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| 13. ABSTRACT (Maximum 200 Words) This is a study of the effects of ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), on the osteogenic response to 9 months of exercise training in healthy, premenopausal women, aged 21 to 40 years (N=102). The hypotheses are: H1 _a : taking short-acting NSAIDS before exercise will diminish increases in bone mineral density (BMD) in response to exercise training H1 _b : taking short-acting NSAIDS after exercise will not diminish the increases in BMD in response to exercise training Participants take either ibuprofen (400mg) or placebo capsules before and after each exercise session. Women are randomized to three treatment arms: 1) NSAID before exercise, placebo after exercise (NSAID/placebo; n=34); 2) placebo before exercise, NSAID after exercise (placebo/NSAID; n=34); and 3) placebo before exercise, placebo after exercise (placebo/placebo; n=34). Eighty-four subjects have completed baseline testing and have been enrolled in the study. Twelve subjects are presently scheduled for or are undergoing baseline testing. These studies could lead to the development of new strategies to reduce the incidence of, and treatment for, stress fractures that occur in response to vigorous physical activity. | | | | |
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INTRODUCTION:

The primary aim of this randomized, double-blinded, placebo-controlled trial is to determine the effects of NSAID (ibuprofen) use on the osteogenic response to 9 months of exercise training in 102 women. The scientific rationale for this study centers on the knowledge that the osteogenic response to mechanical stress is a prostaglandin (PG)-dependent process and that NSAIDs inhibit PG synthesis. There is evidence that regular NSAID use inhibits the normal bone formation response to mechanical loading, increases risk of fracture, and impairs bone healing. The approved statement of work for this project includes 4 years of recruiting, testing, and training subjects as well as completing sample assays, data analysis, and manuscripts.

BODY:

The major objectives for year 3 were to continue enrollment and performance of tests and procedures and to continue assays of biochemical markers on bone turnover and sex hormones. Table 1 is a presentation of the projected and actual enrollment to date in year 3 of the study. Although the date of award was September 20, 2001, there was a stipulation that work could not commence until IRB and HSRRB review and approval processes were completed. The fully executed agreement was signed on January 31, 2002. Therefore, the expected and actual progression displayed in Table 1 is based on a January 31 start date. Thus, in Tables 1 and 2, month 1 of Year 3 is February 2004.

The progression of the study remains largely determined by the rate of enrollment of subjects and their completion of the intervention. Enrollment is defined as being randomized to study medication and start of the intervention. As shown in Table 1, the number of subjects enrolled in the study is slightly behind the projected enrollment (84 vs 90), but we are making a major recruitment effort to complete study enrollment on schedule, by the end of 2004. There are currently 12 subjects undergoing screening and baseline testing for study participation. The number of finishers is also slightly behind the projected number (43 vs 47; Table 2) due to a higher than expected number of dropouts. The reason for the higher dropout rate is not known. However, in several cases, participants indicated they could not continue in the study because of changes in work-related activity (e.g., job stress, unemployment), which may reflect the depressed economic environment in Colorado. Because the goal is to have 25 finishers in each of the 3 treatment groups, we plan to enroll an extra 6 to 9 volunteers to ensure that we meet this goal.

Table 3 outlines the success of the various recruitment methods that have been employed. Since the last report, 260 phone screens and 50 orientation visits have been conducted. Table 4 illustrates that we are close to projected goals concerning race and ethnicity. New recruitment efforts will continue to target minority populations to increase diversity of enrolled subjects. We do this primarily by advertising in newspapers that target minority populations.

Body composition and bone mass data have been analyzed and computerized for 41 of the current 43 finishers (Table 5). When pooled across treatment groups, there is a significant decrease in fat mass and increase in fat-free mass and BMD in regions of the proximal femur. These preliminary findings indicate that the exercise program is sufficient for generating an osteogenic response, which is critical for determining

whether the response is attenuated by NSAID use. At this stage of the project, all indications are that the study is progressing as planned. No changes to the protocol are planned.

The third goal of year 3 of the study was to continue assays of biochemical markers of bone turnover and sex hormones. During year 2 we purchased a new ELISA plate reader and completed preliminary assays to establish the reliability of measurements. All samples for an individual participant in the study are being analyzed in batch. Serum concentrations of sex hormones, gonadotropins, and markers of bone turnover for 28 finishers are reported in Table 6. The values represent samples acquired during the month before and the final month of the exercise intervention, from the early follicular phase and the luteal phase (x2) of the menstrual cycle.

In the review of the last Annual Report, it was suggested that the progress report should include a summary of dietary records and measurements of maximal oxygen consumption (VO₂max), which are reported in Table 7. These data indicate that energy and nutrient intake are remaining constant over the period of study and that the exercise program is sufficiently intense to generate a significant increase in VO₂max.

KEY RESEARCH ACCOMPLISHMENTS:

Consistent with the Statement of Work, the investigators remain blinded to treatment status for all participants. Therefore, there are no treatment-specific study results to report. The key accomplishments to date have been recruiting, enrolling, and testing subjects, and beginning hormone and biomarker assays. Participant enrollment is slightly behind schedule, but we expect to complete enrollment on time through increased recruitment efforts. Because there have been 7 more dropouts than had been projected for this point of the study, we plan to enroll 6 to 9 additional volunteers.

REPORTABLE OUTCOMES:

none

CONCLUSIONS:

Conclusions cannot yet be drawn because the investigators remain blinded to treatment status.

REFERENCES:

none

APPENDICES:

TABLE 1. Year three projected and actual enrollment

| | Month | | | | | | | | | | | |
|------------|-------|----|----|----|----|----|----|----|------------|-----------|-----------|------------|
| | 1* | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Projected† | 69 | 72 | 75 | 78 | 81 | 84 | 87 | 90 | 93 | 96 | 99 | 102 |
| Actual† | 67 | 68 | 72 | 73 | 76 | 79 | 81 | 84 | 89‡ | 95 | 99 | 102 |

* month 1 is February 2004

† numbers represent the cumulative number of enrollees at the end of each month

‡ bold, italicized numbers are projections through January, 2005

TABLE 2. Year three projected and actual finishers and dropouts

| | Month | | | | | | | | | | | |
|---------------------|-------|----|----|----|----|----|----|----|------------|-----------|-----------|-----------|
| | 1* | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Projected finishers | 32 | 34 | 36 | 38 | 40 | 42 | 45 | 47 | 49 | 51 | 53 | 55 |
| Projected dropouts | 11 | 11 | 12 | 13 | 13 | 14 | 15 | 16 | 16 | 17 | 18 | 18 |
| Actual finishers | 31 | 33 | 35 | 37 | 38 | 40 | 42 | 43 | 45‡ | 48 | 51 | 53 |
| Actual dropouts | 12 | 14 | 15 | 18 | 18 | 20 | 23 | 23 | 24 | 24 | 25 | 25 |

* month 1 is February 2004

† numbers represent the cumulative number of finishers and dropouts at the end of each month

‡ bold, italicized numbers are projections through January, 2005

TABLE 3. Recruitment efforts

| Recruiting Media | Number of Phone Screens | Number of Orientations |
|------------------|-------------------------|------------------------|
| Flier | 81 | 18 |
| Newspapers | 144 | 36 |
| Electronic ads | 215 | 61 |
| Word of mouth | 73 | 24 |
| Not specified | 70 | 6 |
| TOTAL | 583 | 145 |

TABLE 4. Projected and actual enrollment by ethnicity and race

| Race/Ethnic Category | Actual Current Enrollment | % Total | Projected Total Enrollment | % Total |
|--|---------------------------|---------|----------------------------|---------|
| RACE | | | | |
| American Indian/ Alaskan Native | 3 | 4 | 1 | 1 |
| Asian | 2 | 2 | 3 | 3 |
| Native Hawaiian/Other Pacific Islander | 0 | 0 | 0 | 0 |
| Black/African American | 2 | 2 | 6 | 6 |
| White | 70 | 84 | 92 | 90 |
| Other/Hispanic | 7 | 8 | 0 | 0 |
| Total | 84 | | 102 | |
| ETHNICITY | | | | |
| Hispanic | 10 | 12 | 20 | 20 |
| Non-Hispanic | 74 | 88 | 82 | 80 |
| Total | 84 | | 102 | |

TABLE 5. Body composition, bone mineral content (BMC), and bone mineral density (BMD) of 42 participants before and after 9 months of exercise training.

| | before | after | change | p value |
|------------------------|---------------|---------------|----------------|-------------------|
| Age, yr | 33 ± 5 | | | |
| Height, cm | 166 ± 7 | | | |
| Weight, kg | 66.8 ± 9.6 | 65.4 ± 8.8 | -1.4 ± 2.5 | 0.0005 |
| Fat-free mass, kg | 44.7 ± 5.1 | 45.4 ± 4.9 | 0.6 ± 1.3 | 0.0037 |
| Fat mass, kg | 22.0 ± 6.5 | 20.0 ± 6.0 | -2.0 ± 2.0 | <0.0001 |
| Total body BMC, g | 2327 ± 332 | 2328 ± 333 | 1 ± 37 | 0.9119 |
| BMD, g/cm ² | | | | |
| total body | 1.159 ± 0.100 | 1.163 ± 0.098 | 0.004 ± 0.022 | 0.2565 |
| lumbar spine | 1.115 ± 0.139 | 1.113 ± 0.136 | -0.002 ± 0.019 | 0.6017 |
| total hip | 0.976 ± 0.114 | 0.983 ± 0.112 | 0.007 ± 0.016 | 0.0056 |
| femoral neck | 0.892 ± 0.123 | 0.891 ± 0.124 | -0.001 ± 0.025 | 0.8127 |
| trochanter | 0.752 ± 0.099 | 0.758 ± 0.099 | 0.006 ± 0.014 | 0.0091 |
| femoral shaft | 1.137 ± 0.141 | 1.150 ± 0.138 | 0.013 ± 0.023 | 0.0006 |

TABLE 6. Sex hormone profiles and markers of bone turnover measured in the early follicular phase (EFP) and twice during the luteal phase (LP1, LP2) of the menstrual cycle before and after exercise training.

| | before | | | after | | |
|--------------|------------|------------|-------------|------------|------------|------------|
| | EFP | LP1 | LP2 | EFP | LP1 | LP2 |
| E2, pg/mL | 61 ± 26 | 105 ± 95 | 93 ± 66 | 61 ± 20 | 89 ± 69 | 91 ± 61 |
| P4, ng/mL | 0.4 ± 0.2 | 4.4 ± 4.6 | 4.6 ± 4.9 | 0.5 ± 0.3 | 3.9 ± 4.5 | 4.2 ± 4.7 |
| SHBG, nmol/L | 281 ± 154 | 326 ± 203 | 314 ± 194 | 267 ± 150 | 297 ± 177 | 303 ± 171 |
| FSH, IU/L | 3.4 ± 3.1 | 1.7 ± 1.6 | 1.8 ± 2.8 | 2.9 ± 1.4 | 1.9 ± 1.7 | 1.8 ± 2.0 |
| LH, IU/L | 5.1 ± 3.3 | 7.5 ± 9.5 | 4.1 ± 4.5 | 5.1 ± 3.5 | 4.6 ± 3.4 | 4.1 ± 3.8 |
| CTx, ng/mL | 0.4 ± 0.2 | 0.3 ± 0.1 | 0.4 ± 0.2 | 0.5 ± 0.2 | 0.4 ± 0.1 | 0.4 ± 0.2 |
| BAP, U/L | 20.5 ± 5.7 | 22.3 ± 7.9 | 25.1 ± 10.1 | 23.2 ± 8.3 | 20.9 ± 6.1 | 20.0 ± 5.3 |

E2=estradiol; P4=progesterone; SHBG=sex hormone-binding globulin; FSH=follicle stimulating hormone; LH=luteinizing hormone; CTx=C-terminal telopeptide of type I collagen (bone resorption marker); BAP=bone-specific alkaline phosphatase (bone formation marker)

TABLE 7. Dietary intake and cardiovascular fitness before and after 9 months of exercise training.

| | before | after | change | p value |
|--------------------------------|------------|------------|-----------|-------------------|
| Energy intake, kcal/d | 1859 ± 451 | 1838 ± 481 | -21 ± 207 | 0.5931 |
| protein, g/d | 78 ± 24 | 76 ± 29 | -2 ± 13 | 0.4366 |
| carbohydrate, g/d | 228 ± 68 | 231 ± 58 | 3 ± 24 | 0.4302 |
| fat, g/d | 69 ± 21 | 67 ± 23 | -2 ± 10 | 0.2794 |
| Calcium intake, g/d | 922 ± 328 | 935 ± 372 | 13 ± 129 | 0.5845 |
| VO ₂ max, mL/min/kg | 32.3 ± 4.6 | 37.1 ± 4.7 | 4.8 ± 3.2 | <0.0001 |
| HRmax, beats/min | 189 ± 10 | 187 ± 9 | -2 ± 7 | 0.0409 |

VO₂max=maximal aerobic power; HRmax=maximal heart rate.