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The Influence of Sex on Peri-Implant Bone Remodeling Processes

La Influencia del Sexo en los Procesos de Remodelación Ósea Periimplantariaa

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SUMMARY: Sex hormones actively participate in skeletal physiology, resulting in known sexual dimorphism in bone size and strength. The aim of this study was to comparatively assess the rate and quality of peri-implant bone remodeling in skeletally mature male and female rabbits 3 months after the insertion of titanium screws into the femoral diaphysis. Titanium screws (5 mm length, 2 mm diameter) were inserted into a standardized osteotomy site. Histological analyses were performed on tissues surrounding the implants. Females exhibited remodeling processes dominated by the resorptive (osteoclastic) phase, characterized by large resorption spaces and precarious structural continuity between newly formed subperiosteal bone and the deeper cortex. In contrast, males demonstrated significantly more advanced remodeling, achieving structural equilibrium between resorption and formation, with minimal empty spaces and the presence of maturing osteon (Haversian systems) indicative of superior cortical reorganization. This disparity highlights a clear lag in the consolidation phase in females at this 3-month time point, suggesting that the androgenic environment in males facilitates a more rapid and robust post-traumatic osseous response.

KEY WORDS: Bone remodeling; Female rabbits; Male rabbits; Titanium screws.

INTRODUCTION

In veterinary and biomedical sciences, it is well-established that sexual dimorphism exists in skeletal morphology and strength, favoring males (Kim *et al*., 2003). This difference is largely driven by a greater rate of periosteal apposition in males compared to females, leading to larger bone diameters and thicker cortices (Iuliano-Burns *et al*., 2001, 2009). Consequently, male bones exhibit superior mechanical resistance, a phenomenon evidenced clinically by the higher incidence of stress fractures in military women compared to men (Jones *et al*., 2002).

For studying bone implants in cortical or spongy bone, the hind limbs of rabbits are frequently used at present. Rabbits offer advantages over large animal models by reaching skeletal maturity at a relatively young age (8-11 months) and advantages over small rodents by transitioning to secondary osteon remodeling (Wancket, 2015). Bone dimensions and cortical area are positively correlated with both body size and mechanical loading, with skeletal tissue being most receptive to mechanical stimuli during the growth phase (Schoenau *et al*., 2001; Riggs *et al*., 2004). The ultimate mechanical competence of the skeleton is a function of its size, geometry, and the density conferred by ongoing remodeling processes (Parfitt *et al*., 2000).

While extensive literature describes sex differences during bone growth and development, the comparison of sex-based kinetics in bone repair and consolidation following trauma remains less explored. Given that peri-implant healing involves a complex, localized repair and remodeling cascade, investigating potential sex-linked variations in this process is critical for orthopedic surgery and implantology. Therefore, the aim of this study was to conduct a comparative investigation into the osseous repair and consolidation response around metallic implants in sexually mature male and female rabbits.

MATERIAL AND METHOD

Animals and Ethical Approval

Ten skeletally mature, 11-month-old German giant rabbits (5 males, 5 females) were used for this study. The rabbits were sourced from a controlled breeding colony at

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the Biobase of the Faculty of Veterinary Medicine, Cluj-Napoca. The animals were housed under standardized conditions (20-24 °C ambient temperature, 12-hour natural light/dark cycle) with commercial granulated feed and water ad libitum. The experimental protocol received approval from the Bioethics Committee of the University of Agricultural Sciences and Veterinary Medicine of Cluj-Napoca (No. 384/ 20.08.2023). The females were intact and considered to be sexually cycling; their specific estrous phase was not determined at the time of surgery or euthanasia.

Surgical Procedure

Anesthesia was induced with an intramuscular injection of Xylazine (5 mg/kg) and Ketamine (35 mg/kg) and maintained via isoflurane inhalation. Fluid therapy was administered concurrently. Following aseptic preparation, a lateral incision was made to expose the femoral diaphysis.

A standardized osteotomy site was created using a 1.8 mm diameter drill bit with continuous saline irrigation. A self-tapping titanium screw (5 mm length, 2 mm diameter) was manually inserted. The soft tissues and skin were closed in layers. Postoperative care included Meloxicam (1 mg/kg s.c. for 3 days) and Enrofloxacin (20 mg/kg s.c. for 5 days).

Tissue Harvesting and Histological Preparation

At three months (90 days) post-implantation, the animals were euthanized (intravenous pentobarbital sodium). The femurs were harvested, and bone segments containing the implant site were fixed in 10 % neutral buffered formaldehyde for 10 days.

The samples were decalcified using trichloroacetic acid, dehydrated through a graded alcohol series, cleared in 1-butanol, and embedded in paraffin wax. Sections were cut at 5 µm thickness and stained using Goldner's Trichrome method for visualization of mineralized bone (green/blue) and unmineralized osteoid (red). Sections were examined using an Olympus BX41 microscope equipped with an Olympus E-330 digital camera.

RESULTS

At 3 months post-implantation, bone remodeling processes were evident along the entire circumference of the bone at the intervention site in both groups. However, there were significant differences in the stage and extent of these processes.

Female Group Findings

The predominant feature in the female group was active bone resorption. A high concentration of osteoclasts was observed at the interface between the newly proliferated subperiosteal bone and the original cortical bone (Fig. 1). This lytic activity resulted in the formation of large resorption spaces (Fig. 2). Zone of Resorption - Female, Goldner's Trichrome, (40X) that were temporarily devoid of newly mineralized tissue.

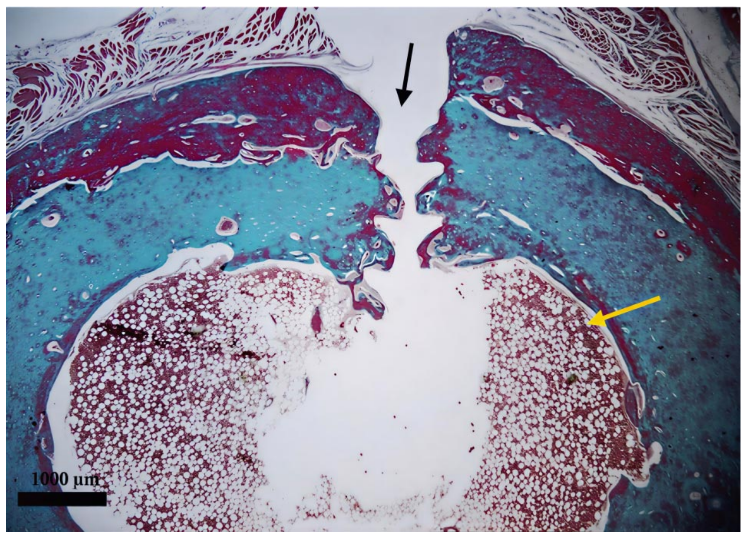

Fig. 1. Peri-implant area - female: black arrow - implant site; yellow arrow - medullary canal (Tricrom Goldner, ob. 2X)

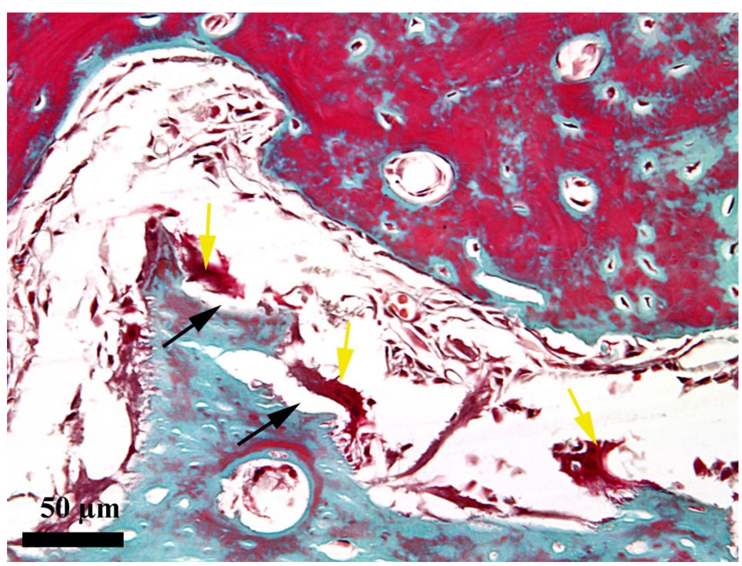

Fig. 2. Peri-implant area - female: black arrow - resorption space; yellow arrow - osteoclasts (Tricrom Goldner, ob. 40X)

The subperiosteal bone proliferation was present but the structural continuity with the deeper cortical bone was precarious over large zones due to the extensive osteoclast-mediated gaps. This morphology indicates that the tissue at this 3-month time point is still primarily in a resorptive or initial consolidation phase, characterized by young, trabecular-like bone with only incipient organization into osteon-like structures.

Male Group Findings

The male group exhibited a significantly more advanced stage of bone remodeling and consolidation compared to the females.

Crucially, the transition zone between the proliferated subperiosteal bone and the deeper cortical bone showed immediate structural continuity, with virtually no empty spaces or significant osteoclast accumulation comparable to the females. This morphology suggests that the bone formation (apposition) phase was in equilibrium with, or had rapidly followed, the resorption phase, indicating a faster overall remodeling turnover.

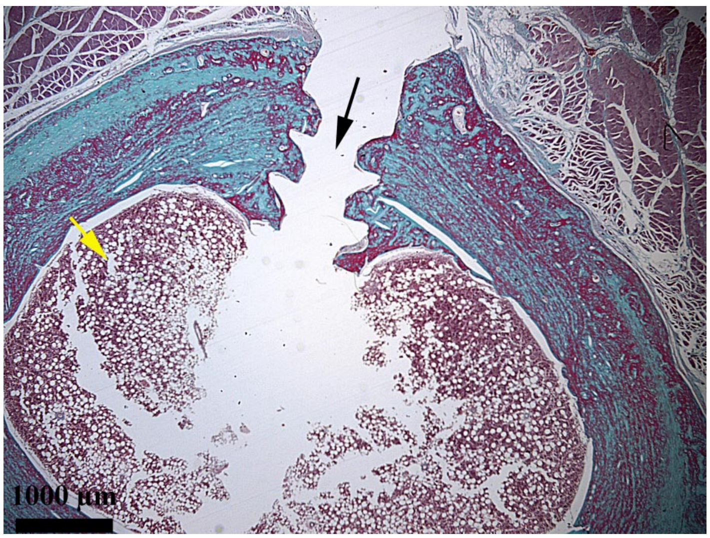

Fig. 3. Peri-implant area - male: black arrow - implant site; yellow arrow - medullary canal (Tricrom Goldner, ob. 2X)

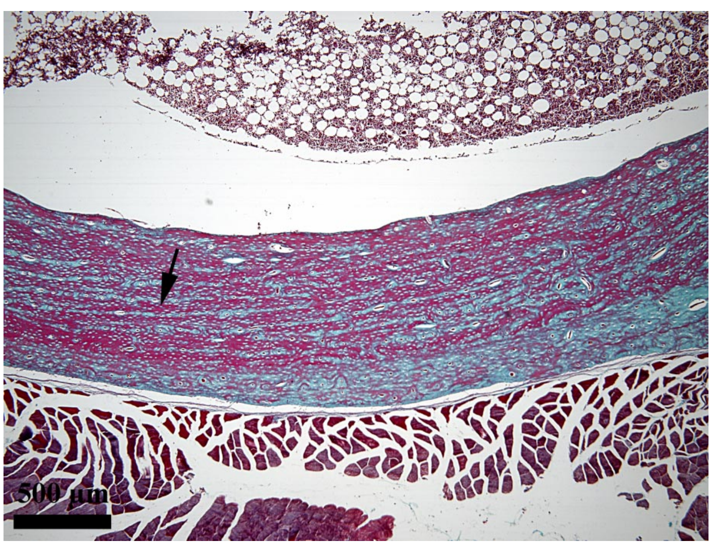

Fig. 4. Peri-implant area - male: black arrow - advanced bone remodelling (Tricrom Goldner, ob. 4X)

Furthermore, the new bone in males demonstrated a high degree of structural maturity and reorganization (Fig. 3). Osteon—complex, concentric lamellar structures indicative of mature cortical bone—were present over wide areas and were observed in medium to advanced stages of organization (Fig. 4). Advanced Remodeling with osteon - Male, Goldner's Trichrome, (40X). The extent and distribution of this highly organized new bone were clearly superior to the females, suggesting a higher mechanical competence of the peri-implant bone.

DISCUSSION

The findings of this study demonstrate a clear and significant sexual dimorphism in the rate of peri-implant bone remodeling in the rabbit model, with males exhibiting a faster and more structurally mature consolidation response at 3 months post-surgery. This distinction is evident in the transition from a resorption-dominant state in females to an equilibrium/formation-dominant state in males.

Remodeling Kinetics and Mechanical Adaptation

The trauma of screw insertion necessitates a systemic adaptation to restore the biomechanical integrity of the compromised long bone. The principle governing this repair is rooted in Wolff's Law, where the bone adapts to mechanical loads (Frost 2003). The implant insertion introduces a new mechanical environment, and the differences in remodeling rates suggest a sex-specific sensitivity or efficacy of the mechanobiological response.

The high osteoclastic activity and resulting large resorption spaces observed in females suggest that the initial phase of lytic removal of damaged bone is robust, but the subsequent phase of osteoblastic bone formation is comparatively delayed or slower (Sabou *et al*., 2023, 2025). This transient situation results in a weak point in the bone structure at 3 months.

In contrast, the male response is characterized by rapid completion of the remodeling cycle, wherein osteoblasts effectively fill resorption cavities to establish continuity. This rapid completion is confirmed by the formation of numerous, organized osteon, which represent the highest level of structural reorganization necessary to restore or even surpass the original strength of the cortical bone (Marcu *et al*., 2022; Duma *et al*., 2023, 2025). This efficiency likely reflects the male body's greater inherent capacity for periosteal bone formation, as established in growth studies (Schoenau *et al*., 2001).

Pantor *et al*. (2022) demonstrated hematogenous marrow's high tolerance to direct titanium implant contact in rabbit femurs, with no rejection or fibrosis after 7 days and rapid new bone covering over half the intra-marrow implant surface, driven by progenitor cells and growth factors. Ratiu *et al*. (2022) revealed that endosteum-penetrating implants accelerate early osseointegration via marrow influence, achieving direct interface bone formation superior to aspirated marrow techniques. Ratiu *et al*. (2025) highlighted periosteum, endosteum, and marrow contributions, forming thick peri-implant bone layers, trabecular extensions, and remodeling osteons by six weeks to restore mechanical integrity. Collectively, these studies confirm marrow's compatibility and stimulatory role, supporting marrow-engaging implant strategies for dental and orthopedic success (Pantor *et al*., 2022; Ratiu *et al*., 2022, 2025).

Role of Sex Hormones

The disparity in remodeling rates is strongly linked to the regulatory role of sex steroids (Fernea *et al*., 2025). The greater bone size, geometry, and strength commonly observed in males (Kim *et al*., 2003) are linked to the action of androgens mediated by the Androgen Receptor (AR) which promotes periosteal apposition (Kawano *et al*., 2003; Venken *et al*., 2006). Androgen deficiency or resistance severely impairs cortical and trabecular bone mass (Vanderschueren *et al*., 2004; Vandenput *et al*., 2004).

The better hormonal balance and higher steady-state levels of androgens in males, which can also be converted to estrogens via P450 aromatase, appear to provide a pro-anabolic environment for bone healing (Riggs *et al*., 2002; Khosla *et al*., 2002). This environment likely promotes osteoblast differentiation and prolongs their lifespan, accelerating the bone formation phase necessary for osseointegration and structural maturity.

While estrogens are primarily known for their anti-resorptive effects and maintenance of bone mass in adult females, the overall balance between resorption and formation is delicate. Estrogens primarily act by inhibiting the apoptosis of osteoblasts and osteocytes while promoting the apoptosis of osteoclasts, thereby maintaining bone balance (Manolagas *et al*., 2000). However, in the immediate post-traumatic environment, the estrogen-regulated balance might be less effective than the potent anabolic drive of androgens in accelerating the formation phase required to fill large defects. The prolonged resorptive phase observed in females may be linked to a less powerful proliferative signal following the initial trauma. Furthermore, deficiencies or fluctuations in estrogens can lead to an increase in bone remodeling rate by increasing the lifespan of osteoclasts (Vanderschueren *et al*., 2004).

Study Limitations

A limitation of this descriptive study is the reliance on qualitative histological assessments. Future work must rigorously apply the proposed quantitative histomorphometric indices (BIC, BA/TA, Oc.S/BS) and use appropriate statistical methods to confirm the magnitude of the observed sex differences. Additionally, the lack of data on the estrous cycle phase for the females means the influence of specific estrogen fluctuations on the observed 3-month outcome remains speculative.

CONCLUSION

Bone remodeling processes around titanium implants are significantly influenced by sex. At 3 months post-implantation, male rabbits demonstrate a markedly faster and more structurally advanced consolidation characterized by organized osteon and osseous continuity. Female rabbits exhibit a significant lag, with persistent large resorption spaces indicating a prolonged dominance of the lytic phase. This finding underscores the necessity of considering sex as a critical biological variable in the design and interpretation of preclinical orthopedic research. However future studies should consider quantitative histomorphometric determinations to reinforce our findings.

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RESUMEN: Las hormonas sexuales participan activamente en la fisiología esquelética, lo que da lugar a un conocido dimorfismo sexual en el tamaño y la resistencia ósea. El objetivo de este estudio fue evaluar comparativamente la tasa y la calidad de la remodelación ósea periimplantaria en conejos machos y hembras con madurez esquelética, 3 meses después de la inserción de tornillos de titanio en la diáfisis femoral. Se insertaron tornillos de titanio (5 mm de longitud, 2 mm de diámetro) en un sitio de osteotomía estandarizado. Se realizaron análisis histológicos de los tejidos que rodeaban los implantes. Las hembras mostraron procesos de remodelación dominados por la fase reabsortiva (osteoclástica), caracterizada por grandes espacios de reabsorción y una continuidad estructural precaria entre el hueso subperióstico recién formado y la corteza más profunda. En contraste, los machos demostraron una remodelación significativamente más avanzada, alcanzando un equilibrio estructural entre reabsorción y formación, con espacios vacíos mínimos y la presencia osteonas en maduración, indicativos de una reorganización cortical superior. Esta disparidad pone de manifiesto un claro retraso en la fase de consolidación en las hembras a los 3 meses, lo que sugiere que el entorno androgénico en los machos facilita una respuesta ósea postraumática más rápida y robusta.

PALABRAS CLAVE: Remodelación ósea; Conejas; Conejos; Tornillos de titanio.

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