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

PRINCIPAL INVESTIGATOR: Wendy Kohrt, Ph.D.
L. Michael Glode, M.D.
Robert S Schwartz, M.D.
Daniel W Barry, M.D.

CONTRACTING ORGANIZATION: University of Colorado Health Sciences Center
Aurora, CO 80045-0508

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14. ABSTRACT The objective is 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 is postulated that, in men on ADT for the treatment of locally advanced 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. 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; and quality of life. Local project support will enable assessment of risk factors for cardiovascular disease (blood lipids, glucose tolerance, arterial stiffness).					
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INTRODUCTION

The aim of the study is 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 is 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. A total of 40 men will 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 will enable 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.

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 underwent local IRB annual renewal in August 2005.

Task 2: Subject recruitment; months 4-21

- enroll 2-3 subjects per month, total of 40
- 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

A high level of attention was directed to this task in the past year, but enrollment remains below the projected level. Recruitment activities included:

In June 2005, radio ads were run on a popular radio station in Denver that is popular among middle-aged and older adults. These ads resulted in 4 calls, 1 orientation and 1 participant currently enrolled. Also in June, our staff gave a lunchtime presentation on the study for a local private urology group to encourage them to refer patients to us. Brochures were placed in the clinic's waiting room. We asked permission to send letters to patients in the clinic database who receive androgen deprivation therapy, and the physicians were amenable to this approach. However, we have been unsuccessful in getting the clinic staff to follow through and send letters to their patients. This interaction provided us with 1 participant who is currently enrolled.

In August 2005, we initiated contact with another private local urology group who offer to send letters to their patients informing them about our study. We sent over 300 letters to patients in the Western Urology practice. This interaction resulted in over 15 calls, 5 orientations, 3 consents and 1 participant who is currently enrolled.

In September 2005, we staffed a booth at University Hospital during prostate cancer awareness week. We also attend the Prostate Cancer Education Council's running race to raise money for cancer research. These efforts resulted in 1 call.

In October 2005, an email announcement was sent to the UCDHSC community that did not generate any calls. Also, in October an ad was placed in the sports section of Denver's two major newspapers, the Denver Post and Rocky Mountain News, which resulted in 6 calls. In October, we had a booth at men's health fair organized by a local private hospital. Brochures were also left at the urology clinic in the hospital. These efforts generated 2 calls and 1 man consented.

Because the University's patient population and several of the clinics that have cooperated with us in recruitment efforts have patients who do not live near our facility, the protocol was modified in October to allow men to exercise at a facility of their choice after becoming familiar and proficient with the exercise protocol in our exercise training facility. A research assistant tracks participant progress and provides exercise prescriptions to be performed at the remote site. Currently, 3 participants are exercising at a facility of their choice and compliance with the exercise program has not been adversely affected.

An ad was placed in a local newspaper that has a large African American readership in November 2005. After running the ad, the publisher asked Dr. Kohrt to write a small article on exercise and prostate cancer, and this appeared in the next issue. Also in November, an email ad was sent to the University of Colorado Hospital prostate cancer support group. Combined, these efforts did not generate any calls.

In January and February 2006, another series of radio ads were aired on a local station that has been very successful for several of our group's other research studies. Small ads were also placed in the Health and Fitness section of the major local newspapers. These ads did not generate any calls.

In March 2006, on the recommendation of the co-investigator on the project who is a medical oncologist (Dr. Glode), a protocol amendment was submitted to and approved by the local IRB to allow the enrollment of men with limited bone metastases in the study. The amendment was sent to the Army Human Subjects Research Review Board (via fax transmission to Mr. Peter Marshall on 10 April 2006). Prior to this, any evidence of bone metastasis was an exclusion criterion to reduce risk of injury during exercise. This protocol amendment was sought because 1) it does not appear to be common for local urologists to prescribe ADT for men with prostate cancer before metastases occur, even though there is recent evidence that early initiation of ADT in men with high-risk features improves metastasis-free survival,¹ and 2) a recent study suggested that men with metastatic prostate cancer can perform resistance exercise safely.² Another study reported that people with multiple myeloma can exercise safely.³ For the amendment to our trial, the risk of fracture in subjects with evidence of bone metastases is minimized by excluding subjects whose lesions are in bone regions at higher risk for fracture during exercise. Thus, volunteers with metastases in the spine, femur or humerus are excluded. Volunteers with metastases at other sites will be evaluated with 2-view plain film x-rays. Films will be reviewed by a doctor experienced in orthopedic oncology and volunteers found to have more than 10% single cortical layer involvement of noncancellous bone or more than 25% of the diameter of cancellous bone will be excluded. Also in March, an announcement was posted in the University's Cancer Center newsletter and another email was sent to the UCDHSC community. March advertising efforts did not generate any calls.

In April 2006, we made initial contacts with two private urology clinics in the Denver metropolitan area. The physicians in one of the clinics is receptive to referring his patients on ADT. Details have not yet been worked out, but we are hoping that he will be amenable to sending out letters to these patients under his signature to make them aware of the study. We have not yet been able to schedule a meeting with the physician in the second clinic but will continue to pursue this interaction.

In summary, 81 men have inquired about the study, 26 of these men came to our facility to attend an orientation session, 25 provided informed consent, and 8 were enrolled in the study. Of the 17 who consented but were not enrolled at the time of this report, 2 were in the screening process, 6 dropped out for personal reasons before beginning exercise, and 9 men who consented did not qualify for the study (2 were not interested in getting hernias repaired, 1 started estrogen therapy, 1 had severe COPD, 3 started antiresorptive therapy, 1 was exercising too much to qualify, and 1 was medically unstable).

Because the enrollment rate has remained below the projected level, our request for a no-cost extension of the award period was granted. In another study in the PI's laboratory that involves a different population of cancer patients, we experienced a similar level of difficulty in recruiting volunteers until we found one good conduit; full recruitment was then completed within a few months. We remain hopeful that we will find an avenue of patient recruitment for the current study that will provide a better yield. On a positive note, the projected sample size for the current study included a 30% participant drop-out rate. To date, there have been no dropouts once the volunteers have been randomized to being the exercise intervention.

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 is progressing as planned, though at a slower rate than projected.

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 is progressing as planned, though at a slower rate than projected.

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 in August 2005. No serious adverse events have occurred.

KEY RESEARCH ACCOMPLISHMENTS

At this stage of the project there are no key accomplishments.

REPORTABLE OUTCOMES

At the stage of the project there are no reportable outcomes.

CONCLUSIONS

Despite vigorous recruitment efforts, we have been frustrated by the slow participant accrual rates. Easing the exclusion criterion for men with metastatic disease should increase the potential pool of volunteers. We remain fully committed to this project because the importance of determining the effectiveness of exercise to counteract some of the effects of ADT has not diminished since we first proposed the study. In fact, recent evidence suggests that the level of importance has only increased. For example, thus far in 2006 alone, there have been 6 published review articles on the devastating effects of ADT on the bone health of men with prostate cancer.⁴⁻⁹ Recent studies indicate that the rate of decline in BMD increases 5- to 10-fold after the initiation of ADT¹⁰ and that the relative risk of osteoporotic fracture is increased by 30% to 300%.¹¹⁻¹³ Although pharmacotherapies that have proven to be effective in preventing fractures in postmenopausal women¹⁴ may also be effective in this population of men, such therapies do not ameliorate other consequences of ADT that are likely to increase morbidity and mortality. Specifically, 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.^{10,15-18} Such changes increase risk for physical disability, cardiovascular disease, and type 2 diabetes mellitus. Because exercise is the *only* intervention that has the potential to favorably influence *all* of these consequence of ADT and improve survival and quality of life in men with prostate cancer, conducting exercise intervention studies, such as the one in process, is the first step in providing preliminary evidence for the effectiveness of exercise in this population. Even if we do not achieve full participant enrollment, we anticipate that important preliminary data will be generated that could stimulate larger clinical trials to fully evaluate this issue.

REFERENCES

1. Moul JW, Wu H, Sun L et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. *J Urol* 2004; 171:1141-1147.

2. Segal RJ, Reid RD, Courneya KS et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2003; 21:1653-1659.
3. Coleman EA, Coon S, Hall-Barrow J et al. Feasibility of exercise during treatment for multiple myeloma. *Cancer Nurs* 2003; 26:410-419.
4. Duncan GG, Corbett T, Lukka H et al. GU radiation oncologists consensus on bone loss from androgen deprivation. *Can J Urol* 2006; 13:2962-2966.
5. Hoesl CE, Altwein JE. Biphosphonates in advanced prostate and renal cell cancer--current status and potential applications. *Urol Int* 2006; 76:97-105.
6. Holmes-Walker DJ, Woo H, Gurney H et al. Maintaining bone health in patients with prostate cancer. *Med J Aust* 2006; 184:176-179.
7. Smith MR, Boyce SP, Moyneur E et al. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol* 2006; 175:136-139.
8. Bruder JM, Ma JZ, Basler JW, Welch MD. Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. *Urology* 2006; 67:152-155.
9. Mottet N, Prayer-Galetti T, Hammerer P et al. Optimizing outcomes and quality of life in the hormonal treatment of prostate cancer. *BJU Int* 2006.
10. Greenspan SL, Coates P, Sereika SM et al. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* 2005; 90:6410-6417.
11. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005; 352:154-164.
12. Lopez AM, Pena MA, Hernandez R et al. Fracture risk in patients with prostate cancer on androgen deprivation therapy. *Osteoporos Int* 2005; 16:707-711.
13. Smith MR, Lee WC, Brandman J et al. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol* 2005; 23:7897-7903.
14. Brown SA, Rosen CJ. Osteoporosis. *Med Clin North Am* 2003; 87:1039-1063.
15. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology* 2004; 63:742-745.
16. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 2006; 91:1305-1308.
17. Boxer RS, Kenny AM, Dowsett R, Taxel P. The effect of 6 months of androgen deprivation therapy on muscle and fat mass in older men with localized prostate cancer. *Aging Male* 2005; 8:207-212.
18. Basaria S, Muller DC, Carducci MA et al. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. *Cancer* 2006; 106:581-588.

APPENDICES

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