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Ellen Rose Brooks

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EFFECTS OF NANDROLONE DECANOATE ON STRENGTH, MARKERS OF BONE FORMATION AND TURNOVER IN OBESE POSTMENOPAUSAL WOMEN WITH NORMAL BONE DENSITY

A Dissertation

Submitted to the Graduate Faculty of the Louisiana State University and Agricultural and Mechanical College
in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The Department of Kinesiology

by

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ABSTRACT

Treatment with androgens and anabolic steroids in conditions of high bone turnover seen in osteoporotic postmenopausal females has resulted in bone density improvement. Research has demonstrated a link between muscle mass and bone due to the mechanical demands placed on bone by muscular contractile force associated with physical activity. This study examined whether treatment with a synthetic anabolic steroid, 30 mg. of nandrolone decanoate every two weeks, or placebo increased lean mass, cross-sectional area of thigh muscle and muscle torque production while preserving bone mineral density (BMD) in 18 dieting, sedentary, obese, postmenopausal females not on estrogen replacement therapy. Obesity has been associated with greater BMD, however, previous work has suggested weight loss can precipitate the occurrence of a decline in BMD. Data that were collected included 24-hour urinary calcium and phosphorus:creatinine ratios, serum osteocalcin, parathyroid hormone, total alkaline phosphatase and 25(OH) D3. Additionally, BMD and content (BMC) were measured in the lumbar spine and bilateral forearms with dual emission x-ray absorptiometry. Subjects treated with nandrolone (n=8) demonstrated a significant treatment by time increase in lean body mass with a concomitant decline in % body fat, non-significant increase in muscle thigh volume, no significant change in fat mass and a non-significant decline in lumbar BMD at six months. Isokinetic muscle testing demonstrated significant increases in torque production and total work of the upper extremities and to a lesser extent the lower extremities torque. Non-significant decreases in weight and body mass index occurred. Overall, there were no effects of treatment on bone turnover. The small changes in % body fat, lean mass and torque did not have any effects on bone status. No changes
occurred in total fat mass, therefore decline in % BF occurred only due to increases in lean mass. Addition of exercise training to nandrolone treatment might have enhanced the increases in lean mass and strength, as well as fat mass loss, facilitating a greater strain-related stimulation for bone formation. Further research on BMD of postmenopausal women undergoing weight loss is indicated since they are at high risk for bone loss.
CHAPTER 1: INTRODUCTION

When older obese women with normal bone density diet to lose weight there is a potential concern for loss of lean body mass as well as bone mineral density and content (BMD and BMC). Due to their postmenopausal state, the risk for bone loss, particularly trabecular bone, is high as weight declines and less adrenal adrostenedione is aromatized to estrone in adipose tissue. Both exercise and pharmacological agents have previously been investigated for their effects on the modeling and remodeling processes of bone tissue to determine if they can elicit a positive effect on minimizing high bone turnover characteristically seen in the postmenopausal state. In order to clearly understand the potential ramifications of significant weight loss by postmenopausal women on bone structure, it is important to understand the basic mechanisms of normal bone turnover, the coupling of resorption and formation and how these activities are controlled through modeling and remodeling of the skeletal system.

Mechanisms of Bone Homeostasis

The mechanism whereby bone is laid down and resorbed is a dynamic process under the control of various endogenous and exogenous forces. Some of the major factors influencing this process are: feedback from the endocrine system, nutritional intake of various electrolytes, appropriate absorption of these minerals from the gastrointestinal system, estrogen status in females, body weight, movement creating a stress-strain relationship of bone and muscle and genetic influences. All of these factors are interdependently associated with bone remodeling in both trabecular and cortical bone.
Parathyroid hormone (PTH) is known to regulate calcium balance via direct action on bone. It stimulates osteoclast numbers and activity, inhibits osteoblast function and increases calcium renal distal tubular reabsorption from the glomerular filtrate, thus increasing serum calcium levels.\(^{(1)}\) PTH is also responsible for inhibition of phosphate reabsorption in the renal proximal tubules and regulates control of activation of 1,25 (OH)\(_2\)D\(_3\), the active form of vitamin D, which is responsible for increasing calcium absorption in the gut.\(^{(13)}\) It is also known that vitamin D and vitamin D metabolite receptors are located on the parathyroid gland, to provide feedback.\(^{(14)}\)

Calcitonin, another calcitropic hormone, acts by directly inhibiting calcium resorption from bone by its action on osteoclasts.\(^{(1)}\) Specific receptors for calcitonin are located on osteoclasts and in renal plasma membranes.\(^{(13)}\) Calcitonin binding to receptors on osteoclasts effectively inhibits resorptive actions such as mineral release from bone, breakdown of collagen and lysosomal enzyme changes.\(^{(1)}\)

Overall, the active process of bone remodeling involves the activity of osteoblasts (initiate bone formation) and osteoclasts (create bone resorption).\(^{(1)}\) The resulting action which occurs from osteoblast to mineralization of the bone is highly regulated and a long-term process, in terms of effects on bone mineral density (BMD) and content (BMC).\(^{(15)}\) The constant interplay of bone turnover between osteoblasts and osteoclasts is normally coupled so that bone formation is favored over resorption, resulting in bone density remaining relatively unchanged.\(^{(13)}\) There is, however, an age-related bone turnover relationship which has been defined as demonstrating a peak lumbar bone density up until age 30-35, with a decline thereafter.\(^{(16)}\)
**Relationship between Muscle Mass and Bone Mineral Density**

A recurrent issue in the literature regarding dynamics of bone density is the suggestion that lean body mass, in the form of skeletal muscle, exerts a tremendous and positive influence on bone preservation and formation. It has been observed that paralysis and immobilization both result in muscle and bone atrophy.\(^{(17,18)}\) Additionally, weightlessness yields similar effects.\(^{(19)}\) Although no precise mechanisms have been identified as to the relationship between lean mass and skeletal bone density, Dalsky (1989) suggests that the stress-strain relationship between bone and muscle, known as Lanyon's minimum effective strain-related stimulus defines that a level of strain is necessary to maintain the modeling action on bone and a higher level is required for remodeling to occur.\(^{(11)}\) This force may serve to stimulate or mediate increases in osteoblastic activity.\(^{(11)}\) Conroy, et al. also assert that skeletal muscle contraction employs a localized force on bone, resulting in mediation of bone turnover with formation proportional to the load applied.\(^{(20)}\) Snow-Harter, et al. concluded that the relationship between muscle and bone is based upon muscular strength, not just mass, and is a much more complex issue than simple anatomy of muscle insertion to bone.\(^{(21)}\)

More specifically, it has been proposed that muscular strength accounts for 15% to as high as 50% of the variance in BMD.\(^{(20,21)}\) Muscle strength in the forms of isometric, isokinetic and isotonic contractions have all been correlated at varying levels with BMD.\(^{(22)}\) Resistance exercise training, in particular, has been observed to account for chronic skeletal loading, resulting in greater muscle mass and strength.\(^{(20)}\) Mikesky has observed in felines that resistance exercise increased muscle mass and strength, which was accounted for by an increase in cross-sectional area (CSA) of the muscle.
fibers (hypertrophy) and an increase in numbers of new fibers (hyperplasia). Muscle mass is a direct product of muscle fiber weight as well as number of myofibrils (contractile tissue), in addition to a smaller portion of non-contractile tissue, according to Gollnick, et al. Changes that occur in muscle mass as a result of chronic resistance training are even seen with resistance training of the elderly, resulting in strength improvement due to hypertrophy and hyperplasia.

The increase in muscle mass resulting from hypertrophy, as well as hyperplasia, may produce a greater strain on bone because of the greater muscle weight and its resulting higher contractile force. Doyle, et al. implicated muscle weight as an important determinant for contractile activity affecting bone mass more than 20 years ago. His methods were crude compared to current technology in that he excised and measured wet muscle and vertebral ash weights from cadavers. This was an important first step to identify a mechanism for muscle and bone interaction: the greater the muscle mass, the greater possible contractile force of muscle acting upon the dynamics of bone turnover. Since then, muscle mass and strength have been noted to serve as predictors for BMD at various regional sites of the body (femoral neck, spine, wrist and ankle). It has also been suggested that the positive effects of exercise on bone turnover may be proportional to the magnitude of the load applied, rather than the total number of loading cycles. It is, therefore, important to consider that if the muscle group is not stressed, such as with exercise, it may not potentiate an altered stress-strain relationship to result in any effects on bone dynamics. Since exercise training is an integral part of chronic muscle fiber stimulation by neurological factors (recruitment of specific motor units) exercise may be a necessary component of the biomechanical
relationship between bone and muscle.\(^{(25)}\) Ironically, Frontera observed that although a relationship between muscle mass, strength and BMD appears to exist and has been documented in previous research, there has been no direct nor consistent correlation between proximity of the muscle stressed and regional BMD.

**Study Rationale**

There are a number of factors that can potentially influence bone turnover dynamics. Estrogen deficiency is an important factor which has clearly been documented to increase women’s risk for Type I Osteoporosis. The estrogen deficient female has been observed in longitudinal studies to lose bone during perimenopausal years, in addition to very rapid resorption at the rate of 2-3% per year and higher for the first 8-10 years after menopause begins.\(^{(26)}\) These women are also much more apt to become sedentary, lose muscle mass and strength as they grow older.

Additionally, decreased BMD is an important issue to the premenopausal female. This group may develop problems with high bone resorption as a result of excessive dieting and weight loss. Lukaski suggests it may be an important concern in dieting females due to results from a 1993 study at a USDA Human Nutrition Research Center. This USDA study focused on obese premenopausal women who lost an average of 2-3% of their whole body bone density, following a five month very low calorie diet regimen.\(^{(27)}\) These women would be at even higher risk for osteoporosis once menopause begins due to the fact that they would be entering estrogen deficiency with a suboptimal peak BMD.

The current investigation presented in this manuscript was part of a larger study evaluating the treatment effects of hypocaloric diet and anabolic steroid treatment over
nine months on reduction in abdominal fat. This research focused on musculoskeletal effects of the treatment regimen. Clearly, this group of subjects faced the risk of accelerated bone loss due to their age and sex. The treatment regimen of the core study included a 500 kcal reduction in daily calorie intake from each subject's resting metabolic rate with the diet based upon the ADA exchange system and a maximum intake of fat at 30% of daily calories. Subjects also had a sedentary lifestyle and no estrogen replacement therapy or calcium supplementation. Because of their postmenopausal status, these women were at some risk for bone loss with weight reduction.

Anabolic steroids have been utilized in various groups of subjects from the nutritionally debilitated individual, to osteoporotic post-fracture patients, to the more publicized abuse by athletes. This particular investigation focused on anabolic treatment effects increasing lean mass, which has typically been observed. Previous research has suggested anabolic steroids could be valuable in the treatment and prevention of osteoporosis due to its effect on muscle mass and direct load on the bone. Because anabolic steroids facilitate an increase in muscle mass (presumably through hypertrophy of the contractile fibers resulting in a greater potential load on the skeleton) these effects on muscle mass and bone were selected as the focus of the current investigation.

Purpose of the Study

The purpose of this investigation was to test the hypothesis that treatment with a synthetic anabolic steroid, nandrolone decanoate, results in increased lean mass with increased muscle torque production and a pattern of BMD and BMC preservation or improvement, in dieting obese postmenopausal females with normal bone density. Drug treatment of the research subjects was accomplished by the administration of either
30 mg. of nandrolone decanoate or a placebo of equal amount administered parenterally every two weeks in a double-blind fashion.

Because muscle mass, strength and bone turnover status as a result of anabolic steroid treatment were important concerns, there were four predominant issues in this study.

First, a significant issue was to observe whether diet and anabolic steroid treatment would result in an increase in lean mass and loss of fat mass. Second, it was important to assess whether BMD could be preserved or increased. Third, assessment of change in maximal muscle force (torque) production was important due to the potential changes in lean mass. Fourth, bone remodeling effects from anabolic treatment and diet were examined to observe whether increasing lean mass, independent of exercise, had any effect on BMD in an estrogen deficient sample. Evaluation of potential changes in muscle CSA was of particular interest due to the drug treatment since anabolic steroids are known to exert a direct effect by increasing lean mass. It was imperative to observe for potential changes through a number of avenues: radiologically, with biochemical markers of bone turnover and endocrine responses.

**Specific Aims**

To test the hypothesis, specific aims were developed for the nine month investigation, which identified biomechanical, biochemical, endocrine and radiological endpoints.

**Aim 1:** To document body composition changes over the nine month study, specifically by determining weight, lean and fat mass, % body fat (% BF), cross-sectional
area (CSA) of the left thigh, body mass index (BMI), arm circumference (AC) and waist:hip ratio (WHR).

- Body composition was evaluated to note if any anthropometric changes in lean and fat mass occurred over time due to treatment. Specifically, it was hypothesized that lean mass (total body and CSA of the thigh) would increase and % BF, BM, BMI, AC and WHR would decrease due to anabolic steroid treatment while fat mass would decrease as a result of diet intervention.

**Aim 2:** To compare treatment and placebo effects, without exercise training, with respect to alterations in maximal muscle force production in both the upper and lower extremities.

- Maximal force production was selected as a dependent variable to document any changes resulting from hypertrophy of the muscle tissue secondary to treatment with nandrolone decanoate versus placebo. It was hypothesized that a pattern of increased muscle torque production would accompany an increase in lean body mass due to nandrolone treatment while the placebo group muscle torque production would decline.

**Aim 3:** To assess biochemical and endocrine patterns of bone turnover, over nine months, in response to treatment with nandrolone versus placebo.

- Urinary levels of calcium and phosphorus were selected as dependent variables because they are indicative of endocrine control of bone homeostasis, as well as reflecting dietary intake of these minerals. PTH, 25 (OH) D₃, total alkaline phosphatase (Alk Phos) and osteocalcin levels were evaluated because of their role in bone remodeling, thus having been used previously as markers for bone turnover. As
noted previously, PTH and vitamin D are known as calcitropic hormones, which are responsible for the major portion of endocrine control (PTH-Vitamin D axis) of bone mineral turnover. Osteocalcin (bone Gla-protein) represents osteoblastic activity at the bone cellular level, in terms of remodeling. Alk Phos reflects turnover due to osteoblastic activity in the bone and is also released from the liver and is proposed to be a marker for bone formation in the serum. It was hypothesized that the following pattern would be observed in subjects treated with nandrolone: a decrease in urinary loss of calcium and phosphorus: creatinine, a decline in PTH, a rise in osteocalcin, alkaline phosphatase and elevated 25 (OH) D₃. Vitamin D (25 (OH) D₃) may be elevated if calcium homeostasis is improved. However, 25 (OH) D₃ was primarily measured to assess vitamin D status in all subjects.

**Aim 4:** To document changes in bone mineral density and content (BMD and BMC) in both trabecular and cortical bone (spine and forearms) as a response to treatment with nandrolone versus placebo over nine months.

- Selection of these endpoints were important due to potential regional skeletal effects on BMD and BMC of trabecular and cortical bone from anabolic steroid treatment. It was hypothesized that BMD and BMC of the spine and forearms would be preserved and possibly increased with nandrolone treatment whereas the placebo group would demonstrate a decline.

**Implications**

Results from this study will improve our ability to identify systemic and mechanistic effects on bone remodeling in response to anabolic steroid treatment. Although anabolic steroids have been utilized previously in clinical treatment of
osteoporosis, there is little evidence as to how they inhibit bone resorption and enhance bone deposition. Perhaps by using the model of the postmenopausal subject with normal bone density, the actions of this class of drugs can be better understood. Data on muscle mass and maximal muscle torque changes gleaned from this investigation could be exceedingly useful since it is the older subject who benefits most from increases in muscle mass and force due to improvement in gait, balance, ability to ambulate and greater independence with activities of daily living. Finally, those women who are not suitable candidates for estrogen replacement therapy may be candidates for low dose anabolic steroid treatment for preservation of both muscle and bone mass.
CHAPTER 2: REVIEW OF LITERATURE

This chapter reviews the current and significant recent scientific literature in the areas of 1) physiology of bone turnover processes, 2) relationship between muscle strength and biomechanical load on the skeletal system (systemically and regionally) and 3) the process of osteoporosis as defined by biochemical markers of bone turnover.

Discussion of various pharmacological interventions used in the current treatment of osteoporosis is reviewed. Additionally, there is discussion of the action of anabolic steroids on muscle tissue and their role in bone mass improvement in osteoporosis treatment. Lastly, discussion focuses on the present study, treatment with nandrolone decanoate and its use in previous osteoporosis research.

Factors Associated with Bone Turnover

Prediction of bone density in individuals is based upon a number of interdependent factors. Although many factors that influence bone density have been identified (including age, sex, race, genetics, estrogen deficiency, calcium intake, vitamin D₃, PTH and osteocalcin levels, exercise, muscle force production, immobility, familial history of low bone density or osteoporosis, smoking, alcohol intake and administration of various medications), none are believed to serve as an independent predictor of bone density. In particular, exercise has been studied extensively for its effect on lean mass, since increasing muscle mass with resultant improvement in contractile force may serve to directly increase forces on the bone. The enhanced biomechanical force on the skeleton may stimulate increases in bone density.
Exercise Training Effects

Observations have been made of exercise training effects on bone mineral density and bone mineral content changes, although a specific causal mechanism has yet to be identified. Cross-sectional studies have shown an association between level of physical activity and bone mineral density. Dalsky suggests that exercise training may increase peak bone mass by as much as 10% and this effect is indirectly related to Lanyon's minimum effective strain-related stimulus. Weight-bearing exercise, which creates a mechanical load on the skeleton and improves bone density, has been an extensively discussed issue in the literature. Post-mortem studies by Doyle, Brown and Lachance showed a strong correlation (r = 0.72) between psoas muscle weight and the ash weight of the L3 vertebrae. From these data, they concluded that greater muscle mass, with its associated higher contractile force exhibited in physical activity, serves to exert a greater direct force on the skeleton than smaller muscle mass and is therefore a major determinant of bone mass. Conversely, muscle disuse and resulting atrophy, reflecting decreased muscle contractile force, may negatively affect bone density in elderly patients. Vastus lateralis muscle biopsies from hip fracture patients during surgical repair of the femur revealed a significant decrease in fiber size, as documented by use of a histological grading scale for muscle fiber atrophy. This was particularly evident in the fast-twitch fibers. Heavy resistance exercise appears to have more consistently resulted in muscle hypertrophy and bone mineral density increase over non-loading isometric and aerobic exercise. Development of muscle fiber hyperplasia and hypertrophy as a consequence of resistance training has been well
documented in animals.\textsuperscript{(23,40)} There are still many questions as to whether resistance and aerobic training may result in regional or systemic skeletal changes in bone density.\textsuperscript{(30,41)}

Exercise training effects on modulation of neuroendocrine responses which are involved with bone remodeling is one final issue which deserves consideration. Although, there are numerous hormonal responses secondary to acute bouts of endurance exercise, few of the hormones that respond are those which are normally related to bone metabolism. Growth hormone (GH), for example, is known to increase with exercise although a less dramatic rise is observed in trained subjects.\textsuperscript{(42)} Since there is no chronic increase in GH observed with training, it is questionable but possible that the altered pulsatility of GH may in some way participate in remodeling for bone preservation. There is also an increased turnover of T\textsubscript{3} and T\textsubscript{4} during exercise, with a reduced concentration of T\textsubscript{3} and free thyroxine at rest.\textsuperscript{(42)} Trained subjects also elicit slight elevations of cortisol during exercise and males exhibit depressed testosterone levels.\textsuperscript{(42)} Chronically elevated levels of cortisol and thyroid hormone as well as depressed testosterone in males would most likely not serve as a positive influence on bone homeostasis and therefore a causal relationship between endurance training and bone formation should be cautiously interpreted until further data becomes available.

In line with these thoughts, in a 1993 study with trained marathon runners using endurance exercise after a period of a three-week training break, Klausen, et al. assessed responses of the calcitropic hormones PTH, 25 (OH) D\textsubscript{3}, 1,25 (OH)\textsubscript{2} D\textsubscript{3} and calcitonin. He observed a significant decline in 1,25 (OH)\textsubscript{2} D\textsubscript{3} while PTH rose significantly. Transient significant reductions in serum calcium and calcitonin were documented with a non-significant drop in 25 (OH) D\textsubscript{3}. Klausen concluded that a mechanism for inhibition
of 1-α hydroxylation of 25 (OH) D₃ may occur with intensified endurance training but did not postulate the specific mechanisms nor justify the decline in calcitonin and rise in PTH. It appears at this time that there is no causal relationship defined between endurance exercise and neuroendocrine responses which may modulate bone remodeling.

Additionally, resistance exercise has been studied for its effects on hormonal responses. Most resistance training studies thus far have not demonstrated an increase in testosterone levels in females, as well as there are conflicting results on responses of testosterone:cortisol ratios. Elevated serum cortisol levels have been observed to occur following heavy bouts of resistance exercise although these levels do not remain chronically high. These results indicate potentially negative effects on bone status, rather than positive influences due to the specific trends which have been documented.

Obviously, further research in the area of resistance training, in terms of both acute and chronic exercise effects on the hormonal milieu need to be addressed before any conclusions can be drawn regarding muscle and bone synthesis from this area of the literature.

Muscle Strength

Significant correlations between muscle strength and bone density have been observed in human studies. More specifically, muscle strength as measured isotonically and isokinetically are good predictors of localized bone density. In females trunk and left knee extensor (quadriceps) strength demonstrated a moderate relationship to bone mass (r =0.40 and 0.49, p = 0.0001, respectively). Rutherford and Jones have also observed a relationship between knee extensors muscle strength and cross sectional area and femoral BMD in the elderly.
Grip strength has also been found to correlate with BMC of the forearm ($r=0.66$, $p<0.001$).\(^{46}\) Less robust results were obtained by Bevier with observed correlation between grip strength, forearm (radius and ulna) and spine (lumbar) density in women ($r=0.37$, $r=0.28$, $p<0.05$) and back strength with forearm and spine density in men ($r=0.46$, $p<0.01$).\(^{31}\) Back strength is believed to serve as a predictor of trunk and peripheral BMD in men.\(^{31,47}\) Additionally, Popcock, et al., observed in postmenopausal women that:

biceps muscle strength was an independent predictor of bone mineral density in three sites of the proximal femur ($r=0.56$, 0.54 and 0.41, $p<0.001$).\(^{48}\)

Conversely, Sinaki, et al., observed in postmenopausal females undergoing a non-loading exercise program for back extensor muscles, that improvement in back strength did not inhibit vertebral resorption ($p=0.002$).\(^{39}\) This disparity between studies may be due to the fact that the spine is composed mostly of trabecular bone, which is far more sensitive to estrogen deficiency after menopause ensues. For this reason, exercise with improvement in strength did not have a protective effect on the spine whereas areas with higher cortical bone (forearm and femur) did show some protective benefit.

**Osteoporosis**

Osteoporosis is the primary cause of bone mineral loss in post-menopausal females.\(^{3,11,32,35,36,49-52}\) According to results from the Mediterranean Osteoporosis Study (MEDOS), those individuals at higher risk for development of osteoporosis and subsequent fractures are very lean, tall females who currently smoke at least 2 packs of cigarettes/day and have a familial history of osteoporosis.\(^{53}\) This bone disease process is defined as loss of structural integrity of the bone due to excessive resorption.\(^{32,54}\) The
longitudinal trabeculae have been observed to become thinner while some of the transverse trabeculae are totally resorbed.\(^{(29,55)}\) When resorption exceeds formation, the integrity of the bone is affected. This results in weakening of the bone such that it becomes brittle and able to endure far less mechanical strain.\(^{(55)}\)

Normally in the skeletal system there exists a homeostasis in which bone is either lost or laid down in direct response to the experience of daily mechanical stress.\(^{(29,55)}\) During early adulthood there is usually a positive balance so that peak bone mass is achieved but in later life when estrogen levels decline, a negative balance between bone resorption and formation can occur.\(^{(31)}\) The time period necessary for completion of initial remodeling through actual bone formation takes approximately 3½ months with mineralization requiring an additional 3-4 months.\(^{(32,56-58)}\)

A widely accepted method of treatment for the prevention of bone resorption in postmenopausal women is estrogen replacement therapy.\(^{(32,59-65)}\) Type I involutional osteoporosis which results in loss of trabecular bone is secondary to postmenopausal estrogen deficiency.\(^{(59)}\) It is believed that trabecular bone may be more sensitive to estrogen deficiency than cortical bone.\(^{(32,68)}\) This may be due to the high surface to volume ratio of trabecular bone, which has a turnover rate eight times that of cortical bone.\(^{(69)}\) Loss of trabecular bone in the Ward’s triangle region of the proximal femur can result in aging-related proximal femur fractures.\(^{(68)}\) Sites for increased incidence of fracture are the femur and spine with a doubling of fracture risk for every 10% decrease in vertebral bone density is approximately ten times greater during the first five years after menopause onset than at any other time in a woman’s life.\(^{(69)}\) In particular, accelerated bone loss from the spine in 60 year old women is as
high as 46.8% due to its high content of trabecular bone.\(^{45,67}\) It is therefore not surprising to observe that the highest incidence of fractures due to osteoporosis are vertebral with the occurrence of hip fractures having a rate only half as high.\(^{54}\) The major health care costs associated with osteoporosis, however, are related to hip fractures due to the associated high morbidity resulting from immobility, which ultimately leads to a high mortality rate.\(^{8,48,70,71}\)

**Biochemical Markers**

Clinical documentation of excessive bone resorption with resulting osteoporosis is often accomplished with the use of numerous biochemical markers of bone turnover. These markers specifically reflect bone formation (osteoblastic activity) and resorption (osteoclastic activity). These include serum PTH, urine hydroxyproline calcium and phosphorus, reflecting bone resorption.\(^{72}\) Those specific for bone formation are bone specific or total alkaline phosphatase, 25(OH)\(_3\) and osteocalcin.\(^{72}\)

Serum PTH is known to have a stimulatory effect on bone calcium resorption. Mid-molecule rather than carboxy terminal fragments of PTH have been previously observed to be significantly lower in postmenopausal subjects, although this has not been a consistent finding.\(^{73}\) PTH is directly responsible for action on the distal tubules to increase renal absorption of calcium as well as increase hydroxylation of 25(OH)\(_3\) to the physiologically active form 1,25 (OH)\(_2\) \(_3\), which functions as a hormone. Activation of vitamin D\(_3\) (to the hormone form) increases intestinal absorption of calcium. High ionized calcium levels are a direct determinant of lowered serum PTH levels through a feedback mechanism.
Plasma bone-GLA protein (osteocalcin) is a specific vitamin K-dependent protein which is synthesized by osteoblasts. \(^{6,65,73}\) Vitamin K is a required co-factor in the synthesis, which occurs due to an interaction utilizing glutamate carboxylase and vitamin K epoxidase enzymes. \(^{74}\) According to Gallop, Lian and Hauschka it is the carboxyl groups of the GLA residues, which enable this protein to exhibit calcium-binding properties. \(^{74}\) Osteocalcin has been demonstrated to bind strongly to hydroxyapatite in the cow, swordfish vertebrae, bovine dentine and human cortical bone. \(^{75}\) A positive correlation has been observed between serum levels of bone-GLA protein and lumbar BMD measured by CAT scan \((r = 0.65, p < 0.001)\). \(^{73}\) Osteocalcin is believed to be a useful indicator of bone formation. \(^{6}\) Currently accepted methods for assay are to analyze for intact osteocalcin and the N-mid fragment by radioimmunoassay. \(^{72}\)

Other markers of bone turnover which have been frequently used are 24 hour collections of urine for calcium and phosphorus. \(^{6,76}\) The fractional excretion of calcium and phosphorus:creatinine is a widely used measure of renal tubular reabsorption of calcium and phosphorus according to Need, et al. \(^{76}\)

**Pharmacological Treatment and Prevention of Osteoporosis**

Numerous studies have been conducted concerning whether improvement in bone density in osteoporotic patients occurs as a result of pharmacological therapy. Although subjects appear to respond well to preventive treatment, there are inconsistent results in those with previously documented bone loss from osteoporosis. \(^{49,77-79}\) Additionally, pharmacological treatment appears to provide no lasting effects. Once therapy is discontinued bone mineral density returns to pre-treatment values. \(^{76,80,81}\) Bisphosphonates, calcium, flouride, androgens, synthetic anabolic steroids, estrogen,
progesterone, calcitonin, vitamin D₃ and its metabolites have all been used in treatment with varying results and side effects.⁷⁻⁹,⁵¹,⁷⁶,⁷⁹,⁸²⁻⁸⁶

Anabolic Steroids

Supplementation with androgens and estrogens have been noted to act as:

"independent additive determinants of peak bone density."⁶⁰ Improvement in bone density has been well documented with anabolic treatment, although the effects diminish when treatment is interrupted.⁶¹⁻⁶⁴,⁸⁷⁻⁹¹ The precise mechanism of action of anabolic steroids to increase BMD is unknown. High affinity androgen binding sites have been demonstrated in human and rat cell lines with osteoblastic phenotypes.⁹²

Androgens may influence intestinal responses of 1,25(OH)₂D₃ to improve calcium uptake.⁹³ Nandrolone decanoate-treated women, with osteoporotic vertebral fractures, showed a statistically significant increase in intestinal calcium absorption after 12 months of therapy.⁹⁴ Increased lean mass, by induction of protein synthesis in skeletal muscle resulting in a positive nitrogen balance, has been clearly documented with anabolic steroid treatment.⁸⁴,⁹⁵ Increase in muscle mass and protein content in rats has been suggested to be dose-dependent.⁹⁶ In rabbit studies, increased wet muscle weight and CSA in limb muscles was documented after 12 weeks of anabolic treatment.⁹⁷ Due to the previous positive effects observed with muscle mass in the scientific literature, evaluation of potential changes in muscle CSA was of particular interest and included in the methodology of the present core study, as well as in this investigation. The question of whether a direct relationship exists between increased lean mass and BMD, without exercise, however, remains inconclusive.²⁹,⁶²,⁹⁸,⁹⁹ Doyle’s post-mortem study, however, is the only evidence of direct correlation between muscle and bone mass, in terms of
contractile forces creating biomechanical stress on the skeleton.\(^{(18)}\) Since many factors are believed to be interdependently associated with tightly regulated bone homeostasis (resorption and formation), it is understandable that this process requires further investigation.

Anabolic steroids have been studied extensively for use in the treatment of postmenopausal osteoporosis. Stanozolol, a synthetic anabolic steroid, has been shown to stimulate bone formation in conjunction with a decrease in urinary calcium excretion, increased urinary cyclic AMP and increased serum skeletal Alk Phos activity.\(^{(87,100)}\) There, however, can be a non-uniform skeletal increase in bone mass.\(^{(49,82)}\) Additionally, there is no information available on the quality of mechanical strength and stability of this bone replacement.\(^{(82)}\) Treatment in two studies, 24 and 26 months, respectively, with methandrostenolone revealed increased lean mass, prevention of further bone density loss but without any increase in BMD in postmenopausal osteoporotic females.\(^{(49,78)}\) Another synthetic anabolic steroid, Org OD 14, has demonstrated increased lumbar bone density (8% increase after 24 months of treatment) and it has been suggested to inhibit bone resorption and stimulate osteoblastic activity.\(^{(51)}\) The question of the precise mechanism for change in BMD, however, remains controversial and unanswered.

**Nandrolone Decanoate**

Nandrolone decanoate (17B-hydroxyestr-4-en-3-one 17-decanoate; Deca-Durabolin (Organon, Inc., West Orange, NJ), the pharmacological treatment for this study, has not been previously studied for its prospective role in improvement of biochemical markers for bone formation and resulting bone mineral apposition in postmenopausal subjects without osteoporosis, although it has been studied in
osteoporotic patients. Androgens are known to be involved in the determination of peak bone mass in both males and females. There is also strong evidence that testosterone or a metabolite is directly responsible for bone development at puberty.\(^{68}\) It has been previously demonstrated that muscular tissues are more responsive to nandrolone treatment than other tissues.\(^{101}\) This is believed to be due to the strong binding capability of nandrolone to androgen receptors, which are located largely in muscular tissue.\(^{101}\) Nandrolone decanoate treatment has resulted in an increase in BMC and BMD of the forearm and lumbar spine as well as increased lean mass and decreased fat mass in osteoporotic postmenopausal females.\(^{37,62,63,76,93,94}\) In addition, increase in renal tubular calcium reabsorption without activation of skeletal Alk Phos has been observed.\(^{93}\) Others have not observed significant changes in BMD with nandrolone treatment, although increases in lean mass and a decline in fat mass were documented.\(^{64}\) It has previously been suggested that increases in BMD from treatment may be related to a decrease in bone resorption rather than an increase in bone mass.\(^{63,102,103}\)

Parenteral administration of nandrolone decanoate has been associated with adverse side-effects. There have been reports of virilizing effects which include hirsutism, hoarseness and deepening of the voice.\(^{63,89,102,104,105}\) Others have reported no virilizing effects after long-term treatment.\(^{103}\) A non-significant decline in serum high-density lipoprotein cholesterol has also been noted with treatment over a two year period.\(^{63}\) Some androgens have been associated with hepatotoxicity, as observed from abnormal liver function tests, jaundice and rare documented cases of hepatic carcinoma.\(^{89,106}\)
Summary

This chapter has set forth a number of important issues regarding control of bone formation and resorption. It is evident that there are a number of interdependent factors that appear to be associated with bone turnover, some of which have effects on resorption, while others may affect formation. Although there is major control by the endocrine system, in terms of bone homeostasis, there are other mechanisms which play some yet-to-be-defined role.

One factor which required further clarification was lean mass effects on bone density. Information has been presented that defined the anatomical and biomechanical relationship between muscle mass, its contractile force during physical activity acting upon bone and this action stimulating bone formation. Lanyon's minimum effective strain-related stimulus\(^{(29)}\) adequately encompasses the biomechanical force relationship that exists between muscle and bone. Further, Doyle, Brown and Lachance have previously demonstrated a strong correlation existed between regional muscle mass and bone density.\(^{(18)}\) Their work served to clarify the importance of muscle force, as a result of its mass and contractile strength on bone mass. Also muscle disuse and loss of contractile strength has been documented to be adversely correlated with bone mass.

There is no doubt that this biomechanical relationship between bone and muscle exists, although the extent to which muscle strength predicts bone mass is unknown. Weight-bearing exercise in the form of resistance training, in particular, has been found to increase strength, muscle mass and BMD. The theory is that increased muscle contractile force may contribute to bone remodeling but the precise definition of the nature of the exercise, relative contributions of muscular force and mass changes as a
result of exercise need to be clarified. Dalsky has noted that exercise training may increase peak bone mass by as high as 10% when optimal hormonal and nutritional conditions exist. It is important to remember, however, when interpreting Dalsky's conclusions that there are many other factors besides exercise that interdependently contribute to remodeling, thus influencing bone mass.

Strength testing has demonstrated that isokinetic, isometric and isotonic muscle strength have all been correlated to varying degrees with bone density. In addition, strength training has resulted in a diversity of responses by bone mass, dependent upon the age, sex and type of training of the subjects. In particular, postmenopausal females who improved back strength from an exercise program didn't inhibit bone loss from the spine.

As previously emphasized, it is the postmenopausal female who faces the greatest risk for bone resorption, without adequate replacement, to occur. Bone homeostasis is no longer guaranteed with the onset of menopause, unless estrogen replacement therapy ensues.

One of the most important aspects of clinical evaluation for bone turnover has been the advent of biochemical markers. These provide significant documentation of the current status of bone formation and resorption in subjects. Additionally, endocrine markers and urinary markers for bone and collagen loss have been extremely useful in developing a clear picture of bone status in subjects.

A review of various pharmacological treatments to improve bone density and decrease risk for fracture has been presented. Few drugs are currently approved by the Food and Drug Administration (FDA) for treatment of osteoporosis, whereas numerous
ones are in the clinical trials phase. What is not clear with many of the treatment options is the quality of new bone that is formed as a result of treatment. It is clear, however, that positive effects on bone mass are only present with concurrent treatment and once treatment is terminated, the positive effects cease. This is also the case with estrogen replacement therapy (ERT), as well.

One drug treatment option which is not approved by the FDA for clinical use is anabolic steroids. This class of drugs has, however, been tested in research settings and shown to increase BMD in osteoporotic subjects. Of particular interest is the question that these drugs may increase vitamin D action on the gut to increase calcium absorption. Additionally, it has been discussed that anabolic steroids have been demonstrated to increase lean mass. Whether this has direct implications in improving BMD is of importance.

Finally, nandrolone decanoate has been discussed in terms of previous research on osteoporotics. It has clearly demonstrated an improvement in BMD and BMC of both the forearms and lumbar spine of osteoporotic subjects. Nandrolone decanoate, like other steroids, has demonstrated, in certain populations, changes in lean body mass and bone similar to effects observed in exercise. This drug posed minimal risk to the subjects being tested but due to this possibility, nandrolone was assigned at a lower dose range than the osteoporosis treatment literature reflects. Although previous studies using anabolic steroids have shown strong evidence of increased lean mass, this investigation served to focus on lean mass changes without exercise and whether preservation of BMD in non-osteoporotic females would occur.
This investigation was needed to focus on the effects of an anabolic steroid on muscular force, lean mass, bone density and biochemical and endocrine indicators of bone turnover. Results will assist in the understanding of the inter-relationships of lean body mass, bone density and indicators of osteoblastic and osteoclastic activity.
CHAPTER 3: MATERIALS AND METHODS

This study determined the effects of treatment with 30 mg. nandrolone decanoate or a placebo on postmenopausal non-osteoporotic obese females on biomechanical, biochemical and endocrine endpoints over a nine-month period. A dosage of 30 mg. was selected, although smaller than the dosage used in the osteoporosis literature, to minimize the virilizing side effects which accompany anabolic treatment. All of the dependent variables were selected because of their importance as markers of bone turnover (synthesis or resorption), bone density and mineral content and muscle strength status.

Subjects

A group of 20 healthy Caucasian postmenopausal females aged 37-62 were recruited from the local and outlying communities by advertisement for the core weight loss study. Subjects had a body mass index (BMI= kg/m²) between 28-42. All participants were either surgically or naturally postmenopausal, which was confirmed by Luteinizing Hormone (LH) levels (> 10 mIU/ml). Subjects were healthy, had normal bone density, no evidence of hyperlipidemia, no musculoskeletal limitations, not taking ERT or calcium supplementation and were basically sedentary, as documented by a physical activity history. Volunteers were asked not to change their level of physical activity over the duration of the study and were reassessed every three months (0, 3, 6, and 9 months) with a physical activity history questionnaire, which quantitated the MET hours/week and MET hours/over the past 3 months expended during work and leisure time. The study protocol was approved by the Louisiana State University Committee on the Use of Humans and Animals and subjects gave their written consent to participate in
the study with all of its associated procedures. Subjects also signed a core study informed consent which outlined the drug treatment, dosage and potential adverse effects due to treatment with an anabolic agent.

All volunteers entering the study completed a stringent screening process which included a physical examination, blood pressure assessment and clinical laboratory evaluation including a complete blood count (CBC), Chemistry 24 panel, lipid profile, fasting insulin and routine urinalysis. All lab work and physical examination results were required to be within normal limits for subject inclusion into the study. Eighteen subjects completed the study with the two drop-outs being from the nandrolone-treated group. These subjects withdrew from the study for medical and personal reasons: one developing migraine-like symptoms while the other subject terminated due to personal reasons. In both cases, the reported adverse effects were not believed to be related to nandrolone treatment.

**Body Composition Assessment**

Body composition for measurement of lean and fat mass (kilograms) was evaluated by dual-energy x-ray absorptiometry (DEXA-Hologic QDR 2000, Waltham, MA). Anthropometric assessment was done by use of measurement of circumferences (waist, hip, and mid-upper arm) and calculation of the waist:hip ratio. The upper arm circumference was assessed using a tape measure on the right arm midway between the acromial and olecranon processes with the elbow bent at a 90 degree angle and the palm supinated. The measurement was made with the arm relaxed and a retractable inelastic tape measure touching the entire arm circumference but not compressing or indenting tissue. Measurement was recorded to the nearest 0.1 cm. The
waist circumference was measured with the subject standing erect and arms at the sides with the natural waist (narrowest part of the torso) exposed. Likewise, the measuring tape was placed horizontal around the waist diameter of the subject without compressing any tissue and recorded to the nearest 0.1 cm. Finally, the hips were measured with the subject standing erect with the arms at the sides and feet together. The examiner squatted at the side of the subject so the level of dorsal protrusion of the buttocks could be noted. The measuring tape was placed around the dorsal protrusion of the buttocks in a horizontal fashion without causing tissue compression or indentation and the measurement was recorded to the nearest 0.1 cm. BMI was calculated from height and weight of the subjects (kg/m²). Height was measured with use of a stadiometer and recorded twice, to the nearest 0.5 mm, and averaged. Weight was measured twice and averaged, using a Detecto digital scale, which was calibrated quarterly using certified weights from the U.S. Bureau of Standards. Measurements were made at baseline and after three, six and nine months of treatment.

Bone Mineral Density and Content

Bone mineral density (BMD=gm/cm²) and content (BMC=gm) of the lumbar spine (L₂-L₄) and bilateral forearms were evaluated by DEXA. Serial comparisons were made at baseline and after six and nine months of treatment, respectively, with use of the compare mode and by matching total area scanned. Lumbar spine scans were all done using an anterior-posterior view. Forearm (total radius and ulna) assessment was made bilaterally to account for both dominant and non-dominant upper extremities. Regions of interest were the ultra distal region and total forearm in an effort to account for changes in cortical and trabecular bone in the appendicular skeleton.
Daily, the DEXA underwent phantom spine calibration prior to use. Data from calibrations were monitored and documented so that the coefficient of variation (CV) of all scans would be within an acceptable range. The DEXA has consistently shown high correlation of precision, long-term reproducibility and longitudinal precision\(^{(52,66,108,110-113)}\) with the dual- and single-photon absorptiometry methods (DPA and SPA).\(^{(70,114-116)}\) The limitation of the DEXA rests with the fact that it does not measure bone volume (cm\(^3\)), but rather area (cm\(^2\)).\(^{(117)}\)

**Isometric Hand Grip Strength**

Bilateral hand grip strength was assessed with use of a Jamar hand dynamometer (TEC, Clifton, NJ). Maximal isometric voluntary contraction (MIVC) was measured bilaterally in newtons of force by having subjects grip the instrument maximally with three repetitions. Subjects were instructed to alternate hand testing so as to provide a period of rest to each hand between maximal contractions. The maximum force measured for three contractions was recorded for each hand and then averaged. Measurements were made at baseline, and after one, three, six and nine months of treatment.

**Isokinetic Muscle Strength Measurement**

The Cybex II (Lumex, Ronkonkoma, NY) was used to measure isokinetic strength of bilateral elbow and knee flexors and extensors. The quadriceps (rectus femoris, vastus lateralis, vastus medialis and vastus intermedius) were the major muscle group utilized in testing knee extensors while the knee flexors (biceps femoris, semitendinosus and semimembranosus) were the group emphasized for the knee flexors. The biceps brachii and the biceps brachioradialis are the major muscles which comprise
the elbow flexors and the triceps brachii were the major focus of the elbow extensors. Subjects were required to complete 6 repetitions (reps) at 180 degrees/sec and 60 degrees/sec. A 10 second rest was given between each rep at 180 degrees/sec and a 30 second rest was given between each rep at the slower speed. Dynamic calibration of the dynamometer was performed by lowering different weights attached to the handle of the input shaft of the dynamometer. This was completed daily before testing of subjects was initiated. Each subject was positioned before testing so that for the extremity being tested the joint of interest was aligned with the dynamometer’s axis of rotation. Peak torque\(^{118}\) (PkTq), mean torque (MnTq) and peak torque/body mass (PkTq/BM) for the six reps were measured and expressed as newton-meters at baseline, three, six and nine months of the study. Total work (area under the torque curve) was measured at baseline and at nine months for all muscle groups tested.

**Thigh Muscle Volume**

The cross-sectional area of the left thigh muscle was measured at baseline and every three months as part of this investigation and the core study methodology, with use of computerized axial tomography (CAT) scan (Siemens,DRH, NJ). Measurement of the CSA of the thigh 100 cm. below the ischial tuberosities was done with a set scan thickness of 8.0 mm. The CSA \(\text{cm}^2\) of the muscle was determined with use of the computer software by summing all pixels within a range of 30-80 Hounsfield units.

**Laboratory Methodology**

Twenty-four hour urinary calcium and phosphorus to creatinine ratios were measured at baseline, and at one, three, six and nine months of the study to observe any change in bone turnover patterns.\(^{6,65,119}\) Subjects were instructed to keep a food record
for 24 hours preceding and during the 24 hours of collection, in order to assess calcium, phosphorus and sodium intake. Written guidelines were also given to the subjects regarding consuming an intake of 800 mg of calcium during this time period, in an effort to provide some control on their calcium intake during urine collection.

Creatinine was measured with use of the Beckman Synchron CX5 (Beckman Instruments, Inc., Brea, CA) using the Jaffé method which creates a creatinine-picrate complex and monitors for rate of change in absorbance.

Urine was acidified by adding 5.0 ml of 6N HCl to the 24-hour container, prior to collection. Analysis was done using a 1:10 dilution with use of the Perkin Elmer P1000 ICP which scanned the chemically specified wavelengths to determine the peak area of the urine specimen, specific for calcium and phosphorus. Additionally, at baseline and every three months, measurements of serum osteocalcin, parathyroid hormone (PTH), 25 (OH) D and total Alk Phos were completed. Total Alk Phos was measured using the Beckman Synchron CX5 using an enzymatic rate method. Serum osteocalcin and 25 hydroxyvitamin D3 were analyzed in duplicate by using a radioimmunoassay method (RIA, INCSTAR), while PTH was assessed using an immunoradiometric assay (IRMA) (INCSTAR, Stillwater, Minn.). These assays were read using a RIASTAR 20 well gamma scintillation counter (Packard Instruments, owners Grove, Il.). Blood samples were drawn after a 12-hour overnight fast between 8:00-8:30 A.M. through an indwelling intravenous catheter in the antecubital space. Samples were drawn and immediately transferred to a glass evacuated tube. The blood was allowed to clot and spun at 1949 rpm for 15 minutes with the serum drawn off
immediately and aliquoted for the various tests. Samples were frozen at -60 degrees C until analysis.

Osteocalcin analysis utilized the simultaneous addition of the iced serum sample, osteocalcin antibody and $^{125}$I osteocalcin, with subsequent overnight incubation for 16-24 hours. Following phase separation, centrifugation, decantation and a 2 hour ± 15 min incubation at 2-8 degrees C, the tubes were read for 60 seconds.\textsuperscript{(64,72)}

Vitamin D was a two-step procedure involving the rapid extraction of 25(OH)D$_3$ and its hydroxylated metabolites from the serum sample. Following this, the sample, tracer and 25(OH)D antibody were incubated for 90 minutes at 20-25 degrees C. There was a subsequent addition of a precipitating complex and re-incubation. Following centrifugation and decantation, the supernate was read. 25(OH)D$_3$ was selected because it is the predominant circulating form of the vitamin and is referenced as the most reliable index of vitamin D status.\textsuperscript{(120)}

PTH utilized an assay with two polyclonal antibodies which are specific to PTH 1-34 (C-terminal region) and 39-84 (mid-region). Iced serum samples were incubated with the N-tact PTH SP bead for 22 ± 2 hours at 20-25 C. Following this, the sample was decanted with the beads washed four times and the intact PTH bound to the SP bead was counted. These biochemical and endocrine markers (serum osteocalcin, total Alk Phos, PTH, 25(OH)D$_3$ as well as urinary calcium and phosphorus/creatinine), in this study were selected in an effort to clearly document any patterns of change in bone turnover as a result of anabolic steroid treatment in the subject sample.
Experimental Design and Statistical Analysis

This out-patient parallel group design with repeated measures involved a nine month period of double-blind drug or placebo treatment, depending upon randomized group assignment of 20 subjects. Eighteen subjects completed the study. It was part of a larger study assessing the energy expenditure, insulin action and abdominal and total body fat loss secondary to treatment with nandrolone decanoate, placebo or aldactone with hypocaloric diet in 30 moderately obese post-menopausal females.

The dependent variables in this study were examined utilizing an analysis of variance (ANOVA) with repeated measures where there was a 1 between-subjects factor (nandrolone drug treatment) and 1 within-subjects factor (time). In situations where the data violated the ANOVA assumption of sphericity the corresponding p-values were corrected using the Huny-Feldt adjustment. Post-ANOVA analysis involved a series of 1 degree of freedom contrasts (selected a priori) or simple ANOVAs depending on the effect being probed. Post-ANOVA tests were driven by the appropriate F-test and the experimentwise error rate (0.05) was maintained throughout all post-ANOVA tests. The time periods selected for re-evaluation of the bone density (baseline, 6 and 9 months) were chosen because they were believed to be of a sufficient period to note changes because of normal bone metabolic mechanisms. (35,40,41,44,79)
CHAPTER 4: RESULTS

Summary tables for treatment by time interactions and post hoc analysis results are listed below (Tables 1 and 2.). Subject characteristics at baseline and additional time by treatment interactions are found in Appendix B.

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<td>Right Elbow Extensors Total Work at 60 dps</td>
<td>0.014</td>
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<tr>
<td>CSA Thigh</td>
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### Table 2. Post Hoc Analysis for Treatment by Time Interactions

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>α</th>
<th>PL</th>
<th>N</th>
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<tbody>
<tr>
<td>LBM</td>
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<td>NSD</td>
<td>BL&lt;6,9M</td>
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<tr>
<td>% BF</td>
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<td>BL&lt;3M</td>
<td>BL&lt;3,6,9M</td>
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<td>Lumbar BMD</td>
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<td>NSD</td>
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<tr>
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<td>NSD</td>
<td>NSD</td>
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<tr>
<td>Right Elbow Flexors PkTq at 180 dps</td>
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<td>NSD</td>
<td>BL&lt;6,9M</td>
</tr>
<tr>
<td>Right Elbow Flexors MnTq at 180 dps</td>
<td>0.025</td>
<td>NSD</td>
<td>BL&lt;6,9M</td>
</tr>
<tr>
<td>Right Elbow Flexors PkTq/BM at 180 dps</td>
<td>0.025</td>
<td>NSD</td>
<td>BL&lt;6,9M</td>
</tr>
<tr>
<td>Left Elbow Flexors PkTq at 180 dps</td>
<td>0.025</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Left Elbow Flexors MnTq at 180 dps</td>
<td>0.025</td>
<td>NSD</td>
<td>NSD</td>
</tr>
<tr>
<td>Left Elbow Flexors PkTq/BM at 180 dps</td>
<td>0.025</td>
<td>NSD</td>
<td>NSD</td>
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<tr>
<td>Right Elbow Flexors MnTq at 60 dps</td>
<td>0.025</td>
<td>NSD</td>
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<tr>
<td>Left Elbow Flexors PkTq/BM at 60 dps</td>
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<tr>
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<td>NSD</td>
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<tr>
<td>Left Elbow Extensors PkTq/BM 180 dps</td>
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<td>NSD</td>
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<tr>
<td>Right Knee Extensors PkTq at 180 dps</td>
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<td>6M&gt;BL,3,9M</td>
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<tr>
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<td>NSD</td>
<td>6M&gt;BL,3,9M</td>
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<td>NSD</td>
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<td>Right Knee Extensors PkTq at 60 dps</td>
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<td>Right Knee Extensors MnTq at 60 dps</td>
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<td>BL&lt;6,9M</td>
<td>NSD</td>
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<tr>
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<tr>
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<td>NSD</td>
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<td>Right Elbow Flexors Total Work 180 dps</td>
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<td>NSD</td>
<td>9M&gt;BL</td>
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<tr>
<td>Right Elbow Flexors Total Work 60 dps</td>
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<td>NSD</td>
<td>9M&gt;BL</td>
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<td>CSA Thigh</td>
<td>0.025</td>
<td>BL&lt;6,9M</td>
<td>NSD</td>
</tr>
</tbody>
</table>

### Body Composition

A significant treatment by time interaction was observed for lean body mass and % body fat. The nandrolone (N) treated group demonstrated a higher lean body mass (LBM) at six months (6M) and nine months (9M) versus at baseline and three months (3M). To the contrary, there were no significant improvements in LBM in the PL group throughout the study period, rather non-significant losses. Additionally, percent body fat
(\% BF) at 3M, 6M and 9M were significantly reduced versus baseline in the N group. The N group started at baseline with a higher (but not significantly) \% BF than placebo (PL) and continued to lose until 6M where it plateaued. The PL group significantly reduced their \% BF at 3M versus baseline but made no additional reductions at 6M and 9M. Initial changes in body fat presumably occurred due to the hypocaloric diet regimen the subjects were assigned to follow throughout the study.

Significant main effects for time were detected for body mass (BM) (p = 0.001), body mass index (BMI) (p = 0.0001), arm circumference (AC) (p = 0.0032) and fat mass (FM) (p = 0.0001) because the baseline values for both groups were greater than any other time point in the study. There were no significant changes observed in the waist:hip ratio (WHR) over the course of the study.

In summary, the nandrolone treated subjects increased lean body mass and decreased their \% body fat over time to a greater extent than the placebo group, however, did not lose fat mass significantly different than placebo-treated subjects. There were no group differences in weight, fat mass, or regional fat distribution as expressed by waist:hip ratio and arm circumference. It is important to emphasize that the resulting significant decline in \% body fat in the nandrolone treated subjects occurred due to the increase in lean mass alone.

**Bone Mineral Density and Content**

There was a significant treatment by time interaction (p = 0.02) for bone mineral density (BMD) in the lumbar spine. Post hoc analysis did not detect significant differences over time for either group but the significant interaction may be due to a slight decline in the BMD at 6M for the N group only. Following this decline, BMD
values returned to near baseline at 9M. Otherwise, no significant difference was observed between the groups for BMD and bone mineral content (BMC) of the lumbar spine.

With respect to the bilateral total forearm (radius and ulna) bone density, the PL group demonstrated a significantly higher BMC than the N group at baseline and throughout the study (left forearm: $F = 7.194, p = 0.0164$; right forearm: $F = 6.171, p = 0.0244$). A significant main effect for time, across both groups, was observed for both BMD of bilateral total forearms and for BMC of the right forearm. This effect was explained by the baseline BMD being significantly greater than the 6M and 9M values for the right total forearm, while BMD was greatest at baseline versus 6M in the left forearm. Additionally, the baseline BMD and BMC were greater than 6M values for the left total forearm. There were no detectable differences across time with use of post hoc analysis for the right total forearm BMC.

A significant main effect of time was observed for BMD of the right ultra-distal (UD) forearm ($p = 0.032$) and BMC of the left UD forearm region ($p = 0.002$). These effects were accounted for by the larger baseline BMC and BMD values versus 6M.

In summary, nandrolone treatment did not serve to protect or preserve the subjects BMD and BMC over PL. In the case of the total forearm and UD forearm, there was loss of BMD and BMC which occurred in both N and PL groups, signifying there were no treatment effects.

**Isometric Hand Grip Strength (MIVC)**

A significant treatment by time interaction was noted only for the left maximal isometric voluntary contraction (MIVC) but not the right. Post hoc testing did not
detect differences over time for either group, with respect to the left MIVC. The interaction was probably caused by the N group grip strength being lower than PL at baseline but higher at 9M.

Isokinetic Muscle Strength Measurement

A significant treatment by time interaction was observed for peak torque (PkTq), mean torque (MnTq) and peak torque per body mass (PkTq/BM) for bilateral elbow flexors at 180 degrees/second (dps). The right elbow flexors torque at 180 dps demonstrated a significant increase from baseline to 6M and 9M for all three dependent variables for N, as was identified by post hoc analysis. The post hoc analysis, however, did not reveal specific differences over time for PL or N-treated groups with respect to the left elbow flexors. The interaction for the left elbow flexors data was due to a marked increase in the N-group from baseline to 3M and with a continued increase from 6M to 9M, whereas the PL group did not change significantly over time. Additionally, at 60 dps there was a significant treatment by time interaction for MnTq of the right elbow flexors caused by the N-treated group with the 6M and 9M torque being greater than baseline. The left elbow flexors showed significant treatment by time interaction for all three dependent variables, with PL demonstrating no significant change over time from the post hoc analysis with N eliciting an increase in torque at 6M and 9M versus baseline.

With regard to the right and left elbow extensors, there was a significant treatment by time interaction for PkTq and PkTq/BM at 180 dps, while the right elbow extensors also showed a time effect for MnTq. The interaction was related to the significantly lower baseline PkTq and PkTq/BM versus at 6M and 9M for the left elbow.
extensors for N while the right elbow extensors torque was significantly lower at baseline versus the PkTq at 9M. The right elbow extensors at 60 dps demonstrated only a time effect for PkTq/BM, for which baseline torque was significantly less than at 6M.

There was a significant treatment by time interaction for PkTq, MnTq and PkTq/BM for the right knee extensors at 180 dps. The post hoc analysis revealed that the N group PkTq, MnTq and PkTq/BM were significantly greater at 6M than at any other time point. There was also a significant treatment by time interaction for PkTq, MnTq and PkTq/BM of the right knee extensors at 60 dps. Post hoc analysis noted a larger torque at baseline than other time points for PL. Finally, the left knee extensors were noted to exhibit a significant effect for time only for PkTq/BM at 180 dps with a peak observed at 6M.

Time by treatment effects for the right knee flexor MnTq at 60 dps were detected and with post hoc analysis it was determined that the differences occurred in the PL group, with a decline in torque over time (9M < 3M and 6M). To the contrary, no differences were detected in the N-treated group.

A significant effect for time was demonstrated for bilateral knee flexors PkTq, MnTq and PkTq/BM at 180 dps and at 60 dps for the right knee flexors for PkTq, MnTq and PkTq/BM. These all revealed that the difference existed at 6M, which was the peak response for all the knee flexors values showing significance.

Total work (area under the torque curve) was measured pre- and post study for all muscle groups tested at both 180 and 60 dps. A significant treatment by time interaction (p = 0.02) was observed for bilateral elbow flexors at 60 dps and the right elbow flexors at 180 dps. Post hoc analysis demonstrated N to show a significant work
increase for the right elbow flexors at 9M versus baseline \((p = 0.025)\) at both speeds and the left elbow flexors at 60 dps. Conversely, PL did not change their total work over time.

A treatment by time interaction was also documented for total work of the right elbow extensors at 60 dps, however no specific differences could be determined by post hoc analysis. This was probably caused by a pattern of increase in total work from baseline to 9M in N. Significant time effects were also observed for the left elbow extensors at both speeds, with total work greater at 9M over baseline.

Regarding the lower extremities, significant time effects for both N and PL treated groups were only seen for bilateral knee extensors at 60 dps with baseline work being greater than at 9M. No time effects were seen for bilateral knee flexors.

In summary, significant differences with respect to the N treated group were observed particularly in the upper extremities over time. Both the left and right elbow flexors torque increased over time when tested at 180 dps for N but not PL, whereas elbow extensors changes were only based upon time effects. In the lower extremities, the PL group demonstrated a decline in torque over time with respect to the right knee extensors and knee flexors at 180 and 60 dps. N only revealed a peak at 6M for the right knee extensors torque (peak, mean and per body mass). Total work increases were seen to a greater extent in the upper extremities. The N group documented significant increases for the elbow flexors and the right elbow extensors between pre- and post study. Bilateral knee extensors at 60 dps only showed time effects for both groups.
Thigh Muscle Volume

A significant treatment by time interaction was noted for cross-sectional area (CSA) of the thigh. Post hoc analysis revealed that the baseline volume was greater than at 6M and 9M for PL. Conversely, the N-treated group demonstrated a non-significant increase in thigh muscle CSA over time.

Endocrine Markers

There were no significant main effects observed for parathyroid hormone (PTH), whereas 25 (OH) D₃ demonstrated a main effect for time for both groups. This was accounted for because vitamin D values for both groups were significantly greater at baseline than at any other time point in the study. The mean coefficients of variation (% CV) for these assays were 10.51 and 6.11%, for vitamin D and PTH, respectively. The normal ranges in this investigation for vitamin D and PTH were 10.00-50.00 ng/ml and 13.00-54.00 µg/L, respectively.

Biochemical Markers

There was a significant main effect for time in the urinary calcium:creatinine ratio with no specific differences detected between time points. Conversely, the phosphorus: creatinine ratio was significantly greater at baseline than at 3M, 6M or 9M. There were no significant differences between the PL and N-treated groups for alkaline phosphatase (Alk Phos), osteocalcin (OC), and urinary calcium:creatinine and phosphorus:creatinine ratios. The mean CV for osteocalcin was 5.14% with a normal range of 1.80-6.60 ng/ml. The mean interassay coefficients of variation for urine calcium and phosphorus were 0.682% and 2.4%, respectively.
Diet records were kept by the subjects 24 hours preceding and the 24 hours during urine collection at baseline, 1M, 3M, 6M and 9M. Subjects received specific written and verbal instructions regarding the required information and amounts to be documented. Additionally, subjects were instructed to consume 800 mg. of calcium in their daily intake of food, to provide consistency of intake. Review of the records and analysis by a nutritional database revealed records were poorly kept by subjects. A significant correlation between phosphorus and sodium intake and urinary phosphorus excretion was observed at 3M for N. Correlations were $r = 0.87$, $p = 0.001$ for phosphorus intake and excretion while $r = 0.69$, $p = 0.010$ for sodium intake and phosphorus urinary loss. No other time points were found to have significant correlation for dietary intake and urinary loss of these electrolytes.
CHAPTER 5: DISCUSSION

This investigation assessed prevention of loss of bone density, with respect to a nine month weight loss program, in obese postmenopausal females with normal bone density. Weight loss was modest in view of the amount of weight that could have been lost over the course of the study. The discussion focuses on treatment effects from nandrolone in this case of minimal weight loss. Numerous treatment by time effects will be discussed which revealed a difference in the pattern of change across time between the placebo and nandrolone-treated groups.

The observation of treatment by time effects on lean body mass is compatible with results from other investigations that have demonstrated increased lean mass with anabolic steroid treatment. The CSA changes of the thigh were consistent with overall LBM increases. The nandrolone-treated group demonstrated a non-significant increase in muscle mass while PL declined (baseline > 6M, 9M). There was a strong trend for a treatment main effect, which reflected muscle mass preservation with nandrolone treatment (F = 4.483, p = 0.0514). Conversely, the placebo group demonstrated a non-significant decline in thigh CSA over nine months.

There was also an expected decline in % BF in both groups which was probably due to the hypocaloric diet utilized in the core study. The N group demonstrated a decline in % BF until 6M, when a plateau occurred, although 3M, 6M and 9M were all significantly reduced from baseline. The PL group also had a significant decline in % BF at 3M and 6M versus baseline. Subjects appeared to have a loss of interest for participation in the calorie restricted phase of the study before 6M, as reflected by the limited amount of weight loss. Unfortunately lack of diet compliance resulted in minimal weight loss which
was not near the anticipated goal. The expected weight loss was that subjects BM would decline by at least 13.64 kg (30 lb.) during the course of the study so that weight loss effects on the postmenopausal skeletal system could be observed. Subjects from the N group went from a weight of 87.4 ± 8.2 kg at baseline to 84.9 ± 8.7 kg at 9M (a loss of 2.5 kg). The PL group began with a mean weight of 86.7 ± 7.5 and completed the study at 81.7 ± 8.1 kg (a loss of 5 kg). These small changes in body weight were reflected in a minimal decline in % BF and a non-significant decline in LBM until 6M when it plateaued in the PL group. N did demonstrate significant improvement in LBM and decrease in % BF. This pattern of change in lean body mass with nandrolone treatment was presumably due to the high binding affinity of this anabolic agent to androgen binding receptors in skeletal muscle because of the low α-reductase activity in skeletal muscle as reported previously.

There must, however, be a cautious interpretation of the significant decline in % body fat from nandrolone treatment. There were no significant differences between groups with regard to loss of body fat which means that the decrease in % BF was strictly due to the increase in lean mass alone, not to total fat mass losses. Additionally, the plateau in the decline in % BF at 6M was concurrent with the plateau in the change in LBM for both groups. The hypothesis was partially supported because LBM increased significantly and a trend was observed for increased thigh CSA. Since weight loss was modest, other body composition changes related to fat mass losses were not seen (BMI, FM, BM, AC and WHR).

The treatment by time interaction for lumbar bone density was an important observation with technical relevance. Evaluating the data one sees that the spine BMD
decreased non-significantly at 6M in the N group and returned to near baseline levels at 9M. The length of time required for osteoblast action and mineralization to occur is a minimum of 6-9 months, therefore other possible anatomical factors or a chance variation in measurement procedures presumably affected the scan resolution. In terms of method, all scans were analyzed in the compare mode and the total area scanned (cm²) was matched to the baseline scan. The core study, which assessed subcutaneous and visceral abdominal fat changes in the subjects provided the best explanation to this phenomenon of decline in BMD at 6M, with return to near baseline levels at 9M. The visceral fat in the N group increased significantly from 153 cm² at baseline to 161 cm² at 6M. The BMD finding is consistent with this investigator’s previous observation that abdominal thickness is correlated with a decline in resolution of the DEXA BMD scan in the lumbar region. This was previously observed using data from lateral thickness measurements and lateral lumbar BMD lumbar scans in this group of subjects (r = 0.516, p < 0.05) and confirmed as a methodological problem by the company that manufactures the DEXA. However, they stand by the quality of A-P lumbar scans as being unaffected by abdominal thickness, except in the case of the morbidly obese.

Additionally, a significant decline in BMD of bilateral total forearm (radius and ulna) was observed over time for both groups as reflected by higher baseline versus 6M and 9M for BMD of the right forearm and baseline > 6M for the left forearm. A strong trend towards significance (p = 0.054) was observed for BMC decline over time for the left forearm, while a significant effect for time was noted for BMC of the right forearm. A trend (p = 0.07) was also noted for a main effect of time for BMD of the left forearm-UD. The overall effect noted was that both groups lost some forearm BMD and BMC.
throughout the investigation, although their results were still well within normal limits for the mean for their age and sex.

In the case of bone density preservation with anabolic treatment, the hypothesis was not supported by these data. The increase in LBM observed in the N group appeared to have no effect on preservation of cortical bone in the appendicular skeleton, as well as trabecular bone in the spine and ultra distal region of the forearms. Aside from the methodological discrepancies of the DEXA, the results demonstrate that nandrolone treatment did not serve as a protective measure for maintaining BMD at least during a 9 month period. Even with significant increases in LBM and PkTq, MnTq and PkTq/BM in isokinetic work, there was no increase nor preservation of baseline BMD and BMC. These results are inconsistent with those of Popcock, et al, who observed muscle strength to serve as a strong predictor for BMD in the femur and forearm. Popcock studied healthy women who did not vigorously exercise, with an average age of 45 years. He concluded that bone loss in the proximal femur may be modulated by muscle strength, body mass and physical fitness of the subject. These, of course are issues related to chronic mechanical loading to facilitate remodeling. Although the small increases in LBM from the current investigation, did not result in any positive effects on BMD, it would be interesting to observe whether larger increases in LBM as a result of drug treatment and exercise could modulate BMD.

One important consideration to the process of bone remodeling is exercise. The subjects in this study were prohibited from increasing their exercise regimen. It is plausible that the muscle biomechanical effects on the skeletal system might have been greater if subjects had been allowed to physically train, in conjunction with the drug
treatment regimen. Increased physical training was, however, viewed as a possible
confounding factor and therefore carefully controlled in the subjects through the course
of the study. It is also important to note that since the expected weight loss did not
occur, there was less of a real test to skeletal system remodeling in an estrogen deficient
sample population. Additionally, the nandrolone dosage utilized in this investigation was
lower than reported in the literature as having positive effects on BMD in osteoporotics.
It is conceivable that this may have been a suboptimal dosage, which would not elicit the
expected effects on the skeletal system. However, serious consideration would have to
be given before increasing the dosage since even at this treatment level some subjects
demonstrated virilizing effects.

Another consideration which must be addressed is that these subjects began the
study with normal BMD and BMC in the lumbar spine and forearm regions, even though
they were estrogen deficient. Nandrolone decanoate has been used in clinical trials for
treatment of osteoporotics in which subjects initiated treatment with BMD significantly
below the mean for their age and sex. Therefore, even small changes in BMD in
reported samples would be significant. Conversely, the sample in the present
investigation began with an above average BMD presumably due to their obesity. In this
population, changes in LBM and strength did not effect any change in BMD.
Additionally, if exercise had been a concurrent part of the treatment regimen with
nandrolone it is not known whether a resulting increase or preservation of BMD would
have been observed. It is also not known what effects this treatment regimen would
have demonstrated in subjects with an initial low BMD.
The association between higher BMD and obesity has previously been attributed in the literature to several possible mechanisms. First, it has been suggested that in overweight subjects aromatization of androstenedione to estrone occurs in subcutaneous adipocytes, which may serve to keep the subject in an estrogen sufficient state.\(^{(120,121)}\) Although adrostenedione and testosterone both decrease with the onset of menopause (1800 to 750 pg/ml and 300 to 250 pg/ml, respectively) total estrogen production may actually be greater in the obese over the slender subject.\(^{(123,124)}\) This effect is presumably even more predominant with obese postmenopausal subject since extraglandular formation of estrone from androstenedione is the primary route of conversion for this hormone.\(^{(124)}\) Additionally, increased LBM to support the greater fat mass in the obese may also serve as a larger biomechanical force on the skeleton, which could have resulting effects on facilitating higher BMD and BMC.

In this investigation the left hand grip MIVC treatment by time interaction for the N-group showed an increase in isometric strength between the 6M and 9M time points, whereas PL showed no significant change over time. Of interest is that this increase was only observed with the left hand and not the right. This may have been reflective of a non-dominant side strength increase as a result of anabolic steroid treatment as well as the N group beginning at baseline with a lower grip strength than the PL group and increasing past PL values at 9M. These data support the hypothesis due to improvement in strength.

Isokinetic muscle strength data demonstrated increases in elbow flexors and extensors torque over time with nandrolone treatment. Bilateral elbow flexors-extensors increased in torque production over time with both speeds (180 and 60 dps). Post hoc
analysis did clearly demonstrate a significant response over time for torque production of N versus the PL group.

Upper extremity total work also increased between pre- and post study for N with respect to the right elbow flexors at both speeds and left elbow flexors at 60 dps. There was also an observed trend for significance for treatment by time interaction for the left elbow flexors and right elbow extensors at 180 dps at 60 dps with 9M being greater than baseline (p = 0.059 and 0.07, respectively).

The right knee extensors also demonstrated an increase torque over time, using 180 dps, with the greatest torque for the N group observed at 6M. Why the torque production declined after 6M is not clear, although it is possible the drug treatment effects were maximized by 6M and declined without concurrent exercise training. At 60 dps, for all strength related variables only the PL group were observed to decline in torque over time with baseline having the largest value and the N group was noted to have no significant differences. The right knee flexors, alone, were observed to decline in torque significantly for the PL with no effects on N. To the contrary bilateral knee extensors demonstrated increased work over time only at 60 dps with no changes seen for the knee flexors.

Overall, nandrolone treatment was associated with small but consistent increases in muscle torque production, which supported the hypothesis of expectation of increased torque production with nandrolone treatment, whereas PL torque remained approximately the same or decreased over time. Whether the nandrolone-treated group increases in LBM resulted in hypertrophy of muscle tissue, as well as increases in connective tissue in these subjects is unknown. Resistance exercise characteristically has
been associated with increased gains in strength, particularly when combined with anabolic steroid treatment.\textsuperscript{(25)} Although resistance exercise is associated with increases in LBM for the specific areas trained, change in \% BF is not seen with anaerobic exercise. Subsequent studies could include resistance exercise in combination with calorie restriction and anabolic steroid treatment to facilitate increases in LBM and torque production. Thus, new RNA and resulting protein synthesis would effect increases in LBM and torque production. These factors could then interact with the skeletal system to facilitate bone formation during remodeling.

Possibly, the lack of consistency in torque production (particularly in the lower extremities) resulted in the large standard deviation for the means for isokinetic testing and was responsible for lack of consistent increases in torque in all extremities tested. Many of the subjects had no conception of what a maximal effort meant because they were generally very sedentary and most had never been involved in a training program or fitness testing.

Regardless of the lack of effect on bone formation, improvements in torque production occurred from treatment with nandrolone. These changes, alone could be beneficial to many in the elderly population. The long-term result of no treatment effects on bone density may have been related to the following: variation in torque production between subjects, the major time by treatment effects appearing only in the upper extremities and no chronic training of the muscles via exercise. In addition, there was no preservation of bone mass in the forearms even though elbow flexors-elbow extensors torque did improve over time in the N treated group. In particular since subjects were not participating in exercise training, effects from the increase in LBM
were minimized. This was clearly evident in terms of the positive changes observed in torque production of the upper extremities without changes in forearm BMD. Small differences in BMD over time presumably could have been detected by the DEXA if they existed. Short-term precision for DEXA of the spine has been observed to be 1.08%, with long-term precision as low as 1.01%.\(^{(112)}\)

Nandrolone treatment produced a non-significant increase in the thigh muscle volume, whereas the PL subjects lost CSA over time. The occurrence of a strong trend \((F = 4.48, p = 0.0514)\) for group effects was observed. Unfortunately, data for one of the N subjects at 9M was lost by the diagnostic facility where the CAT scans were completed and analyzed. This left only \(n = 7\) to be statistically analyzed for 9M and this particular subject had shown a clear increase in CSA over time up to 6M. Perhaps if the data for this subject had been included, statistically significant differences could have been documented. Due to the lack of documentation of statistically significant differences between groups, the hypothesis was not supported with respect to these data.

If exercise training had been permitted possibly there would have been a further increase in muscle volume, as well as peak torque production due to hypertrophy of the muscle tissue. In particular, resistance exercise training using a high strain rate and a low number of repetitions would have potentially yielded positive results in terms of both muscle and bone mass. Naturally, aerobic exercise would also be a necessary part of the program to facilitate weight loss, since resistance exercise is not associated with those benefits.

With respect to the endocrine markers, 25 (OH) D\(_3\) was the only one to demonstrate a change from baseline values. This decrease from baseline can be readily
attributed to the seasonal variation which normally occurs in vitamin D as less is produced in the skin during the winter months. Subjects were initially screened and entered the 9 month study during the summer and were followed through the fall, winter and completed all study requirements in the spring.

It was anticipated that preservation of bone calcium and phosphorus associated with nandrolone treatment would occur resulting in a decline in these minerals lost in the 24-hour urine samples. Specifically what was seen was a significant decline in phosphorus:creatinine ratio at 9M versus all other time points. Although a main effect for time for both groups was demonstrated for the calcium:creatinine ratio, no significant differences were noted with post hoc analysis. Contrary to the findings in this investigation with non-osteoporotics, Need demonstrated a decrease in calcium loss in the urine with nandrolone treatment of osteoporotics.\(^{93}\) It is important to remember that urinary electrolyte losses can be reflective of dietary intake as well as accounting for bone resorption. This relationship was demonstrated with the 3M phosphorus data for N. Additionally, there were three trends of interest related to diet intake and urinary loss of minerals. The PL group was observed to show a moderate correlational trend for dietary intake of calcium and sodium with calciuria at baseline (\(r = 0.56, p = 0.054\) and \(r = 0.53, p = 0.064\) for calcium intake and sodium intake to calcium urine loss, respectively). Also N demonstrated a modest correlational trend related to calcium intake and urinary loss at 1M (\(r = 0.46, p = 0.063\) ) In this specific case, calcium loss in the urine did not increase. This is substantiated by the lack of change in osteocalcin (OC) and alkaline phosphatase (Alk phos).
Overall, because there were no effects of nandrolone treatment on biochemical and endocrine markers of bone turnover these data did not support the hypothesis. The small changes in % BF, LBM and muscular torque did not have any effects on bone status, nor the bone specific markers which represent the dynamic process of bone resorption and formation. These results conflict with Johansen’s group which documented both increases in LBM and BMD in osteoporotic subjects with nandrolone treatment,\(^{(64)}\) although the current investigation evaluated subjects with normal BMD, presumably due to obesity.

In conclusion, the results from this study do not support the hypothesis since the nandrolone treated group did not demonstrate bone preservation compared to PL in the lumbar spine, bilateral forearms (total radius and ulna) and ultra-distal regions of bilateral forearms. Previously, nandrolone has been observed to have positive effects on bone formation in both trabecular and cortical bone of osteoporotic subjects. In this investigation, these effects were not documented. A possible reason for lack of change could be too low a dose of the nandrolone (normally administered at 50 mg every 3-4 weeks) and insufficient treatment time since 6-9 months was the earliest time when changes would be observed.

Another issue which may have affected study outcome is that if this study had used exercise training within the investigation differences in BMD and BMC when combined with anabolic steroid therapy, may have been demonstrated. Anabolic treatment combined with minimal weight loss did not have an effect on BMD preservation. With exercise, the chronic and repetitive stress to the increased lean mass could have resulted in greater hypertrophy and possible hyperplasia of the muscle tissue.
as well as increased recruitment of fibers. These factors would interplay effecting a
greater peak torque production, thus creating a larger load on the skeletal system. These
greater contractile forces during exercise may have acted on osteoclastic activity to
promote bone remodeling and osteoblastic processes to increase bone formation, since
Lanyon suggests that it is the strain-related stimulation for which the bone cells are not
accustomed that define the character of the remodeling stimulus of bone.\(^{(125-127)}\) It is
evident that anabolic steroid treatment, without exercise, did not mediate this activity
through biomechanical means vis-à-vis the different pattern of change in LBM over the
study for the nandrolone-treated subjects. It is then reasonable to expect exercise
training could have potentiated this effect. Aurbach believes that physical activity may
be a critical factor in determining bone mass for the postmenopausal female:

Thus integral physical load (a function of physical activity, muscle strength
and weight) may be a determinant of peak bone mass and may thereby help
to determine the population at risk for osteoporosis. If this concept is
correct, prophylactic exercise programs (initiated well before menopause)
should reduce the incidence of fractures.\(^{(1)}\)

Additionally, the use of exercise as an integral part of a weight loss program
cannot be over emphasized. Although exercise was strictly controlled due to possible
confounding effects, presumably subjects would have lost a greater amount of % BF if
aerobic exercise had been combined with diet and nandrolone treatment.

Let it also be clear that bone homeostasis is not proposed to be rigidly controlled
only by biomechanical factors. Hormonal interaction to achieve calcium balance is
critical to bone status and its involvement in this process should not be minimized. In
terms of biochemical and endocrine markers assessed in this investigation, there were no
obvious changes in the PTH-Vitamin D axis as a result of treatment. This was also
reflected in the non-significant changes in Alk Phos, osteocalcin and the urine calcium and phosphorus: creatinine ratios throughout the investigation.

Although diet records did show evidence of correlation between intake of these minerals to urinary output this relationship was not statistically significant for most collection periods. There was a wide variation in calcium intake of subjects during collection periods despite specific written instructions to consume 800 mg./day. The PL group consumed a daily range of 184-2006 mg. of calcium while N intake was in the range of 333 to 1666 mg. over the various collection periods.

Clearly, there were several problems with controlling calcium intake during urine collection. First, subjects demonstrated through their food records that they had no concept of calcium sources in whole foods since many did not even meet premenopausal RDA requirements for daily calcium consumption. Second, since food records were poorly kept, it is possible many foods that were eaten by subjects were not documented and calcium, sodium or phosphorus intake may have been higher or even lower. Third, even though there was an attempt to control intake for consistency and analysis of records for calcium, phosphorus and sodium, there was no evidence of bioavailability of calcium in the gut and whether anabolic steroid treatment had any effects on gut absorption of calcium. If calcium intake was indeed well below RDA standards then this may have contributed to bone loss, rather than preservation, with nandrolone treatment. This problem has previously been observed in ovariectomized canines treated with nandrolone decanoate yet ingesting calcium deficit diets.\(^{128}\)

Utilization of random urine samples rather than 24-hour collection, which is tedious for free-living subjects, is one alternative to obtaining these important data.
Significant correlations have been demonstrated between these two methods recently ($r = 0.967, p \leq 0.0001$). Future studies would also do well to assess gut absorption of calcium using stable strontium ($^{88}\text{Sr}$) uptake since mechanisms of vitamin $D_3$ action at the level of the gut with anabolic steroid treatment have never been clarified.

Results from this study do not indicate that nandrolone decanoate, at the dose used in this investigation, would serve as a suitable substitute for ERT when estrogen is not the appropriate course of treatment due to prior personal and family medical history. However, further studies are suggested with this form of drug therapy, if a larger dose can be determined to have a greater benefit:risk ratio, for postmenopausal subjects who may be placed at risk for increased bone resorption due to weight loss. Since it has been shown that osteoblast-like cells have demonstrated in cell cultures to have androgen receptors, then continued investigation into this area is highly suggested. It would be potentially beneficial for further investigations to combine drug treatment and exercise training, as well as providing measures to gain better compliance with hypocaloric diet regimen. Larger body weight changes are needed to better test this hypothesis, since minimization of weight loss did not sufficiently stress bone status in these women.

Failure of the subjects to reach their target weight is not a new problem in treating and studying obesity. Rather, it further emphasizes the need to approach weight loss in a realistic manner: calorie reduction, behavior modification and exercise to achieve goals of weight loss. Future studies in the area of postmenopausal women undergoing weight loss should remain a very important focus, since these women are at greater risk for loss of BMD. Continued research in the area of pharmacological approaches to maintenance of BMD is critical for the postmenopausal female.
REFERENCES


APPENDIX A: INFORMED CONSENT

The Effects of Nandrolone Decanoate, Aldactone or Placebo on Muscular Strength, Biochemical Markers of Bone Formation and Bone Mineral Acquisition

I, ________________________________, voluntarily consent to participate in the following investigation which is designed to determine the effects of nandrolone decanoate, aldactone or placebo treatment on improvement in lean body (muscle) mass, prevention of bone mass loss and increased bone density. I understand this is an ancillary study to “Synthetic Hormones and Fat Distribution in Obesity” which is assessing increased lean mass and fat loss with nandrolone or aldactone treatment.

In deciding to participate in this 9-month study, I understand that I will be required to undergo muscle strength testing in my arms and legs at baseline (before drug treatment) and after 3, 6, and 9 months of drug or placebo treatment. This will consist of flexing and extending my arms and legs (individually) against a fixed resistance throughout the exercise. I understand I will also have grip strength of both hands measured by squeezing a device maximally.

I understand I will be required to save a 24-hour urine sample at baseline, 1, 3, 6, and 9 month intervals during the study. The purpose of this is to measure markers in the urine for bone formation. I understand I will be required to eat a set amount of calcium in my diet 24 hours prior to urine collection and during the 24 hours I collect urine. I understand I will receive specific instructions on calcium intake and urine collection.

I understand I also will be required to have a blood sample analyzed every 3 months to determine bone formation. I understand this will not require an additional venipuncture, rather additional blood (about 1 tsp. extra) will be drawn at the same time a sample is drawn for Dr. Lovejoy’s main Synthetic Hormone study.

I understand I will be required to undergo bone density measurements of both forearms and the spine with use of the DEXA three times during the study (baseline and at 6 and 9 months in the study). I understand the radiation exposure from the DEXA is 40mRem which is not whole body exposure, rather specific only to the regions of interest (the spine and forearm). I understand that the radiation exposure from the pre- and post-study scans amounts to only 1/3 of the natural background exposure for 1 year.

I understand Pennington Biomedical Research Center is paying for all testing and personnel and I am not responsible for any payment. I also understand that in the event physical injury resulting from research procedures, I would be personally and financially responsible to seek medical treatment. I understand that Pennington Biomedical...
Research Center is a research facility only and would not be a source for medical treatment.

I understand I am free to withdraw my consent to participate in this study at any time. I also understand if I am not compliant with all study procedures, the Principal Investigator can terminate my participation in the study.

I understand that through my participation in this study I will be contributing to the body of knowledge of biomedical science. I have been informed that the results of this study may be published, but my privacy will be protected and my name will not be published. I also understand that results from this study will be shared with me once the scientific and statistical analysis is complete.

My signature on this sheet indicates that I have completely read this form and consent to participate. I will have an opportunity to ask questions prior to the start of the study or at any time during the study by contacting the principal investigator, Ellen Brooks, R.N., at 765-2560, a co-investigator, Donna Ryan, M.D. at 765-2514 or the Clinical Trials Staff at 765-2672.

Volunteer's Signature ___________________________ Date ___________________________

Social Security # ___________________________

Witness ___________________________ Date ___________________________

Ellen R. Brooks, R.N., M.N., Principal Investigator
Chief, Clinical Research Unit
Coordinator, Clinical Trials

Jennifer Lovejoy, Ph.D., Co-Investigator

Donna H. Ryan, M.D., Co-Investigator
Associate Executive Director for Science
### APPENDIX B: TABLES

#### Table 3. Group Means for Baseline Dependent Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Nandrolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass (kg)</td>
<td>86.4 ± 7.3</td>
<td>87.1 ± 8.6</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>33.4 ± 2.9</td>
<td>33.9 ± 4.3</td>
</tr>
<tr>
<td>Lean Body Mass (kg)</td>
<td>41.2 ± 4.9</td>
<td>40.1 ± 2.5</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>43.3 ± 5.6</td>
<td>43.7 ± 6.5</td>
</tr>
<tr>
<td>% Body Fat</td>
<td>49.3 ± 4.6</td>
<td>50.7 ± 2.9</td>
</tr>
<tr>
<td>Waist:Hip Ratio</td>
<td>0.86 ± 0.06</td>
<td>0.83 ± 0.05</td>
</tr>
<tr>
<td>Arm Circumference (cm)</td>
<td>37.4 ± 2.5</td>
<td>36.4 ± 3.1</td>
</tr>
<tr>
<td>CSA Thigh (cm²)</td>
<td>71.1 ± 10.9</td>
<td>71.8 ± 6.8</td>
</tr>
<tr>
<td>BMD L₂-L₄ (gm/cm²)</td>
<td>0.963 ± 0.132</td>
<td>0.940 ± 0.127</td>
</tr>
<tr>
<td>Left Forearm Total BMD (gm/cm²)</td>
<td>0.562 ± 0.620</td>
<td>0.547 ± 0.530</td>
</tr>
<tr>
<td>Right Forearm Total BMD (gm/cm²)</td>
<td>0.567 ± 0.630</td>
<td>0.544 ± 0.520</td>
</tr>
</tbody>
</table>

#### Table 4. Lean Body Mass (kg) over 9 Months in Subjects Treated with Placebo (N=10) or Nandrolone (N=8)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean ± Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>B/L</td>
<td>41.2 ± 4.9</td>
</tr>
<tr>
<td>N</td>
<td>B/L</td>
<td>40.1 ± 2.5</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>40.5 ± 4.5</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>41.0 ± 2.8</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>40.0 ± 4.5</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>43.1 ± 3.3</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>39.9 ± 4.4</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>43.0 ± 3.8</td>
</tr>
</tbody>
</table>

Time * treatment interaction ANOVA p = 0.0001
Post hoc analysis: α = 0.025
Table 5. Percent Body Fat over 9 Months in Subjects Treated with Placebo or Nandrolone

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean ± Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>49.3 ± 4.7</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>50.7 ± 2.9</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>46.9 ± 5.0</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>47.8 ± 4.3</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>47.1 ± 6.0</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>45.7 ± 4.4</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>47.5 ± 5.8</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>45.9 ± 5.1</td>
</tr>
</tbody>
</table>

Time * treatment interaction ANOVA p = 0.013
Post hoc analysis: α = 0.025

Table 6. Lumbar Bone Mineral Density (gm/cm²) over 9 Months

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean ± Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>0.963 ± 0.132</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>0.940 ± 0.127</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>0.974 ± 0.138</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>0.910 ± 0.100</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>0.963 ± 0.137</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>0.930 ± 0.125</td>
</tr>
</tbody>
</table>

Time * treatment interaction ANOVA p = 0.020
Post hoc analysis: α = 0.025
Table 7. Left Maximal Isometric Voluntary Contraction
(Newtons)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean ± Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>311.2 + 37.2</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>276.2 + 42.6</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>309.2 + 37.5</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>300.7 + 61.9</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>300.6 + 36.5</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>286.0 + 55.6</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>297.1 + 48.9</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>313.1 + 52.7</td>
</tr>
</tbody>
</table>

Time * treatment interaction ANOVA p = 0.03
Post hoc analysis: α = 0.025

Table 8. Right Elbow Flexors Torque at 180 Degrees per Second
9 Months (Newton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Peak Torque</th>
<th>Mean Torque</th>
<th>Peak Torque/Body Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>19.4 + 2.5</td>
<td>17.1 + 2.1</td>
<td>0.226 + 0.037</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>15.4 + 5.6</td>
<td>13.3 + 4.7</td>
<td>0.179 + 0.066</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>18.5 + 4.5</td>
<td>16.7 + 4.8</td>
<td>0.226 + 0.056</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>18.7 + 3.9</td>
<td>16.6 + 4.0</td>
<td>0.223 + 0.049</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>18.3 + 4.6</td>
<td>17.0 + 4.7</td>
<td>0.227 + 0.054</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>20.8 + 3.3</td>
<td>19.1 + 3.3</td>
<td>0.250 + 0.057</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>17.9 + 5.0</td>
<td>16.2 + 5.1</td>
<td>0.222 + 0.058</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>21.0 + 5.6</td>
<td>19.4 + 5.8</td>
<td>0.250 + 0.078</td>
</tr>
</tbody>
</table>

Variables are expressed as means ± std. dev.
Peak torque time * treatment interaction ANOVA p = 0.013
Mean torque time * treatment interaction ANOVA p = 0.016
Peak torque/body mass time * treatment interaction ANOVA p = 0.034
Post Hoc Analysis: α = 0.025
Table 9. Left Elbow Flexors Torque at 60 Degrees per Second over 9 Months (Newton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Peak Torque</th>
<th>Mean Torque</th>
<th>Peak Torque/BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>22.5 ± 6.2</td>
<td>20.0 ± 4.6</td>
<td>0.260 ± 0.067</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>20.9 ± 3.4</td>
<td>18.8 ± 3.2</td>
<td>0.239 ± 0.034</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>23.6 ± 5.2</td>
<td>21.6 ± 4.3</td>
<td>0.292 ± 0.067</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>24.3 ± 4.4</td>
<td>22.6 ± 4.2</td>
<td>0.292 ± 0.057</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>23.5 ± 4.6</td>
<td>21.6 ± 3.6</td>
<td>0.291 ± 0.053</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>26.2 ± 6.3</td>
<td>24.0 ± 5.6</td>
<td>0.310 ± 0.075</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>23.0 ± 5.6</td>
<td>21.0 ± 4.2</td>
<td>0.282 ± 0.065</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>27.5 ± 6.2</td>
<td>25.0 ± 6.4</td>
<td>0.327 ± 0.086</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± std. dev.
Peak torque time * treatment interaction ANOVA p = 0.004
Mean torque time * treatment interaction ANOVA p = 0.02
Peak torque/body mass time * treatment interaction ANOVA p = 0.03
Post Hoc Analysis: α = 0.025

Table 10. Left Elbow Flexors Torque at 180 Degrees per Second (Newton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Peak Torque</th>
<th>Mean Torque</th>
<th>Peak Torque/BODY Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>19.6 ± 5.2</td>
<td>15.9 ± 3.6</td>
<td>0.227 ± 0.063</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>17.4 ± 1.9</td>
<td>14.9 ± 2.4</td>
<td>0.201 ± 0.027</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>19.6 ± 4.7</td>
<td>17.3 ± 5.0</td>
<td>0.241 ± 0.064</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>19.5 ± 3.9</td>
<td>17.2 ± 3.8</td>
<td>0.235 ± 0.047</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>19.5 ± 4.3</td>
<td>17.7 ± 3.9</td>
<td>0.241 ± 0.057</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>20.5 ± 5.8</td>
<td>17.4 ± 5.6</td>
<td>0.241 ± 0.059</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>18.5 ± 3.2</td>
<td>16.2 ± 3.8</td>
<td>0.229 ± 0.043</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>23.4 ± 8.6</td>
<td>20.1 ± 7.5</td>
<td>0.278 ± 0.109</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± std. dev.
Peak torque treatment * time interaction ANOVA p = 0.013
Mean torque treatment * time interaction ANOVA p= 0.02
Peak torque/body mass treatment * time interaction ANOVA p = 0.03
Post hoc analysis: α = 0.0225
Table 11. Left Elbow Flexors Torque at 60 Degrees per Second (Newton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Peak Torque</th>
<th>Mean Torque</th>
<th>Peak Torque/Body Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>22.5 ± 6.2</td>
<td>20.0 ± 4.6</td>
<td>0.260 ± 0.067</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>20.9 ± 3.4</td>
<td>18.8 ± 3.2</td>
<td>0.239 ± 0.034</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>24.0 ± 5.2</td>
<td>21.6 ± 4.3</td>
<td>0.292 ± 0.067</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>24.3 ± 4.4</td>
<td>22.6 ± 4.2</td>
<td>0.292 ± 0.060</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>23.5 ± 4.6</td>
<td>21.6 ± 3.6</td>
<td>0.291 ± 0.053</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>26.2 ± 6.3</td>
<td>24.0 ± 5.6</td>
<td>0.310 ± 0.080</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>23.0 ± 5.7</td>
<td>21.0 ± 4.2</td>
<td>0.282 ± 0.065</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>27.5 ± 6.2</td>
<td>25.0 ± 6.4</td>
<td>0.330 ± 0.090</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± std. dev.

- peak torque treatment * time interaction ANOVA p = 0.004
- mean torque treatment * time interaction ANOVA p = 0.02
- peak torque/body mass treatment * time interaction ANOVA p = 0.03

Post hoc analysis: α = 0.025

Table 12. Torque for Right and Left Elbow Extensors at 180 Degrees per Second over 9 Months (Newton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Peak Torque</th>
<th>Peak Torque/Body Mass</th>
<th>Peak Torque</th>
<th>Peak Torque/Body Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>17.8 ± 3.5</td>
<td>0.2 ± 0.04</td>
<td>16.1 ± 2.9</td>
<td>0.187 ± 0.400</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>14.6 ± 4.3</td>
<td>0.2 ± 0.05</td>
<td>14.1 ± 4.1</td>
<td>0.160 ± 0.042</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>17.1 ± 3.4</td>
<td>0.2 ± 0.05</td>
<td>16.0 ± 4.3</td>
<td>0.200 ± 0.060</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>16.5 ± 2.7</td>
<td>0.2 ± 0.04</td>
<td>16.4 ± 4.2</td>
<td>0.195 ± 0.050</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>17.7 ± 3.2</td>
<td>0.2 ± 0.05</td>
<td>16.2 ± 3.4</td>
<td>0.201 ± 0.045</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>18.6 ± 3.5</td>
<td>0.2 ± 0.05</td>
<td>17.1 ± 4.2</td>
<td>0.204 ± 0.050</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>15.9 ± 3.2</td>
<td>0.2 ± 0.04</td>
<td>15.9 ± 3.1</td>
<td>0.197 ± 0.036</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>19.0 ± 5.6</td>
<td>0.2 ± 0.08</td>
<td>18.0 ± 5.2</td>
<td>0.220 ± 0.700</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± std. dev.

- Peak torque time * treatment interaction ANOVA p = 0.005
- Peak torque/body mass time * treatment interaction ANOVA p = 0.014
- Peak torque time * treatment interaction ANOVA p = 0.032
- Peak torque/body mass time * treatment interaction ANOVA p = 0.05

(Post hoc analysis: α = 0.025)
Table 13. Right Knee Extensors Torque at 180 Degrees per Second

(Neton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Peak Torque</th>
<th>Mean Torque</th>
<th>Peak Torque/Body Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>76.5 ± 22.3</td>
<td>70.4 ± 21.6</td>
<td>0.885 ± 0.255</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>67.5 ± 9.02</td>
<td>64.1 ± 10.8</td>
<td>0.777 ± 0.093</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>68.7 ± 16.7</td>
<td>65.5 ± 17.4</td>
<td>0.845 ± 0.232</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>66.4 ± 12.1</td>
<td>61.5 ± 14.6</td>
<td>0.795 ± 0.156</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>76.7 ± 18.0</td>
<td>69.5 ± 18.2</td>
<td>0.954 ± 0.260</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>88.0 ± 15.6</td>
<td>80.2 ± 15.8</td>
<td>1.054 ± 0.238</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>69.0 ± 19.1</td>
<td>63.8 ± 16.2</td>
<td>0.850 ± 0.252</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>72.0 ± 14.7</td>
<td>64.2 ± 16.6</td>
<td>0.853 ± 0.184</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± std. dev.
peak torque treatment * time interaction ANOVA p = 0.02
mean torque treatment * time interaction ANOVA p = 0.008
peak torque/body mass treatment * time interaction ANOVA p = 0.009
Post hoc analysis: $\alpha = 0.025$

Table 14. Right Knee Extensors Torque at 60 Degrees per Second

(Neton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Peak Torque</th>
<th>Mean Torque</th>
<th>Peak Torque/Body Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>115.5 ± 24.1</td>
<td>110.2 ± 25.0</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>110.2 ± 19.0</td>
<td>104.0 ± 21.0</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>107.0 ± 25.5</td>
<td>102.0 ± 24.2</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>106.0 ± 26.0</td>
<td>100.0 ± 27.0</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>106.0 ± 25.0</td>
<td>98.0 ± 26.0</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>116.4 ± 23.0</td>
<td>109.2 ± 22.3</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>99.4 ± 23.1</td>
<td>93.0 ± 22.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>115.0 ± 22.1</td>
<td>108.3 ± 23.0</td>
<td>1.4 ± 0.3</td>
</tr>
</tbody>
</table>

Variables are expressed as mean ± std. dev.
Peak torque treatment * time interaction ANOVA p = 0.0003
Mean torque treatment * time interaction ANOVA p = 0.0002
Peak torque/body mass treatment * time interaction ANOVA p = 0.004
### Table 15. Right Knee Flexors Mean Torque at 60 Degrees per Second

(Neton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean + Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>70.2 ± 12.8</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>69.1 ± 13.9</td>
</tr>
<tr>
<td>PL</td>
<td>3M</td>
<td>72.4 ± 12.8</td>
</tr>
<tr>
<td>N</td>
<td>3M</td>
<td>66.4 ± 12.7</td>
</tr>
<tr>
<td>PL</td>
<td>6M</td>
<td>72.4 ± 14.2</td>
</tr>
<tr>
<td>N</td>
<td>6M</td>
<td>76.1 ± 14.0</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>64.7 ± 10.2</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>71.0 ± 12.0</td>
</tr>
</tbody>
</table>

Mean torque treatment * time interaction ANOVA p = 0.03

### Table 16. Right Elbow Flexors Total Work at 60 Degrees per Second

(Neton-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean + Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>190.6 ± 22.7</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>174.2 ± 51.9</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>186.0 ± 32.0</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>238.5 ± 65.6</td>
</tr>
</tbody>
</table>

Total work treatment * time interaction ANOVA p = 0.0004
Post hoc analysis: α = 0.025
Table 17. Left Elbow Extensors Total Work at 180 Degrees per Second
(Neuro-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean ± Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>47.5 ± 18.0</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>43.0 ± 11.1</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>47.7 ± 12.0</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>57.8 ± 21.4</td>
</tr>
</tbody>
</table>

Total work trend for treatment * time interaction ANOVA p = 0.06

Table 18. Right Elbow Extensors Total Work at 60 Degrees per Second
(Neuro-Meters)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean ± Std. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>BL</td>
<td>194.4 ± 40.0</td>
</tr>
<tr>
<td>N</td>
<td>BL</td>
<td>187.4 ± 49.3</td>
</tr>
<tr>
<td>PL</td>
<td>9M</td>
<td>192.2 ± 35.3</td>
</tr>
<tr>
<td>N</td>
<td>9M</td>
<td>241.0 ± 94.0</td>
</tr>
</tbody>
</table>

Total work treatment * time interaction ANOVA p = 0.014
Post hoc analysis: α = 0.025
Figure 1. Lean body mass treatment by time interaction (p=0.0001) (Mean ± SD).
Figure 2. % Body fat (BF) treatment by time interaction (p=0.013) (Mean ± SD)
Figure 3. Lumbar bone mineral density (BMD) treatment by time interaction (p=0.02) (Mean ± SD).
Figure 4. Left maximal isometric voluntary contraction treatment by time interaction (p=0.03) (Mean ± SD).
Figure 5. Right elbow flexors peak torque (180 degrees/second) treatment by time interaction (p=0.0003) (Mean ± SD).
Figure 6. Isokinetic mean torque for right elbow flexors at 180 degrees/second treatment by time interaction (p=0.0009) (Mean ± SD).
Figure 7. Isokinetic right elbow flexors peak torque/body mass treatment by time interaction 180 degrees/second (p=0.002) (Mean ± SD).
Figure 8. Left elbow flexors at 180 degrees/second peak torque treatment by time interaction (p=0.013) (Mean ± SD).
Figure 9. Left elbow flexors mean torque at 180 degrees/second treatment by time interaction (p=0.02) (Mean ± SD).
Figure 10. Peak torque/body mass left elbow flexors treatment by time interaction (p=0.034) (Mean ± SD).
Figure 11. Mean torque for right elbow flexors treatment by time interaction at 60 degrees/second (p=0.042) (Mean ± SD).
Figure 12. Peak torque at 60 degrees/second treatment by time interaction \((p=0.004)\) for left elbow flexors (Mean ± SD).
Figure 13. Mean torque for left elbow flexors at 60 degrees/second treatment by time interaction (p=0.02) (Mean ± SD).
Figure 14. Peak torque/body mass at 60 degrees/second treatment by time interaction (p=0.03) for left elbow flexors (Mean ± SD).
Figure 15. Peak torque for right elbow extensors treatment by time interaction (p=0.005) at 180 degrees/second (Mean ± SD).
Figure 16. Peak torque/body mass at 180 degrees/second for right elbow extensors treatment by time interaction (p=0.014) (Mean ± SD).
Figure 17. Peak torque at 180 degrees/second treatment by time interaction (p=0.03) for left elbow extensors (Mean ± SD).
Figure 18. Peak torque/body mass for left elbow extensors at 180 degrees/second treatment by time interaction (p=0.05) (Mean ± SD).
Figure 19. Right knee extensors peak torque/body mass at 180 degrees/second treatment by time interaction (p=0.009) (Mean ± SD).
Figure 20. Mean torque for right knee extensors at 180 degrees/second treatment by time interaction (p=0.008) (Mean ± SD).
Figure 21. Peak torque/body mass for right knee extensors at 180 degrees/second treatment by time interaction (p=0.009) (Mean ± SD).
Figure 22. Peak torque for right knee extensors at 60 degrees/second treatment by time interaction (p=0.0003) (Mean ± SD).
Figure 23. Mean torque at 60 degrees/second treatment by time interaction (p=0.0002) (Mean ± SD).
Figure 24. Peak torque/body mass for right knee extensors at 60 degrees/second treatment by time interaction (p=0.004) (Mean ± SD).
Figure 25. Mean torque for right knee flexors at 60 degrees/second treatment by time interaction (p=0.03) (Mean ± SD).
Figure 26. Total work right elbow flexors at 180 degrees/second treatment by time interaction (p=0.02) (Mean ± SD).
Figure 27. Total work at 60 degrees/second right elbow flexors treatment by time interaction (p=0.0004) (Mean ± SD).
Figure 28. Total work of left elbow flexors at 60 degrees/second treatment by time interaction (p=0.0002) (Mean ± SD).
Figure 29. Total work at 60 degrees/second right elbow extensors treatment by time interaction (p=0.014) (Mean ± SD).
Figure 30. Cross-sectional area of the thigh trend in treatment effects (p=0.051) (Mean ± SD).
VITA

The author is a 1977 graduate of Texas Christian University with a Bachelor of Science in Nursing. After working for several years in the critical care setting as a staff and charge nurse, she entered graduate school at Louisiana State University Medical Center School of Nursing. She graduated with a Master of Nursing, specializing in the adult medical-surgical field, in December 1981. She is a licensed medical-surgical Clinical Nurse Specialist in Louisiana.

She has been a member of Sigma Theta Tau Nursing Honor Society, Beta Alpha chapter (TCU) and a charter member of Epsilon Nu chapter (LSUMC). In addition, she is a member of the American College of Sports Medicine. She has published one article and one abstract and co-authored 6 articles and one abstract in the areas of nursing, exercise physiology and nutrition.

In May 1994, she was one of 25 recipients of the Baton Rouge District Nurses Association "Outstanding Professional Achievement in Nursing" award. She is married with two children and is currently Chief of the Clinical Research Unit at Pennington Biomedical Research Center, Baton Rouge, Louisiana.
Candidate:  Ellen R. Brooks

Major Field:  Kinesiology

Title of Dissertation:  Effects of Nandrolone Decanoate on Strength, Markers of Bone Formation and Turnover in Obese Postmenopausal Women with Normal Bone Density

Approved:

[Signatures]

Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

[Signatures]

Michael Keenan

[Signature]

[Name]

[Name]

[Name]

Date of Examination:

August 4, 1994