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The Effect of Androgenic Agents as A Strategy and Indicator of Recovery in the Postoperative Period of Femur Fracture in Newborns and Domestic Kittens (10-40 Weeks)

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ABSTRACT

Sex steroids play an essential role in maintaining bone health throughout life, and the adverse effects of hormone deficiency are seen in both young and old male and female animals. The mechanism of these effects is not fully understood and is a subject of extensive research effort, although the potential therapeutic implications in this area are considerable. The question that arises at this stage is whether these hormones can statistically play a significant and determining role in bone formation and healing.

Therefore, the aim of this study is to investigate how steroid hormones can be used as a strategy and indicator in fractures and bone healing in neutered and unneutered male animals, and even in female animals and animals that are somehow deficient in or impaired by steroid hormones. In this study, ten apparently healthy male kittens were selected from the laboratory type and sterilized using the scrotal method. Four holes with diameters of 1, 2, 3, and 4 mm were implanted on the tibia from the side along the length of the bone. Then, they were divided into two groups.

Group 1: Nandrolone decanoate was injected intramuscularly at intervals of 0, 1, 2, 4, 8, and 12 weeks. Group 2: Cyproterone was administered to the kittens every other week until the eighth week.

Independent variables: Nandrolone decanoate and cyproterone acetate

Dependent variables: Bone tissue formation rate - Callus formation rate - Pressure tolerance

In the data collection section, radiographic evaluation was performed at 0, 2, 4, 8, and 12 weeks. Histopathological evaluation was performed in the last week (12 weeks) of bone samples sent to the pathology laboratory and gait assessment was performed at intervals of 1, 2, 4, 8 and 12 weeks. For the temporal evaluation of radiographs, which had a normal distribution, analysis of variance tests were used at a significant level of 0.05. For gait, which was on a rank scale, the Kruskal-Wallis test was used. Statistical calculations were performed using the SPSS statistical program. The results showed that the gait of kittens in both groups improved significantly from one to eight weeks. On the other hand, there was no significant difference between the two groups at different times and between different times in each group. Except for the first week, where this difference was completely normal.

There was a significant difference in the amount of callus formed in the two groups at some times. In terms of pathology, the evaluation of the first and second groups indicated the occurrence of healing and formation of bone callus in both groups, but comparatively, the first group had a wider and more voluminous callus and the entire healing process was at a more advanced stage.

Keywords: *Nandrolone-Cyproterone-Bone healing. Cat*

1. INTRODUCTION

The mechanisms of the skeletal effects of sex steroids are not yet fully understood, but in recent years there have been significant advances in our knowledge of how estrogens, and to a lesser extent androgens, affect bone remodeling. New insights into estrogen receptors, recent discoveries of increased osteoclast activity, and lessons learned from genetic mutations in humans and animals have all contributed to our understanding of the skeletal effects of estrogen in both males and females (1, 2).

Sex steroids are essential for skeletal growth and bone health during puberty, and estrogen deficiency plays a role in osteoporosis. In the past few decades, there have been significant advances in our understanding of how sex steroids influence skeletal growth and bone health during puberty. Estrogen deficiency is a major factor in the development of osteoporosis (2, 3).

The mechanisms of the skeletal effects of sex steroids are still not fully understood (4). However, in recent years there have been significant advances in our knowledge of the role of estrogens and, to a lesser extent, androgens in bone remodeling (5).

New insights into estrogen receptors, recent discoveries in the field of increased osteoclast activity, and lessons learned from genetic mutations in humans and animals have all contributed to our understanding of the skeletal effects of estrogens in both males and females (6,7).

On the other hand, fracture healing generally proceeds in an orderly manner with the appropriate mechanical and biological components that are currently available (8).

Improved surgical techniques and grafting techniques allow surgeons to treat relatively complex bone fractures with successful outcomes; however, some complications occur following fractures, leading to delayed bone union, nonunion, and malunion of the fractured bone. The goal of this study is to improve and enhance the mechanical strength and function of bone for better and faster weight bearing, prevent delayed union and nonunion, and ultimately restore function to the injured bone (9).

Estrogen has a diverse range of actions, including growth, differentiation, and function, in many target tissues. The mechanisms by which these actions are mediated are not fully elucidated, but it is thought that many of the effects of estrogen are mediated through genomic pathways involving ligand/receptor interactions. The importance of nongenomic mechanisms by which ligands interact with plasma membrane receptors is increasingly recognized with the consideration of rapid responses to estrogen. In addition, there is evidence for nongenomic effects of estrogen on osteoclasts, as thionine (white and crystalline amino acid) phosphorylated several proteins, including Src, has been reported in avian osteoporosis after administration of 17-estradiol (10).

2. ESTROGEN RECEPTORS

Estrogen receptors (ERs) belong to a family of steroid hormone receptors that includes receptors for mineralocorticoids, progestins, androgens, and glucocorticoids and may be considered ligand-regulated regulators. ERs consist of several domains that have been defined according to their function. The AF-1 and AF-2 domains (activating functions 1 and 2) activate the regulatory gene. The C domain contains a conserved DNA-binding domain with two zinc-containing strands that are essential for DNA binding. The classical estrogen response element consists of a single inverted hexane-nucleotide repeat (A/GGGT.CA) separated by three nucleotides. The hormonal domain is a band (linker) at the COOH boundary of the molecule and facilitates ligand binding and specific recognition. The ER domain and possibly the C domain contain a 90-kDa heat shock protein. (At least two major ER subtypes exist, namely ER and ER. ER has been cloned primarily from the uterus. Recently, ER has been cloned from a mouse prostate-associated cDNA complex. This ER shows close structural similarity to the ER molecule, particularly in the DNA binding domain and to a lesser extent in the ligand binding domain. The binding affinity of estradiol and other ligands, including SERMs and phytoestrogens, is very similar in the two ER subtypes. Some ER isoforms and at least two ERs, which are formed by subcellular or primary transport, have been identified (mainly at the mRNA level); one of them does not bind estrogen and may act as a negative inhibitor of ER-mediated activity (4,6,11).

A. Effects of Estrogen on Osteogenic Cells

A number of estrogen-stimulated effects on gene expression in osteogenesis have been described. These include stimulation of TIEG, a TGF-inducible gene that inhibits DAN synthesis, IGF-I, and TGF. Reports on the effects of estrogen on DAN synthesis and bone matrix protein production and proliferation have yielded conflicting results, probably due to differences in the in vitro systems and, in particular, the stage of osteoclast differentiation examined in these systems. Thus, in osteogenic cells, where estrogen acts as a mitogen, an increase in alkaline phosphatase and type I collagen has been reported. Whereas in cells that show no proliferative response to estrogen, stimulation of type I collagen and osteocalin expression is evident without any increase in alkaline phosphatase. Third, in systems where estrogen has antiproliferative effects, stimulation of alkaline phosphatase has been reported, through suppression of osteocalin and its diverse effects on type I collagen. Estrogen also upregulates the expression of receptors for 1,25(OH)2D, growth hormone, and progesterone; regulates RTH sensitivity in osteogenic cells; and upregulates IGFBP 4 expression and reduces the degradation of its cleavage protein (12, 13).

B. Effects of estrogen on osteoclast differentiation and activity

The report by Pensler et al. that ERs are present in osteoclasts has been confirmed by groups with bone from humans, chicks, mice, and kittens. The level of ER present in osteoblasts is generally low, and the anti-osteoporotic effects of estrogen may

be largely mediated by regulation of cytokine production by cells in the bone environment, with few direct effects on osteoblasts. Although estrogen-stimulated reductions in mRNA levels and secretion of several lysosomal enzymes, including cathepsin L, -glucuronide, and cathepsin K, have been reported in osteoblasts in vitro, the osteoinhibitory action of estrogen is likely mediated largely, if not exclusively, through effects on the number and activity of osteoblasts. Studies in ovariectomized rodents have shown an increase in the proliferation and differentiation of osteoblast precursors, an increase in the number of osteoblast/osteogenic cells, and a decrease in osteoblast apophysis. The number of osteoblasts increases after menopause. Increased production of TNF, GM-CSF, and IL-1 by mononuclear cells in the bone microenvironment after natural or surgical menopause. These changes are reversed by the action of exogenous estrogen. In support of these observations, treatment with TNF-binding protein prevents bone loss in ovariectomized mice but has no effect in estrogen-excessive animals. The increase in IL-1 activity associated with estrogen deficiency is not only a consequence of IL-1 synthesis but also a decrease in IL-1ra production (14, 15, 16). Treatment of ovariectomized mice with IL-1ra reduces bone loss by blocking the proliferation and differentiation of osteoclast precursors. Mice that cannot synthesize or respond to IL-1 or TNF do not exhibit the bone loss seen in normal animals after ovariectomy, nor do they exhibit the inhibition of IL-1 and TNF activity that is absolutely necessary to prevent bone loss after ovariectomy in normal newborn mice. However, these animals have a normal bone phenotype with no signs of abnormal remodeling activity when sex hormones are in the normal range. These observations emphasize the independent nature of ketone regulation. IL-1, IL-6, and TNF not only induce their own synthesis but also exert autocrine effects, with TNF and IL-1 acting to increase TNF and IL-6 production, and PTH acting to stimulate TNF and IL-6 production (17,6).

C. Skeletal Effects of Estrogen in Animal Models

Ovariectomy has been shown to accelerate the rate of reticular bone loss in some species, particularly in rats, by increasing osteoclasts, osteoblast numbers, and osteoclast size. In young rats, reticular bone loss is predominantly due to increased resorption of hardened cartilage by osteoclasts. Bone formation in rats is increased, and these changes persist for at least a year after ovariectomy. Studies of reticular bone structure in ovariectomized rats have shown little bone loss; in the cortical bone, increased bone resorption leads to an increase in the medullary canal in the tibia; although there is an increase in bone formation at the periosteal level that may increase intraosseous resorption. The number of osteoclasts is increased at the interosseous level. These changes in both cortical and reticular bone may be prevented by estrogen action (18, 19).

It is important to emphasize that sexually mature rodents should be used as models to demonstrate the effects of estrogen deficiency on longitudinal growth. Other animals used in these studies include rats, dogs, cats, monkeys, ferrets, and pigs. A cat fracture is shown in Figure 1.

Figure 1. Image of a cat's fracture

D. Effects of estrogen on the human skeleton

Historphometric (monomorphic fibroblast) changes in the skeleton associated with menopausal bone loss are limited and scattered. Some of these studies have provided evidence for increased bone turnover during menopause, although changes in both the cortex and reticulum have been associated with a return to postmenopausal values of biochemical markers of bone formation and resorption (20).

A consistent finding in untreated postmenopausal women has been a decrease in wall thickness, which includes decreased bone formation at the cellular level and a subsequent decrease in osteoclast activity. The age at which this decrease occurs is unknown. Thus, Lips et al. reported an age-related decrease in mean wall width in 22 men and 14 women aged 18 to 82 years, while another study reported a decrease in both women and men after the age of 50 years. Whether this change is specifically related to estrogen deficiency is unknown; similar changes occur in men, and conventional estrogen replacement

therapy during menopause has not been defined to reverse these changes. Decreases in wall width in cortical bone have been reported in some studies, but not in all age groups. Measurements of resorption depth show little or no change in postmenopausal women. However, careful studies of estrogen deficiency in postmenopausal women suggest that there may be a transient and transient increase in resorption depth. In these women, the rate and sign of reticular bone distribution seen in the cortex after 6 months of treatment have been suggested to be an increase in the depth of resorption through the horcine system in these patients (21, 22).

The age-related distribution of reticular bone in women, more than in men, also supports the association between estrogen deficiency and increased depth of resorption. Studies on reticular bone in women have clearly demonstrated a decrease in the persistence of the reticular structure and its complete loss after menopause. Some studies have reported significant or slight decreases in reticular width, while others have found no change (8).

There have been few relevant histomorphometric studies of the effects of hormone replacement therapy. The fact that hormone replacement causes a decrease in bone mass was first reported by Rigza et al. in a study of 17 women with advanced osteoporosis. Alveolar bone apical biopsies taken before 2.5–4 months (short-term) or 26–42 months (long-term) of estrogen replacement showed a significant decrease in bone resorption but not in bone formation levels, both measured by microradiography. In contrast, a significant decrease in both resorption and formation levels was seen after 26–42 months. Thus, these data suggest that estrogen replacement reduces bone mass and that an inhibitory effect on bone resorption is followed by a subsequent decrease in bone formation (23).

H. Effects of Progesterone on Bone

Little is known about the effects of progesterone on bone metabolism. Osteogenic cells in the normal individual express progesterone receptors, and stimulation of these cells in response to high levels of progesterone has been reported. (24) In ovariectomized rats, one study reported that progesterone had effects similar to estrogen but involved other opposing actions. Estrogen therapy in postmenopausal women with an intact uterus is combined with a progestin to prevent the increased risk of endometrial cancer associated with the use of estrogen alone (25).

Some of the progestins used in these formulations, particularly 19-nor testosterone derivatives, may independently have beneficial effects on bone mass, although the evidence is conflicting in this regard. Thus, preservation of bone mineral density in postmenopausal women treated with nortestosterone was determined in the cortical bone of the palm (3), but Hart et al. reported that norgestrel treatment was associated with a significant decrease in bone density in this area in a similar group. In a study of the effects of medroxyprogesterone on early postmenopausal women, Galaghi et al. determined preservation of total bone mineral density but noted significant decreases in the clavicle, forearm, and palmar cortex (26).

Whether decreased ovarian progesterone production is related to changes in bone mineral density is a matter of physical debate. Pryor et al. have reported decreased pelvic bone mineral density in women with periods of anovulation or periods with short-lived corpus luteum phases, both of which are associated with decreased endogenous progesterone production. Serum estradiol levels were consistently normal in these women, suggesting a role for progesterone deficiency in the pathogenesis of low bone mineral density (27).

Skeletal Effects of Endorgens and Their Mechanisms of Action Endorgens have important effects on bone growth and homeostasis. The increasing recognition of the incidence and mortality of osteoporosis in men has attracted much interest in recent years in the mechanisms of androgen action on bone.

1- Androgen receptor

The androgen receptor was cloned in 1988 and its presence was subsequently demonstrated in osteogenic cell lines in humans and mice and in healthy human osteogenic cells in vitro, and in subsequent studies, receptors were expressed in proliferating chondrocytes, osteoblasts, osteoblasts, and mononuclear cells and endothelial cells in the bone marrow (28).

2- Regional metabolism of sex steroids

Although testosterone is the major male androgen, there is evidence that its skeletal effects are, at least in part, mediated by enzymes in bone. Thus, the presence of both aromatase, which converts testosterone to estradiol and androstendione and dehydroepiandrosterone (DHEA) to estrone, and the reducing enzyme, which reduces testosterone to androstendione and DHT, has been reported in bone. In addition, androstendione can be converted to 17-HSD. Case reports from a man with ER resistance and patients with aromatase deficiency emphasize the importance of normal aromatase activity for bone health in both sexes. Thus, in a 28-year-old man with a small change in the ER gene, complete estrogen resistance is associated with severe skeletal growth defects resulting from delayed epiphyseal closure and bone age, height status, increased bone mass, and severely reduced bone mineral density. At these ages, the aromatase deficiency phenotype in women includes poor physical maturation and delayed bone age, whereas in men it is associated with homozygous and severe aromatase deficiency and a phenotype characterized by height status, delayed skeletal change, and osteoporosis (28,29).

3. Effects of androgens on osteogenic cells

The effects of androgens on osteogenic cells have been demonstrated in both humans and animals. Stimulation is accompanied by proliferation and possibly differentiation of these cells through increased expression of TGF mRNA, and responsiveness to IGF-II and FGF has been reported. Other reported effects on osteogenic cells include inhibition of the cAMP response to PTH or PTH-related peptidase (any of the amides derived from amino acids), decreased prostaglandin production in the cranial nerves, and inhibition of IL-6 production by stromal cells. Increased production of type I collagen has also been reported, although these findings are not generalizable (30).

4. Skeletal Effects of Androgens in Animal Models

In vivo animal studies have shown that androgens promote chondrocyte turnover, metaphyseal ossification, and long bone growth; this is counterbalanced by the effect of estrogens, which promote epiphyseal closure and subsequent reduction in longitudinal growth. The effect of androgens on bone growth, particularly by affecting bone size, is evident, with males having both longer bones and thicker membranous membranes than females. In neonatal male rats and mice, castration is associated with a reduction in membranous and reticular bone volume, possibly leading to an increase in bone volume and osteoclastic activity. Although in response to ovariectomy in females, the reduction in bone matrix volume is largely due to a reduction in periosteal bone formation. In neonatal, castration rats, castration is also associated with a reduction in membranous and reticular bone, with evidence of increased bone volume in the first few months after castration followed by a phase of lower volume (21).

5. Effects of Androgens on the Human Skeleton

The mechanisms by which androgen saturation and depletion affect the human skeleton have been less studied. Studies in testicularly enucleated men have shown rapid bone loss associated with increases in biochemical markers of bone resorption and formation, including increased bone mass. However, in the absence of histomorphometric data, it is not possible to determine the effects of androgen deprivation on the remodeling of the balance or structure of bone tissue or reticular formation. Similarly, the mechanisms of prominent age-related bone loss are not clearly elucidated, although wall thickness decreases with age, including decreased osteogenic activity, and greater bone remodeling than seen in aging women, suggesting that the increased activity of osteoblasts may be less pronounced, although there may be some increase in bone mass (23,31).

Androgens play an important role in the female skeleton. Thus, in women affected by androgen insensitivity syndrome, there is resistance to androgens, and endogenous estrogen production is reduced. Low bone mineral density is a frequent finding in these patients, even in women undergoing long-term estrogen replacement therapy. Furthermore, the addition of testosterone to estrogen replacement in healthy postmenopausal women has been reported to result in greater bone mineral density than estrogen therapy alone, and there is evidence that age-related bone loss in women is related to serum androgen levels (32, 33).

3. METHODS

3.1 Materials used

Ten apparently healthy male laboratory-type kittens with a weight group of 1-2.5 kg and an age group of 1-2 years, nylon thread No. 3.5, scalpel blade No. 25, sizes 2 and 5 mm, consumables available in the surgical department and histopathology laboratories.

Drugs included: acepromazine2, rampon3, ketamine4, penicillin5, rabies vaccine6, radiographic film, nandrolone decanoate7, cyproterone acetate8

In addition to the usual surgical set, an orthopedic surgical set was used including an orthopedic drill, orthopedic drill heads No. 1, 2, 3 and 4 mm, radiology device and microtome.

3.2 Methods

In this study, newborns and kittens were randomly assigned to two groups of five after surgery and were given the same maintenance and nutritional conditions including carrots, lettuce, and pellets.

Group one: Newborns and kittens received nandrolone decanoate injection after surgery.

Group two: Newborns and kittens received cyproterone acetate tablets orally after surgery.

The newborn cats were kept in standard conditions for two weeks before the experiment and were injected with rabies vaccine after confirming clinical health.

In the week of surgery, newborns and kittens were transferred to the operating room in order and were completely and repeatedly examined. After placing the kitten on the operating table, the animal was anesthetized by intramuscular injection

of a mixture of acepromazine (0.1 mg/kg body weight) and vactamin (30 mg/kg body weight). The animal's right leg was completely shaved and disinfected with betadine. After drying the area, the incision was made so that the medial tibia of the right leg was exposed.

An incision of about 6 cm was made on the medial surface of the metatarsal bone with a scalpel blade. After cutting the skin, fascia, tendons, and muscles surrounding the bone were slowly removed without cutting or damaging them. In this way, the tibia was easily exposed.

Next, four holes with diameters of 1, 2, 3, and 4 mm and a distance of one centimeter from each other were made along the length of the bone to pierce the opposite cortex.

The holes were started with a one-meter drill from the bottom of the tibia and ended with a four-millimeter drill at the top of the tibia.

After ensuring that the tibia was not cracked, the area was washed with Ringer's solution and the remaining bone particles resulting from the holes were removed by suction. After that, the muscles were returned to their original position and the skin was sutured with nylon thread all over and the skin was sutured with nylon thread individually.

In the next stage, the suture area of the animal, which had been shaved previously, was disinfected and the animal was sterilized scrotally.

Radiography of the tibia was performed in both groups in the same way, so that immediately after the operation (week zero) and also at weeks 15, 30, 45 and 60 after the operation, two perpendicular radiographs were taken.

Intramuscular injection of penicillin 3: 3: 6 was performed, one injection before the operation and three injections after the operation every 48 hours. The sutures were also pulled 10 weeks after the operation.

Group 1: At intervals of zero and 1, 2, 4, 8 and 12 weeks, nandrolone decanoate was injected intramuscularly into the muscle at a dose of 2 mg/kg.

Group 2: Cyproterone acetate tablets were fed to newborns and kittens at a dose of 5 mg/kg weekly until week 8.

3.3 Evaluation methods

- Assessment of gait status 1

The gait status was assessed based on the developed Smith method. The animals' gait status and hind legs were divided into grades 0 to 4 as follows:

Grade 0: No weight bearing on the operated limb completely.

Grade 1: The animal placed the tip of the paw on the ground.

Grade 2: The animal placed the tip of the paw and part of the toes on the ground.

Grade 3: The animal fully bore weight but with lameness.

Grade 4: The animal bore weight without the slightest lameness.

The animals' gait status was evaluated by an individual at different weeks after the operation until the end of an 8-week period. To examine the gait status of each group, they were compared with the other groups at 0, 1, 2, 4, 8 and 12 weeks.

In this evaluation, the process of filling the holes created in the tibia in terms of callus formation was evaluated on the radiographs prepared at 0, 1, 2, 4, 8 and 12 weeks. In this way, by filling the holes created at different time intervals, the amount of callus formation was determined in different weeks after the operation.

- Histopathological evaluation

In this study, 8 weeks after the operation, all animals were killed by intraperitoneal injection of 1 high dose barbiturates, and the areas of the bone where callus had formed were separated from the site of adhesion to the surrounding tissues and harvested. The samples were placed in 10% formalin solution and transferred to the laboratory for microscopic studies. For accurate assessment of the week of the lesion, the samples were first decalcified with a 5% aqueous solution of citric acid fixed with a 1% urea solution, and then the bone tissue was stained using the usual hematoxylin and eosin (H8E) method.

4. RESULTS

4.1 Results related to gait status

In Table (1), the mean and standard deviation of the scores related to the gait status of the recessions in the two groups are recorded. As is clear, the gait status in each group improves significantly from week one to 60 weeks. ($P<0.05$). On the other hand, there is no significant difference between the two groups at different times and between different times in each group

(P>0.05).

Except for week one and week seven, where there is a significant difference in both groups (P<0.05), which is completely normal.

For example, the gait status in both groups showed an improvement of 80% in the first week and almost 100% from the fourteenth week onwards.

4.2 Radiographic results

In Table (2) and (Figures 2 to 10), the mean and standard deviation of the amount of callus formed in 12 weeks after the operation have been recorded. It is clear that there is a significant difference between the amount of callus formed in the two groups at some times. (P<0.05).

In such a way that the amount of callus formed until the thirtieth week in the two groups is not significant. (P>0.05).

However, between the thirtieth week and the forty-fifth week and the forty-fifth week to the sixtyth week, there is a significant difference in both groups.

As in the one group, a hole with a diameter of one and two millimeters was filled (Figure 5), and in the sixtyth week, holes with a diameter of 3 and 4 millimeters were filled. (Figure 6). In the second group, callus was formed by week 30 (Figures 7 to 9).

At week 45, the hole was filled with a diameter of 2 mm, which was a significant difference from week 30 to week 60 (Figure 9) in both groups (P<0.05). However, there was no significant difference from week 0 to week 30 (P>0.05).

There was a significant difference between the two groups at some times (P<0.05) and at other times there was no significant difference (P>0.05). Thus, there was no significant difference between the two groups at weeks 0, 4 to 8, but there was a significant difference between the two groups at weeks 8 to 12. (P<0.05).

4.3 Pathological Results

Histopathological evaluation of sections prepared from newborns and kittens of groups 1 and 2 indicated the occurrence of healing and formation of bone callus in both groups. However, comparing the sections obtained from these two groups showed that qualitatively the formation of bone callus in kittens of group 1 was more extensive and voluminous and basically showed the whole process of bone healing to be at a more advanced stage than in animals of group 2. In the histological study of soft tissues, all the observed changes were non-specific and not of particular importance.

Table 1: Mean and standard deviation of gait status within 12 weeks after Smith's breeding operation

	WEEK									
	12	10	8	6	4	3	2	1	0	**Group**
*	0±4	0±4	0/1±3/8	0/2±3/7	0/2±3/7	0/4±3/5	0/2±3/5	0/2±3/1	0	1
*	0±4	0±4	0/1±3/8	0/2±3/7	0/1±3/7	0/2±3/5	0/2±3/5	00/2±3	0	2
	PV	PV	PV	PV	PV	PV	PV	PV	PV	

* There is a significant difference. (P<0.05)

PV There is no significant difference. (P>0.05)

Table 2: Mean and standard deviation of radiographic callus formation at 60 weeks after surgery in millimeters

	12	8	4	2	0	Group
*	4	2	0	0	0	1
*	2	1	0	0	0	2

	*	*	PV	PV	PV	

* There is a significant difference. (P<0.05)

PV There is no significant difference. (P>0.05)

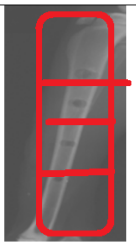

Image 2- Radiography of group one at week

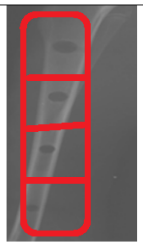

Image 1- Radiography of group one at week 0

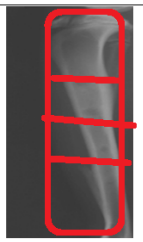

Image 4- Radiography of group one at week 12

Image 3- Radiography of group one at week 6

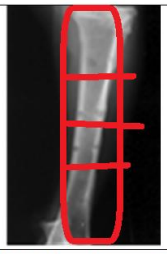

Image 6- Radiography of group two at week 4

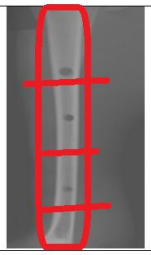

Image 5- Radiography of group two at week 0

Image 8- Radiography of group two at week 12

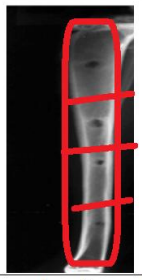

Image 7- Radiography of group two at week 6

5. DISCUSSION

Nandrolone causes a significant increase in bone mineral content (IA). In one study of ovariectomized monkeys, cortical bone had higher levels of phosphate and collagen but lower levels of carbonate one to two years later. Treatment with nandrolone reversed most of the effects of ovariectomy to the point where bone formation reached levels comparable to those in the control group, i.e., the ovariectomized group. However, the bone formed after ovariectomy is chemically different from that of healthy bone, especially in certain areas of the bone, which results in a decrease in bone quality. (6A,3A,5A). However, in another study, it was shown that the decrease in bone quality was not significant. (4A).

Nandrolone treatment increased bone to the point where bone mass reached levels comparable to those in non-sterile animals

(6A,5A,4A).

According to the above results, nandrolone treatment did not affect the degree of bone mineralization in terms of phosphate to protein ratio, but the phosphate content in the tibia increased due to ovariectomy and the carbonate content decreased compared to the control group (7A, 4A). Contrary to some other theories (3A), no changes in carbonate content were observed in the trabecular areas, and it was determined that nandrolone treatment caused the return of lost carbonate. (7A, 6A, 5A, 4A).

Another effect of nandrolone is a 60% increase in body weight after 25 mg every three weeks (7A).

In another study, two groups were studied, with estrogen and progesterone used in the first group and estrogen and progesterone with nandrolone in the second group. It was found that the bone mass increased by 21% in the first group and 29% in the second group after 6 months, and then remained stable, resulting in a significant increase in bone density in both groups compared to baseline. ($P<0.55$). However, there was no significant increase between the two groups. This result is in conflict with some sources (A 8 and A 10).

Another study showed that intramuscular injection of 50 mg of nandrolone is effective on calcium metabolism and bone density. Thus, in samples that have used corticosteroids for a long time and have developed osteoporosis, nandrolone prevented the abnormal effects of corticosteroids with the mentioned amounts and also seemed to prevent bone resorption. Without stimulating bone formation. (A 9).

It was also shown that bone formation is clearly reduced during treatment with estrogen and progesterone, but if long-term treatment with anabolic steroids (nandrolone) is performed at the same time, it does not cause bone disorders (A10). In another study, it was shown that treatment with nandrolone increases Bone mineral content is reduced, which is not a direct result of increased bone formation, but rather a combination of decreased bone resorption and increased muscle mass, both of which have beneficial effects on bone maintenance (A11). Abnormal and excessive use of androgens causes loss of libido and, in association with antiandrogens, affects all androgen-dependent organs and their activity, for example, the gonads, spermatogenesis, skin. There is a difference between steroidal antiandrogens such as spironolactone acetate and pure nonsteroidal antiandrogens such as foltamide and anandrone. (B1).

Antiandrogens are used in cases including androgen-dependent disorders, acne, alopecia, seborrhea, advanced prostatic carcinoma, precocious puberty, and hypersensitivity in males. They are lipophilic and can penetrate the hair follicles. B)1). In cases of treatment with these drugs, the secretion of gonadotropins and estrogen is completely stopped and bone maturation is also slowed down (B 2 and B11).

Estrogen, progesterone, medoxogestrone and cyproterone acetate cause changes in body composition such as weight gain, decreased muscle mass, increased body fat, decreased bone density and anemia and hair changes (B 3 and B11).

In another study, two groups were examined. In the first group, males who underwent sex reassignment to females (estradiol and cyproterone acetate were administered) and in the second group, females who underwent sex reassignment to males (testosterone was administered). The results obtained were that estrogen and cyproterone acetate caused a decrease in bone formation, and in the second group, androgen administration caused an increase in bone formation.(B 9).

Intramuscular administration of anti-androgens (cyproterone acetate) causes a severe decrease in plasma testosterone levels and also leads to premature and incomplete mineralization of antlers in deer.(B 12).

According to the studies conducted and the results obtained from this research, it seems that despite the discrepancies that exist in some cases, the steroidal androgens nandrolone can cause calcium deposition and faster formation of bone tissue in cases of bone defects

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