of demonstrating differences between the groups in the adaptations to exercise. These updates to the protocol were submitted to Mr. Peter Marshall at Fort Detrick, MD, after they were approved by the local IRB (23 Aug 2006). As indicated in the 2007 progress report, confirmation from Mr. Marshall was received in November 2006 that updates were being processed. All materials related to the protocol amendment (and the intervening local IRB continuing review) were re-submitted to the USAMRMC in November 2007. In January of 2008, the PI received an email message regarding the amendment approval from Julie Wilberding, PhD, who requested additional documentation of local IRB approvals. After submitting those documents, the PI received a notice from Dr. Wilberding on 29 January 2008 that the protocol was up to date on continuing review and that all of the amendments were approved on the DOD end.

Based on the recommendation of Dr. Wilberding, the protocol was further modified in February 2008 to include current standard DOD language; this amendment was approved by the local IRB on 19 Feb 2008. In the past year, the consent form underwent minor changes to update standard language used by the local IRB (approved 17 June 2009) and to update study personnel and contact information (approved 17 June 2009).

KEY RESEARCH ACCOMPLISHMENTS

The investigators were not successful in enrolling the targeted number of participants for the trial. One reason that recruitment may have been hampered was that trials of bisphosphonate therapy for the preservation of bone mass in men undergoing ADT for prostate cancer were initiated around the time the current study began. Some of the local physicians indicated that they were referring their patients to these trials, which excluded them from participation in our trial. Also, it remains uncertain whether the suppression of sex hormones in men has an effect to markedly reduce spontaneous physical activity, as occurs with sex hormone suppression in some species of female animals. If this does occur, this may have contributed to the lack of enthusiasm of

patients on ADT for participating in an exercise intervention trial. We were successful in getting 10 men to complete 1 year of intensive resistance exercise training.

Plans for publishing findings:

To increase the chances of publishing the findings (in the absence of the originally planned control group), we plan to take advantage of an ongoing NIH-supported clinical trial of one of the co-investigators (RS Schwartz). The trial utilizes the same 1-year resistance exercise training intervention and has the same primary outcomes as the current trial. It is being conducted in men with low normal serum testosterone levels who are randomized to receive placebo therapy or testosterone supplementation. When the testosterone trial is completed (in approximately 1 year), we will take subsamples of men from the placebo and testosterone arms in that study who are matched with the finishers in the current study on age and body mass index. This will enable us to evaluate BMD and body composition changes in response to exercise in men with very low testosterone levels (current study), low normal testosterone (placebo), and higher testosterone levels (testosterone supplementation). This will enable us to evaluate the importance of testosterone and estradiol as mediators of body composition and bone adaptations to exercise training.

REPORTABLE OUTCOMES

At the time of enrollment, the participants were aged 65±10 years (mean ± standard deviation) and had a BMI of 27.8±4.2 kg/m^2. Their systolic and diastolic blood pressures were 139±14 and 82±9 mmHg, respectively. Six men had undergone prostatectomy.

The changes in body composition in response to exercise training were not significant. Based on previous reports that ADT causes an increase in total body and central adiposity, the findings of no increase in total fat mass (26.4±7.8 kg before vs 26.4±8.7 kg after) and a small decrease in trunk fat mass (14.9±4.1 kg before to 14.5±4.6 kg after) suggest that exercise helped to prevent fat accrual. Similarly, the maintenance of fat-free mass (56.1±8.6 kg before vs 56.3±6.9 kg after) suggests that resistance exercise training can help preserve muscle mass in men with prostate cancer undergoing ADT.

As with body composition, there were no significant increases in BMD in response to exercise training. BMD tended to be maintained at the total hip (0.995±0.080 g/cm^2 before vs 0.994±0.100 g/cm^2 after) and the shaft (1.180±0.121 g/cm^2 before vs 1.183±0.130 g/cm^2 after) and trochanter (0.780±0.103 g/cm^2 before vs 0.785±0.098 g/cm^2 after) subregions of the hip. However, BMD at the femoral neck, a common site of osteoporotic fracture, decreased over the year of exercise training (0.807±0.076 g/cm^2 before vs 0.788±0.080 g/cm^2 after) by an average of -2.4±2.8%. Lumbar spine BMD (L1-L4) was preserved (1.090±0.119 g/cm^2 before vs 1.086±0.119 g/cm^2 after).

There was no significant change in fasted glucose in response to exercise training (95.0±11.8 mg/dL before vs. 93.2±10.9 mg/dL after) and a tendency for fasted insulin to increase (7.4±4.3 uU/mL before vs. 10.8±6.9 uU/mL after). This suggests that, if anything, there was a trend for insulin resistance to increase, which occurs in men on ADT. Total cholesterol decreased 18% (171±46 mg/dL before vs 138±32 mg/dL after), HDL-cholesterol decreased 15% (46±13 mg/dL before vs. 39±9 mg/dL after), triglycerides were unchanged (124±57 mg/dL before vs. 121±44 mg/dL after), and LDL-cholesterol (calculated using the Friedewald Equation) decreased 25% (100±37 mg/dL before vs 75±27 mg/dL after) in response to exercise training.

Because the study was carried through two no-cost extensions to try to increase the enrollment, expenditures for personnel were greater than originally planned. Sex hormone and bone turnover marker assays have not yet been run, but will be completed in the future (at the PI's expense). The importance of serum testosterone and estradiol concentrations as mediators of the adaptations to exercise, and whether exercise influenced either bone resorption or formation, will be examined in the future, as described above.

CONCLUSIONS

Throughout the period of award, we had difficulty enrolling volunteers in the study. The expectation was that the inclusion of a medical oncologist (Dr. Glode), who enthusiastically agreed to be a co-investigator to facilitate the recruitment of patients, would ensure the success of this aspect of the project. Because this did not occur, the investigators tried both general advertising mechanisms (e.g., newspaper, radio) and more targeted approaches (e.g., other oncology and urology providers and prostate cancer support groups in the Denver Metropolitan area). Most successful referrals came from a few providers. Future studies in this area would require very strong associations with key referring physicians

As described in the Key Research Accomplishments section above, we believe we will be able to publish the findings of the study in the future when some convenience comparison groups become available through

another ongoing trial in our lab. The importance of determining the effectiveness of exercise to counteract some of the effects of ADT remains high. There have been numerous published reviews in the past few years on the devastating effects of ADT on the bone health of men with prostate cancer.[2,4,8,10,14,18-21,26,28,31,33,34,38,39,42,43] Recent studies indicate that the rate of decline in BMD increases 5- to 10-fold after the initiation of ADT[15] and that the relative risk of osteoporotic fracture is increased by 30% to 300%.[25,36,41] In 31 men undergoing ADT who were treated with placebo in a bisphosphonate intervention trial,[32] the lumbar spine T-score decreased from an average of -0.8 to -2.5 after only 3 years; all of the participants were classified as either osteopenic (n=13) or osteoporotic (n=18). In one recent retrospective cohort study, the prevalence of osteoporosis for 390 men with prostate cancer undergoing ADT increased from 35% in hormone-naïve patients to 43%, 49%, 60%, 66%, and 81% after 2, 4, 6, 8, and 10+ years of ADT, respectively.[27] In a recent prospective cohort study, the age-adjusted incidence of fracture was higher in men with prostate cancer (31.6 per 1000 person-years) when compared with those without cancer (22.1 per 1000 person-years), and even higher in men with prostate cancer on ADT (40.2 per 1000 person-years).[1] Pharmacotherapies that have proven to be effective in preventing fractures in postmenopausal women[7] may also be effective in men undergoing ADT, based on improvements in BMD that have been observed.[16,32] There is some evidence for anti-fracture efficacy of bisphosphonates in men on ADT, although not from randomized controlled trials.[30] However, even if proven to prevent fractures, pharmacologic osteoporosis therapies do not ameliorate other consequences of ADT that are likely to increase morbidity and mortality.

When compared with either healthy men or men with prostate cancer who are *not* on ADT, men with prostate cancer on ADT lose more muscle, gain more fat (particularly in the abdominal region), and become more insulin resistant and glucose intolerant.[3,5,15,37,40] A recent study of 72 men undergoing intermittent ADT found that lean mass decreased by 2.4±0.4% and fat mass increased by 13.8±2.3% (both $p<0.01$) in only 36 weeks.[12] The prevalence of the metabolic syndrome in men undergoing ADT may be more than 50%.[6] In a retrospective study of men with prostate cancer who did (n=1231) or did not (n=7250) receive ADT, the relative risk of incident type 2 diabetes associated with ADT was 1.36 ($p<0.01$).[24] In men with type 1 diabetes, ADT adversely affected glycemic control, C-reactive protein, fibrinogen, PAI-1, t-PA, and lipid profile.[17] A recent retrospective cohort study found that men with newly diagnosed prostate cancer who were on ADT for at least 1 year had a 20% higher risk of serious cardiovascular morbidity compared with those who did not receive ADT.[35] It appears that even short-term ADT increases risk for cardiovascular disease and diabetes. The time to fatal myocardial infarction was found to be shorter in men who had received 6 mo of ADT plus radiotherapy than in those who received radiotherapy only.[9] A large observational study found that ADT increased the risk for coronary heart disease (16%), myocardial infarction (11%), sudden cardiac death (16%), and diabetes (44%), and that increased risk was apparent with only 1 to 4 months of ADT.[23] Collectively, these observational cohort studies strongly suggest that although ADT may be of benefit for attenuating the progression of prostate cancer, the metabolic consequences of ADT increase risk for physical disability, cardiovascular disease, and diabetes.

Because exercise is the *only* intervention that has the potential to favorably influence *all* of these metabolic consequences of ADT and improve survival and quality of life in men with prostate cancer, conducting exercise intervention studies is the first step in providing preliminary evidence for the effectiveness of exercise in this population. Despite the suggestion by Galvao et al that exercise training can prevent or reverse some of the adverse effects of ADT,[13] the evidence to support this remains sparse. In fact, the suggestion was based largely on a small study by those investigators that evaluated changes in body composition, muscle strength, and BMD in response to 5 months of resistance training in 10 men with prostate cancer undergoing ADT (i.e., same study design as our modified protocol).[11] There were significant improvements in muscle strength and functional performance. Fat-free mass and BMD were maintained, but did not increase. Those investigators recently described plans for a large randomized controlled trial of exercise to ameliorate the side-effects of ADT in men with prostate cancer.[29] A recent email message from them inquired about our interest in being a study site for that trial, suggesting that they, too, are facing recruitment and enrollment challenges.

The findings of our study that exercise training preserved body composition and BMD of some skeletal sites is encouraging. Based on the literature discussed in the preceding paragraphs, it is likely that adverse changes in BMD, body composition, and other metabolic parameters would have occurred in the absence of an exercise intervention. However, in the absence of the planned control group, evidence for such benefits is lacking. As discussed above, we plan to utilize convenience comparator groups from an ongoing trial of exercise and testosterone supplementation in older men with low normal testosterone levels to evaluate whether serum testosterone and/or estrogen levels mediate the body composition and BMD adaptations to exercise training. We will use analytical approaches similar to those we used recently for another clinical trial.[22] All future costs for completing the serum assays, analyzing the data, and publishing the findings will be borne by the PI.

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APPENDICES

Appendix A – IRB continuing review Certificate of Approval
Appendix B – List of personnel receiving pay

Colorado Multiple Institutional Review Board
13001 E. 17th Place
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Denver Health Medical Center
Veteran's Administration Medical Center
The Children's Hospital
University of Colorado Denver
Colorado Prevention Center

Certificate of Approval

24-Jun-2009

Investigator:	Wendy Kohrt
Sponsor(s):	
Subject:	COMIRB Protocol 02-958 Continuing Review
Effective Date:	17-Jun-2009
Expiration Date:	16-Jun-2010
Title:	EXERCISE TO COUNTERACT LOSS OF BONE AND MUSCLE DURING ANDROGEN DEPRIVATION THERAPY IN MEN WITH PROSTATE CANCER

All COMIRB Approved Investigators must comply with the following:

- For the duration of your protocol, any change in the experimental design/consent and/or assent form must be approved by the COMIRB before implementation of the changes.
- Use only a copy of the COMIRB signed and dated Consent and/or Assent Form. The investigator bears the responsibility for obtaining from all subjects "Informed Consent" as approved by the COMIRB. The COMIRB REQUIRES that the subject be given a copy of the consent and/or assent form. Consent and/or assent forms must include the name and telephone number of the investigator.
- Provide non-English speaking subjects with a certified translation of the approved Consent and/or Assent Form in the subject's first language.
- The investigator also bears the responsibility for informing the COMIRB immediately of any Unanticipated Problems that are unexpected and related to the study in accordance with COMIRB Policy and Procedures.
- Obtain COMIRB approval for all advertisements, questionnaires and surveys before use.
- Federal regulations require a Continuing Review to renew approval of this project within a 12-month period from the last approval date unless otherwise indicated in the review cycle listed below. If you have a restricted/high risk protocol, specific details will be outlined in this letter. Non-compliance with Continuing Review will result in the termination of this study.

You will be sent a Continuing Review reminder 75 days prior to the expiration date. Any questions regarding this COMIRB action can be referred to the Coordinator at 303-724-1055 or UCHSC Box F-490.

Review Comments:

Continuing Review (CRV007), 1st Review: All information required for continuing review and re-approval of the protocol and consent form was included and found to be satisfactory with the exception of the requested itemized changes below.

Continuing Review Frequency: The committee determined that the continuing review frequency is 12 months. The reason for this frequency is due to the specific experience of the PI and other members of the research team, the risks / adverse events are anticipated to be minimal considering the scope of the study, low subject accrual, close monitoring of subjects, and oversight by a Safety Officer.

Risks: The committee determined that the risks were appropriately minimized as outlined. The committee made the following risk assessment for the population to be enrolled:

Appendix B – Personnel Who Received Pay

DAMD17-03-1-0276

Daniel Barry

Heather Brooks

Daniel Dahl

Michael Glode

Catherine Jankowski

Wendy Kohrt

Michael Witten