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Original Article

## Effects of staphylococcal infection and aseptic inflammation on bone mass and biomechanical properties in a rabbit model

Hui Li <sup>☆</sup>, Shutao Zhang <sup>☆</sup>, Shicheng Huo, Haozheng Tang, Bin'en Nie, Xinhua Qu <sup>\*\*</sup>, Bing Yue <sup>\*</sup>

Department of Bone and Joint Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, China

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## ABSTRACT

**Background/objective:** Orthopaedic implants are important devices aimed at relieving pain and improving mobility. Staphylococcal infection and aseptic loosening are two common events associated with inflammatory osteolysis that lead to implant failures. Bone mass and biomechanical properties are important indicators that could influence patient outcomes after revision surgery. However, the dynamics of bacterial infections and their influence on bone mass and biomechanical properties remain unclear. Hence, in this study, we developed rabbit aseptic inflammation and staphylococcal infection models to determine the effects of coagulase-positive and coagulase-negative bacterial infection, as well as aseptic inflammation, on the mass and biomechanical properties of the bone.

**Methods:** Sixty New Zealand white rabbits were randomly assigned to 6 groups, and each group had 10 rabbits. The medullary cavities in rabbits of each group were injected with phosphate-buffered saline (100  $\mu$ L), titanium (Ti)-wear particles (300  $\mu$ g/100  $\mu$ L), a low concentration of *Staphylococcus epidermidis* ( $10^5$ /100  $\mu$ L), a high concentration of *S. epidermidis* ( $10^8$ /100  $\mu$ L), a low concentration of *Staphylococcus aureus* ( $10^5$ /100  $\mu$ L), and a high concentration of *S. aureus* ( $10^8$ /100  $\mu$ L), respectively. At four and eight weeks after surgery, the rabbits were sacrificed, and the tibias on the surgical side were analysed via histopathology, microcomputed tomography, and nanoindentation testing.

**Results:** Histopathological analysis demonstrated that inflammatory responses and bacterial loads caused by high concentrations of staphylococcal infections, particularly coagulase-positive staphylococci, are more detrimental than low concentrations of bacterial infection and Ti-wear particles. Meanwhile, microcomputed tomography and nanoindentation testing showed that high concentrations of *S. aureus* caused the highest loss in bone mass and most biomechanical function impairment in rabbits experiencing aseptic inflammation and staphylococcal infections.

**Conclusions:** Inflammatory osteolysis caused by a high concentration of coagulase-positive staphylococci is significantly associated with low bone mass and impaired biomechanical properties.

**The translational potential of this article:** It is necessary to obtain an overall assessment of the bone mass and biomechanical properties before revision surgery, especially when *S. aureus* infection is involved. In addition, a better understanding of these two parameters might help develop a reasonable treatment regimen and reduce the risk of adverse events after revision surgery.

## Introduction

Orthopaedic implants are important devices for patients to relieve pain and improve mobility. In the United States, there are approximately 600,000 joint replacements and 2 million fracture-fixation devices

inserted annually [1]. As the number of indwelling medical devices (such as prosthetic joints and internal fixation devices) used in orthopaedic surgery has been rising, implantation failures have led to significant increases in morbidity and mortality rates [2,3]. One of the most common causes of implant failure is aseptic loosening (75%); other reasons for

<sup>\*</sup> Corresponding author. Department of Bone and Joint Surgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, 145, Shandong Road, Shanghai, 200011, China.

<sup>\*\*</sup> Corresponding author. Department of Bone and Joint Surgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, 145, Shandong Road, Shanghai, 200011, China.

E-mail addresses: [xinhua\\_qu@126.com](mailto:xinhua_qu@126.com) (X. Qu), [advbmp2@163.com](mailto:advbmp2@163.com) (B. Yue).

<sup>\*</sup> These authors contributed equally to this work.

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which implants require revisions are infection (7%), recurrent dislocation (6%), periprosthetic fracture (5%), and technical errors at the time of surgery (3%) [4–7]. Although the orthopaedic device-related infection rate is lower than that of aseptic loosening, prosthetic joint infections still remain a devastating complication after surgery and account for a substantial proportion of healthcare expenditures [8]. Patients who experienced implantation failure after primary surgery require prolonged drug treatments and multiple revision operations [9,10]. Therefore, it is necessary to investigate the effect of aseptic loosening and infection on the success rate of prosthetic revision surgery.

Bone is a metabolically active organ that undergoes continuous remodelling throughout life; however, its remodelling cycle is sensitive to chronic inflammation [11–14]. After orthopaedic surgery, aseptic loosening and prosthetic joint infection are major causes of the immune system/inflammatory pathway activation. As a result, proinflammatory cytokines are released into the local bone microenvironment and induce the aggregation of immune cells. In addition, these cytokines stimulate the proliferation and differentiation of osteoclasts that form actin-rich sealing zones that delimit the resorption lacuna [15–17]. Bone mass and biomechanical properties are important for evaluating the activity of multinucleated osteoclasts, and the level of bone mass is usually related to the number of trabecular bones and the degree of their connectivity. Proinflammatory cytokine-induced enhancement of osteoclast bone resorption may cause the cancellous bone at the site of inflammation to become compressed, which often produces chronic pain after surgery. In addition, biomechanical properties are closely related to the mineral composition and collagen content. Once inflammatory osteolysis upsets the balance between minerals and collagen fibres, the elastic modulus of the cortical bone declines precipitously, which increases the chance of periprosthetic fractures after a fall [18]. Therefore, chronic inflammation caused by aseptic loosening or infection is an important factor in reducing bone mass and biomechanical properties.

Implant-derived wear particles are a common cause of chronic inflammatory responses that cause aseptic osteolysis and implant failures. The presence of wear particles can enhance macrophage phagocytosis and release numerous proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), and prostaglandin E2 [19,20]. This immune response not only induces cell oedema and necrosis but also stimulates osteoclast differentiation and osteoblast apoptosis [21,22]. Therefore, aseptic osteolysis is a devastating complication that could increase the bone resorption rate while reducing the bone mass and perturbing its biomechanical properties. Staphylococcal infection is another risk factor for inflammatory osteolysis; the highly virulent pathogen responsible for orthopaedic device-related infection is *Staphylococcus aureus* [23]. It has previously been demonstrated that *S. aureus* induces osteoblast apoptosis and stimulates osteoclast differentiation or expression of osteolytic factors, thereby exacerbating the osteolytic effect [24,25]. Moreover, *S. aureus* protein A binds directly to TNF receptor 1, resulting in an inhibitory effect on osteoblast proliferation and the stimulation of receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) expression [26]. Unlike *S. aureus*, which can produce numerous extracellular enzymes and toxins, *Staphylococcus epidermidis* is the most commonly isolated type of coagulase-negative staphylococci that retains a limited number of virulent factors and is normally unable to infect healthy hosts [27,28]. However, largely because of its ability to form biofilm on indwelling devices, *S. epidermidis* can cause persistent infections in patients receiving orthopaedic implants. In addition, *S. epidermidis* appears to trigger relatively low levels of proinflammatory cytokines and high levels of IL-10, which may contribute to subacute infections [29].

Although many studies have elucidated the possible mechanisms underlying staphylococcal infections and aseptic inflammation, it remains unclear whether (1) aseptic inflammation affects biomechanical properties; (2) staphylococcal infections affect bone mass and biomechanical properties; (3) coagulase-positive bacteria (that are highly toxic) and coagulase-negative bacteria (that have low toxicity) have different

effects on bone mass and biomechanical properties, and (4) high and low concentrations of bacteria have different effects on bone mass and biomechanical properties. Therefore, we constructed aseptic inflammation and staphylococcal infection models in rabbits and investigated the aforementioned questions using histopathological analysis, micro-computed tomography (micro-CT), and nanoindentation tests.

## Materials and methods

### Animals and experimental procedures

All procedures were performed in accordance with the guidelines of the Animal Ethics Committee. The titanium (Ti)-wear particle osteolysis model and staphylococcal infection model were devised separately in the cavity of the tibia. Briefly, 60 New Zealand white rabbits (body weight, 2.2–2.5 kg) were randomly assigned to 6 groups, and 5 rabbits in each group were sacrificed after 4 weeks and 8 weeks of surgery. Then, each rabbit was subjected to a lateral knee incision. After dislocating the patella, the knee joint was highly flexed to expose the tibial plateau, into the centre of which a 1.5-mm diameter hole was drilled. Then, 100  $\mu$ l phosphate-buffered saline, Ti-wear particles (300  $\mu$ g), a low concentration of *S. epidermidis* ( $10^5$  colony-forming units (CFU)), a high concentration of *S. epidermidis* ( $10^8$  CFU), a low concentration of *S. aureus* ( $10^5$  CFU) and a high concentration of *S. aureus* ( $10^8$  CFU) were injected into the medullary cavities of rabbits in each group, respectively. Bone wax was used to close the hole, and the wound was stitched layer by layer. During the observation time, no rabbit died because of improper operation, and the rabbits have not been given antibiotic treatment after surgery. At four and eight weeks after surgery, the rabbits were sacrificed, and the tibia on the side of the surgery was harvested and fixed in 4% paraformaldehyde for 24 h. The specimens were then stored in 70% ethanol at  $-20$  °C for subsequent analyses.

### Histopathological evaluation

After four and eight weeks of infection, tissue inflammation and bacterial load associated with staphylococcal infections and aseptic inflammation was assessed in the tibia. For histopathological staining, excised tibia specimens were fixed in 4% paraformaldehyde and embedded in paraffin. The tibia was cut, subjected to Gram staining and observed under a light microscope.

### Micro-CT analysis

The fixed tibias were analysed using high-resolution micro-CT ( $\mu$ CT-100; Scanco Medical AG, Bassersdorf, Switzerland). The osseous tissue below the tibial plateau was selected as the region of interest and scanned. The scanning protocol was set at an isometric resolution of 10  $\mu$ m, and X-ray energy settings of 70 kV and 1170 mA, with a voxel size of 10  $\mu$ m in all three spatial dimensions, were used. Two hundred consecutive slices at the midpoint of the tibias were chosen for further quantitative analysis. The parameters of bone volume/tissue volume (BV/TV, %), bone mineral density (g/cc), cortical thickness (mm) and trabecular separation (mm) of each sample were measured to assess the bone microstructure of the tibias using the Evaluation, v6.5-3 software (Scanco Medical AG, Bassersdorf, Switzerland).

### Nanoindentation measurement

The nanoindentation test of the tibial cortex was performed after the micro-CT scan was completed. The tibia sample was first subjected to gradient ethanol dehydration and hard tissue embedding. The sample was then sectioned and polished with multiple grit sandpapers. The force and displacement of the tibial cortical cross-section sample during indentation were measured using the Nano Indenter XP system (MTS Nanoindenter XP, Oak Ridge, TN, USA). Each sample was tested under a

50× magnification optical microscope with 10 points in the tibial cortical area selected as indentation points. A Berkovich indenter tip ( $E_i = 1141$  Gpa,  $\nu_i = 0.07$ ) was used for the nanoindentation tests, and the displacement control was used for the indentation procedure. We increased the indenter to 1000 nm at 10 nm/s to eliminate the effects of polished bone surface roughness. A typical indentation load–displacement curve consists of four sections: a loading segment, a 10-s holding segment at maximum load, an unloading segment, and a 50-s holding segment for thermal drift measurement at 10% of the maximum load elastic modulus. Through this detection process, the elastic modulus and hardness, with functions reflecting the intrinsic properties of the tibial cortex, were separately recorded.

#### Statistical analysis

The data are expressed as the mean  $\pm$  standard deviation from at least 3 independent experiments. The results were analysed via the Student t test or one-way analysis of variance using the SPSS 23.0 software (SPSS Inc., Chicago, IL, USA).  $p < 0.05$  indicated a significant difference between groups.

## Results

#### Effect of Ti-wear particles and staphylococcus on the medullary cavity

As shown in Fig. 1, the medullary cavity of the sham-operated group injected with phosphate-buffered saline was of a dark red colour, indicating normal bone marrow contents. Similarly, the tibial bone marrow cavity in which the wear particles were injected also showed a dark red content similar to the sham-operated group. However, the medullary cavities in the bacteria-injected groups showed varying degrees of infection symptoms (Fig. 1A). Low concentrations of *S. epidermidis* and *S. aureus* caused scattered purulent lesions in the medullary cavity, which were slightly turbid in appearance. The altered medullary cavity appearances were more obvious in the high-concentration bacteria-injected groups; high *S. aureus* caused suppurative changes in the entire medullary cavity. After injection into the medullary cavity at a high dose, *S. epidermidis* also produced a clear jelly-like suppurative lesion. Eight weeks after the model construction, the medullary cavities of the sham operation and the wear particle groups were similar (Fig. 1B). In the infected group, however, the symptoms of medullary cavity infection were somewhat improved, and suppurative lesions caused by low-concentration bacteria were no longer obvious. Infected lesions could still be observed in the medullary cavities of the high-concentration bacterial injection groups but were less extensive than they were at the four-week time point.

#### Effect of Ti-wear particles and staphylococcus on bone microarchitecture

Four weeks after surgery, micro-CT revealed a lower BV/TV in the region of interest of the Ti-wear particle group than in that of the sham operation group (Fig. 2A). The BV/TV values of each bacteria-infected group were reduced by varying extents compared with that of the wear particle group, with the BV/TV reduction in the high-concentration bacteria group being the most prominent. The coagulase-positive *S. aureus* resulted in a more pronounced decrease in BV/TV than *S. epidermidis*. Similarly, Ti-wear particles and bacteria both caused a decrease in the cortical thickness, with high concentrations of *S. aureus* having the greatest effect. Moreover, the trabecular separation of the sacral cavity in the sham operation group was lower than that in the experimental groups. Ti-wear particles and low-concentration bacteria caused a certain degree of trabecular separation, with trabecular bone looseness most prominent in the high-concentration bacteria groups. At eight weeks after surgery (Fig. 2B), the trabecular separation of the high-concentration *S. aureus* group was significantly higher than that of the Ti-wear particle group.

#### Effects of Ti-wear particles and staphylococcus on biomechanical properties

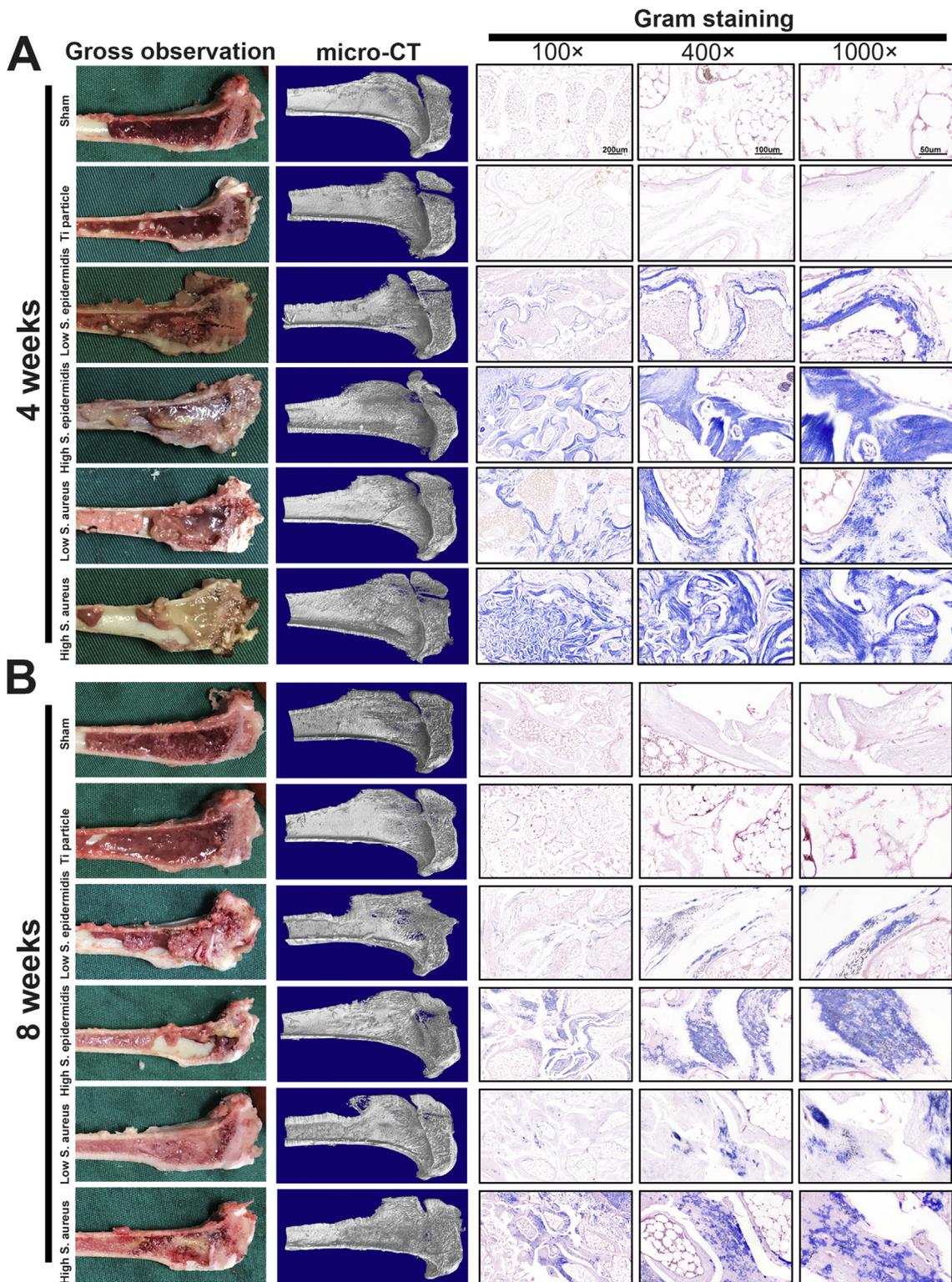
To determine the effect of Ti-wear particles and bacteria on the tissue-level biomechanical properties of the tibial cortex, we performed nanoindentation testing on each set of samples (Fig. 3). The elastic modulus and hardness of the tibial cortex treated with Ti-wear particles were slightly (but not significantly) lower than those of the sham group. Both low and high concentrations of *S. epidermidis* reduced the elastic modulus and hardness of the cortical bone, with this decrease more obvious at high concentrations. Coagulase-positive *S. aureus* had a greater influence on the elastic modulus and hardness of the cortical bone. At low concentrations, *S. aureus* infection produced a similar effect to that of high-concentration *S. epidermidis*, whereas at high concentrations, it produced the most severe damage to the mechanical properties of the tibia cortex of all groups.

## Discussion

In this study, aseptic inflammation and staphylococcal infection models were devised to explore the effect of inflammatory osteolysis on bone mass and biomechanical properties. Histopathological analysis showed that the distribution of gram-positive bacteria was denser in the high-concentration group than in the low-concentration group. Meanwhile, visual inspection of the medullary cavity revealed that *S. aureus* caused a more severe inflammatory response than did coagulase-negative *S. epidermidis*, suggesting that the presence of coagulase allows the bacteria to produce more intense tissue damage. Then, micro-CT scanning demonstrated the loss of bone mass in the tibia cortex caused by staphylococcal infection was more pronounced than that caused by Ti-wear particles. Moreover, high-virulence bacteria led to a lower bone mass than did the coagulase-negative staphylococci. These phenomena indicated that the inflammatory osteolysis caused by bacteria has more severe consequences than aseptic inflammation in the local bone microenvironment. Finally, nanoindentation measurements demonstrated that staphylococcal infection had a worse effect on the elastic modulus and hardness of the tibia cortex than Ti-wear particles, and a high concentration of *S. aureus* led to the worst inflammatory osteolysis-caused impairment of the biomechanical properties of the cortical bone. Taken together, these results indicate that staphylococcal infection leads to more severe bone loss than aseptic loosening.

Bone is a mineralised tissue that continuously undergoes dynamic change; osteoblasts, osteoclasts and osteocytes are three types of cells that work together to remodel the bone. Both aseptic loosening and prosthetic infection are able to stimulate the proliferation and differentiation of osteoclasts. The primary roles of osteoblasts are to synthesise the components of the bone matrix and to regulate osteoclast differentiation. Once osteoblasts were invaded by bacteria, they play a significant role in the initiation and maintenance of the immune response, which is complex and involves numerous cytokines and signalling pathways [30, 31]. Moreover, *S. aureus* can induce the secretion of soluble RANKL from osteoblasts, which in turn recruits osteoclasts and induces their differentiation, resulting in a marked reduction in bone mass and alteration of its biomechanical properties. In addition, osteoblasts have the capacity to survive bacterial infections and differentiate into osteocytes, which in turn may recruit leukocytes and phagocytes to the site of inflammation via the expression of cytokines [24]. Therefore, osteoclast activation combined with osteoblast apoptosis act in concert to reduce bone mass and impair its biomechanical properties.

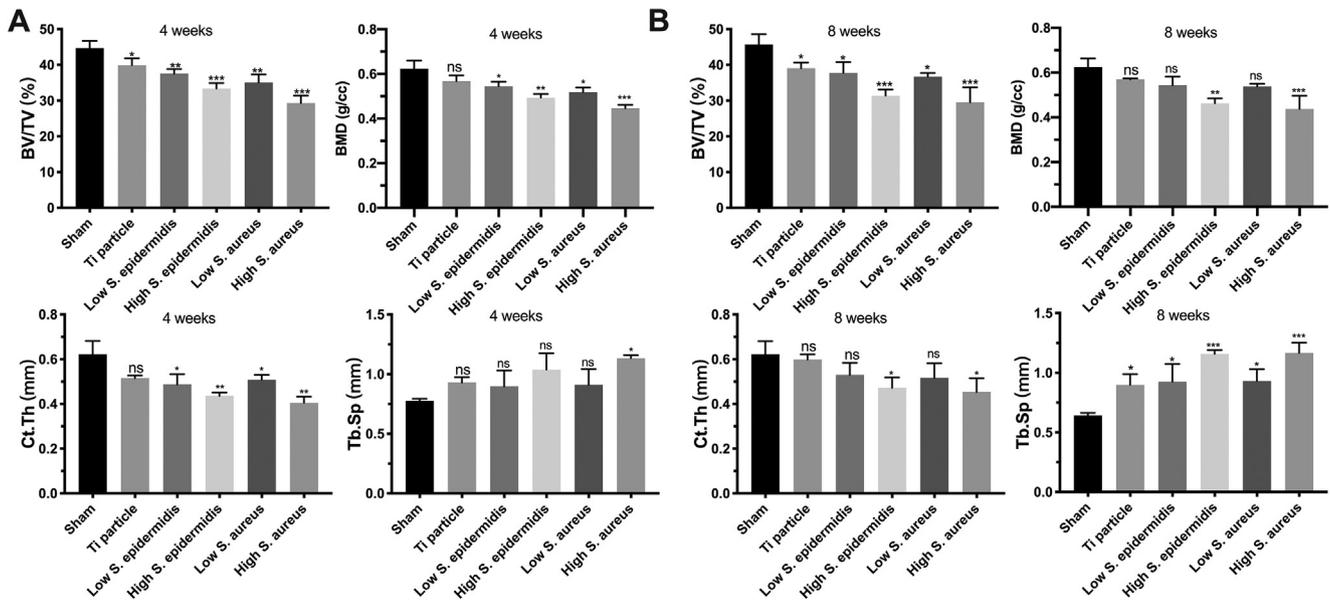
Aseptic loosening caused by wear particles is a persistent problem that limits the long-term success of arthroplasty. Studies over the past decades have elucidated the mechanism by which aseptic inflammation promotes osteoclast differentiation and reduces bone mass. For example, RANK–RANKL interaction was found to be the most important signalling pathway associated with wear particle-induced osteolysis [32,33]. Numerous proinflammatory cytokines such as TNF $\alpha$  and IL-1 are able to stimulate osteoclast differentiation via activation of the NF- $\kappa$ B signalling pathway. TNF $\alpha$  has been shown to have a key role in the pathogenesis of



**Figure 1.** Inflammatory response and bacterial load caused by titanium-wear particles and staphylococcal infection. Inflammatory response and bacterial load in the tibial medullary cavity of the rabbits (A) four weeks, (B) eight weeks after infection.

aseptic osteolysis and can act synergistically with RANKL to induce osteoclast differentiation. Similar to  $TNF\alpha$ , IL-1 has the capacity to directly target mononuclear osteoclast precursors and promote osteoclast differentiation (requiring RANKL to do so). Therefore,  $TNF\alpha$  and IL-1 are required but not sufficient for osteoclast differentiation. RANKL, its receptor RANK, and the antagonist molecule osteoprotegerin are essential for regulating osteoclast activity.

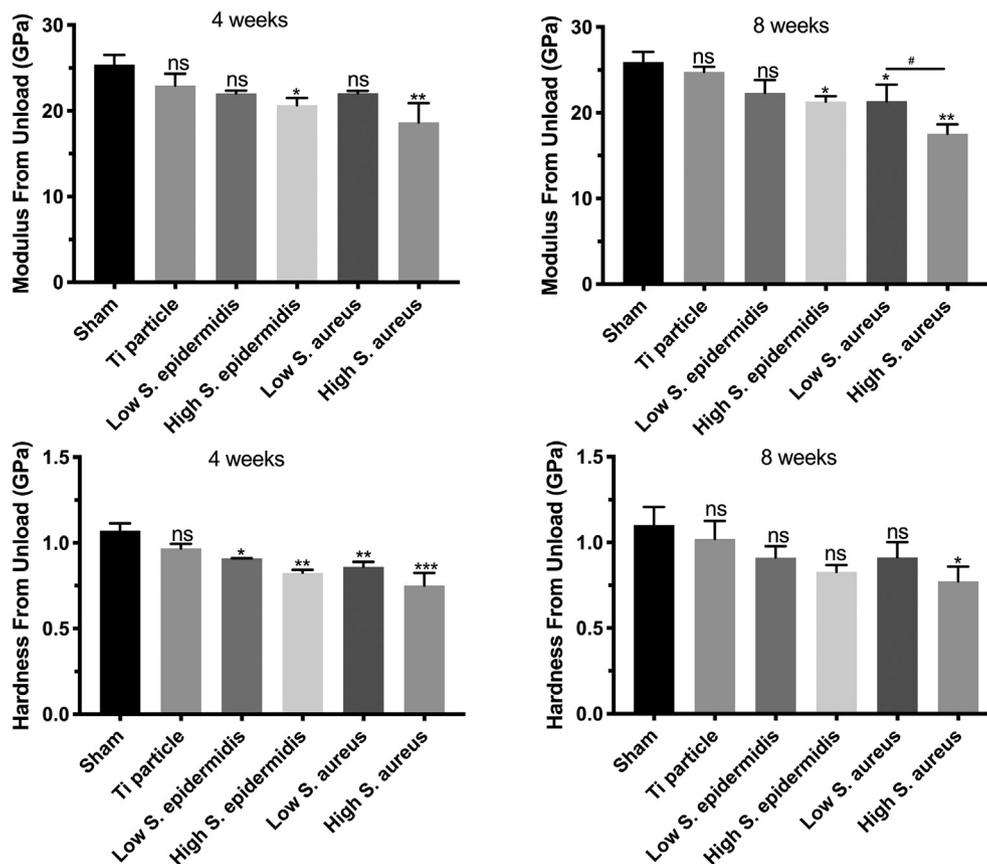
*S. aureus* is one of the most common coagulase-positive bacteria which is associated with orthopaedic device infections. The coagulase produced by *S. aureus* could protect it from phagocytosis and isolate it from other defences of the host. What is more, *S. aureus* not only causes tissue inflammation by producing a large amount of toxins and enzymes but also invades osteoblasts to affect bone metabolism. For example, *S. aureus* can produce a large amount of the pathogenic substance



**Figure 2.** Effect of titanium-wear particles and staphylococcus on bone microarchitecture. (A) Four weeks, (B) eight weeks after infection, the change in bone volume/tissue volume (BV/TV, %), bone mineral density (BMD, g/cc), cortical thickness (Ct. Th., mm), and trabecular separation (Tb. Sp., mm) were quantified by micro-computed tomography analysis.  $n = 5$ ,  $**p < 0.01$ , and  $***p < 0.001$  versus sham, “ns” means no significance compared with sham.

staphylococcal protein A, which promotes osteoclastic differentiation and fusion and enhances osteoclastic bone resorption. Staphylococcal protein A has been shown to suppress osteoblast proliferation, accelerate osteoblast apoptosis, and inhibit the process of bone mineralisation.

However, much less is known about the direct interaction between *S. epidermidis* and osteoclasts, although it is thought that *S. epidermidis* can induce the release of proinflammatory cytokines and enhance bone destruction in similar ways. The main pathogenic mechanisms of



**Figure 3.** Effects of titanium-wear particles and staphylococcal infection on biomechanical properties. Four and eight weeks after infection, the changes in the elastic modulus and hardness of the tibial cortex were quantified using nanoindentation tests.  $n = 5$ ,  $**p < 0.01$ , and  $***p < 0.001$  versus sham, “ns” means no significance compared with sham.

*S. epidermidis* are adhesion to host proteins and the formation of biofilm that acts as a shield against the host immune defence and antibiotics. Therefore, *S. epidermidis* is associated with prolonged infections; its cure rate (75%) is lower than that of *S. aureus* (84%) [34]. Taken together, a high concentration of *S. aureus* can activate a severe inflammatory response that leads to lower bone mass and biomechanical properties.

Bone mass and biomechanical properties are two important indicators of bone metabolism, which is mainly regulated by osteoclasts and osteoblasts. A good bone turnover rate can help increase the odds of revision surgery success and prolong the lifespan of the prosthesis. In contrast, abnormal bone metabolism is prone to cause aseptic loosening and prosthesis sinking after revision surgery. Our data indicated that it is necessary to evaluate bone mass and biomechanical properties before revision surgery because a better understanding of these two parameters will assist doctors in developing a reasonable treatment plan. For patients with inflammatory osteolysis caused by a high concentration of *S. aureus*, not only should the dead tissues be thoroughly removed but also local microfractures and cortical fractures during the revision operation should be avoided as well. This study also indicated that it is advisable for patients to take antiresorption drugs in the early postsurgical stage to reduce the risk of accidents. Even after revision surgery, patients with staphylococcal infections should continuously take antibiotics and antiresorption compounds to improve bone mass and biomechanical properties. In addition, our results indicated that proper surgical intervention is also important when deciding to perform revision surgery. For example, bone cement could be an excellent tool for the treatment of trabecular fractures caused by low bone mass because of its strong compressive force and weak shear and tension. However, the use of cortical grafts for additional strength support might be a reasonable option for cortical fractures owing to their abnormal biomechanical properties. Taken together, our data indicated that a more thorough evaluation of the bone mass and biomechanical properties before revision surgery could produce major benefits for the patients.

Although the bone mass and biomechanical properties have been examined as thoroughly as possible, several limitations ought to be noted in this study. First, prosthetic joints were not used in rabbits to construct aseptic loosening and prosthesis infection models. Suitable prostheses for rabbits are difficult to obtain, and the Ti-wear model for particle-induced aseptic inflammation has long been used in previous studies. Second, inflammation osteolysis caused by rheumatoid arthritis was not explored for the purpose of analysing bone mass and biomechanical properties. The success rate of constructing animal models is very low, and devising effective program-building models of rheumatoid arthritis in rabbits is difficult. Finally, models of bone loss because of fungal infections caused by orthopaedic implants have not been devised; however, such fungal infections are rare and are usually found in immunosuppressed patients. Nevertheless, a suitable model might be required to examine bone mass and biomechanical properties associated with fungal infection.

In conclusion, our results suggested that inflammatory osteolysis caused by staphylococcal infection produces more serious consequences than Ti-wear particles. Meanwhile, high concentrations of *S. aureus* caused the greatest loss in bone mass and impairment of biomechanical properties among the conditions tested. Our data indicate that it is necessary to perform a thorough assessment of the bone mass and biomechanical properties of patients before revision surgery, especially those with *S. aureus* infection. In addition, a better understanding of both these parameters might help develop an effective treatment regimen and reduce the risks associated with revision surgery.

#### Conflicts of Interest

The authors have no conflicts of interest to disclose in relation to this article.

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