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MINIREVIEWS

Silver nanoparticle technology in orthopaedic infections

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Abstract

The irrational and prolonged use of antibiotics in orthopaedic infections poses a major threat to the development of antimicrobial resistance. To combat antimicrobial resistance, researchers have implemented various novel and innovative modalities to curb infections. Nanotechnology involves doping ions/metals onto the scaffolds to reach the target site to eradicate the infective foci. In this connotation, we reviewed silver nanoparticle technology in terms of mechanism of action, clinical applications, toxicity, and regulatory guidelines to treat orthopaedic infections.

Key Words: Antimicrobial resistance; Biofilms; Silver; Nanoparticles; Orthopaedics

Core Tip: To overcome antimicrobial resistance, researchers explored the alternate technology to curb infections in musculoskeletal disorders. Nanotechnology forms an eye opener in the usage of silver nanoparticles to eradicate infections in osteoarticular system.

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INTRODUCTION

Globally, Orthopaedic infections pose a great challenge among orthopaedic surgeons and orthopaedic researchers. In the literature, the incidence of infection after orthopaedic surgeries was 1% to 2% in closed fractures and approximately 30% in open fractures[1]. Universally, there is no accepted classification for infection after orthopaedic surgeries. To overcome these infections, antibiotics were used irrationally which led to antimicrobial resistance (AMR) due to the development of biofilm by the micro-organisms[2,3]. Jefferson reported that biofilm formation is due to (1) protection from host defense; (2) colonization; (3) local environment benefits; and (4) planktonic cultures as *in vitro* artifacts[4]. Aparna *et al*[5] gave 5 stages of the growth cycle of a biofilm namely stage 1 – attachment phase, stage 2 – irreversible binding phase, stage 3 – maturation 1 phase, stage 4 – maturation 2 phase, and stage 5 – cellular dispersion phase.

In humans, 80% of microbial infections are due to non-healing chronic wounds, osteomyelitis, prosthesis- and implant-related infections, endocarditis, rhinosinusitis, and cystic fibrosis[6-9]. Literature states that both gram-positive and gram-negative bacteria form biofilms on the surface of medical devices which are *E. faecalis, S. aureus, S. epidermidis, S. viridans, E. coli, K. pneumoniae, P. mirabilis*, and *P. aeruginosa*[10]. Out of all these organisms, *S. aureus* and coagulase-negative staphylococci pose a greater risk of forming biofilms in orthopaedic implants[11,12], whereas *P. aeruginosa* sustain and survive in harsh environments and forms a resistant biofilm[13].

With the rise of AMR, antibiotic prophylaxis has become ineffective in curbing infections. Novel techniques such as nanomedicine, bacteriophage therapy, antimicrobial peptides, sonic therapies, scaffold-loaded nanoparticles, antimicrobial adjuvants in the form of silver, electrical and electromagnetic methods, bioacoustic effects, surface modification of biomaterials, antimicrobial photodynamic therapies, biosensors, hyperbaric oxygen, and fecal microbiota transplantation have been introduced to combat AMR[10,14,15]. With the profound literature evidence of the antimicrobial property of silver (Ag), nanotechnology experts doped nanoparticles (NP) with Ag for targeted drug delivery and enhanced interaction with the surrounding environment to curb biofilm-producing organisms[16]. In this article, the usage of AgNP in curbing orthopaedic infections is narrated.

AGNP TECHNOLOGY

In literature, Ag has been identified to have antimicrobial properties[17-19], but in recent years clinicians have demonstrated this property in various clinical conditions. The oligodynamic action of Ag refers to the toxic nature of metal ions on microbes by integrating with microbial deoxyribonucleic acid (DNA)[20-22]. Few studies have emphasized the precipitation of DNA within the microbial cell[23]. Ag exerts antibacterial action by inhibiting cell wall synthesis[24,25].

Recent technologies use NP to load Ag ions which may be used as an antimicrobial agent in a target-specific manner [23]. AgNP permeates into cells and interferes with the enzymes of bacterial respiratory chains to inhibit ATP production and growth of the bacteria[16,26]. The particle size of AgNP determines the bactericidal activity. 10-nm Ag demonstrates the complete bacterial interaction, henceforth AgNP exerts a higher bactericidal effect[27]. The mechanism of action of AgNP in infections is as follows (as depicted in Figure 1).

Direct contact with microbes through leakage of cellular contents and bacterial death due to the damage of cell membrane and higher production of reactive oxygen species and free radical species, release of Ag+ ions through interaction with sulfhydryl groups (cysteine) in cell wall proteins and enzymes, induction of bacterial death when Ag^+ ions in AgNPs by bombarding the electron transport chain in bacterial mitochondria. Entering of Ag+ ions into periplasmic space which leads to the separation of the cytosol from the cell membrane, occurrence of cellular pits after the exposure of Ag+ ions, inhibition of ribosomal functions leading to enhanced ROS production, malformation of proteins resulting in improper DNA function, antibiofilm activity of AgNPs, and dose-dependent cytotoxic and genotoxic effects of AgNP on osteoblasts and impaired cellular viability of AgNPs at 10 μg/g.

To impart biocompatibility of AgNP in musculoskeletal tissues: (1) Biosynthesis process from bacteria, yeast, and fungi; (2) physical property adjustment; and (3) biomolecule combinations can be tried.

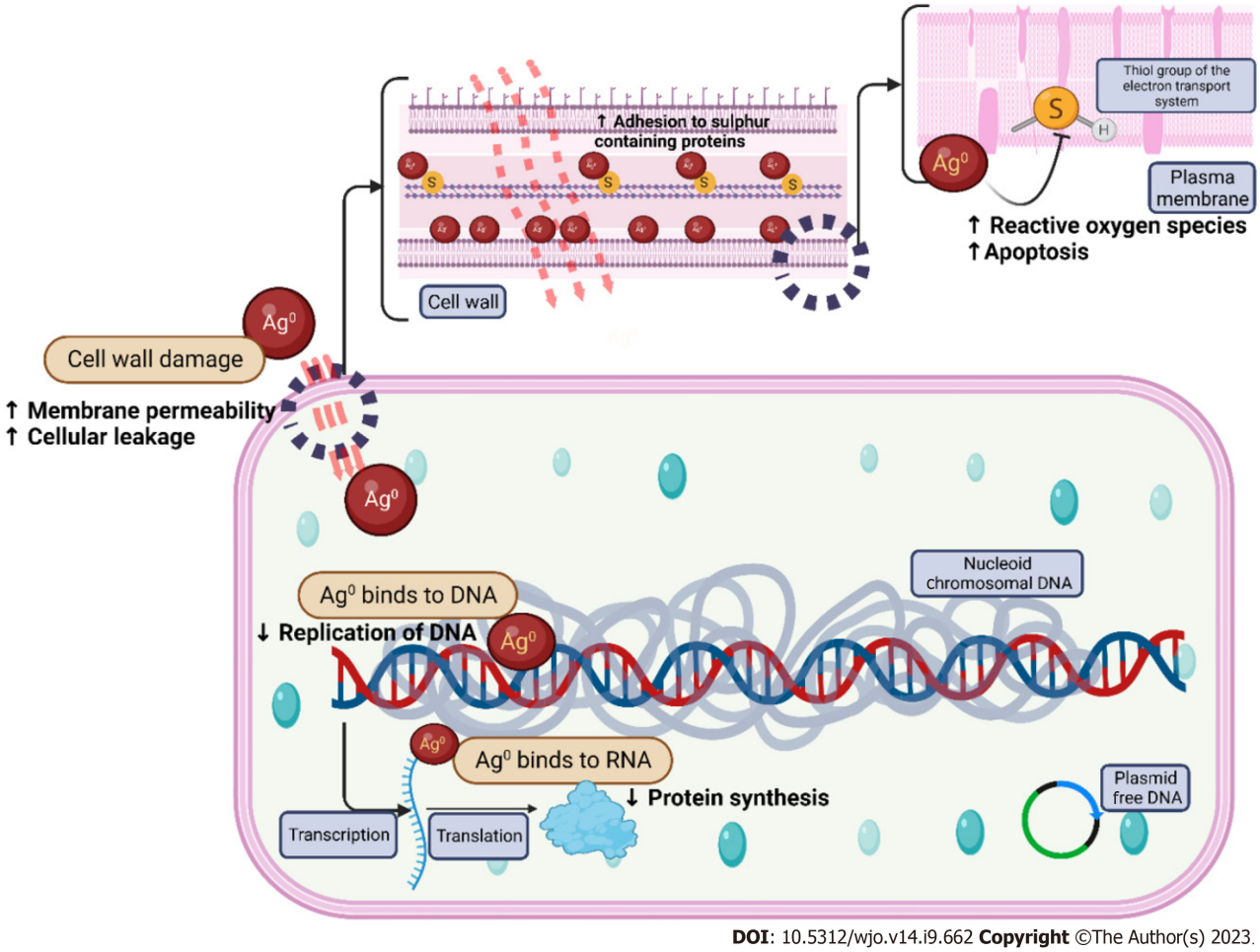

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Figure 1 Mechanism of action of silver nanoparticles. DNA: Deoxyribonucleic acid.

AGNP IN ORTHOPAEDIC INFECTIONS

Recently, the modification of orthopaedic implants with the application of AgNPs on the surface leads to the prevention of implant-associated infections. With the availability of AgNP-coated external fixators, mega prostheses, and AgNP-coated bone cement, orthopaedic infections are showing a downtrend. Since AgNP-coated orthopaedic implants demonstrate antimicrobial activity, the specific molecular mechanism of osteogenic-related cells warrants an understanding. Due to dose-dependent cytotoxicity, the effect of AgNP on osteoblast and osteoclast is controversial. Aurore *et al*[28] demonstrated the bactericidal effect of AgNP against non-virulent E.coli and virulent MRSA at non-toxic concentrations. Macrophage polarization towards the M1 phenotype enables the cells to kill the engulfed microorganisms. Elevated reactive oxygen species (ROS) responses were found in AgNP-treated osteoclasts. The modification of orthopaedic implants by using AgNPs enhances antimicrobial effects through plasma immersion ion implantation (PIII), magnetron sputtering, plasma electrolytic oxidation, and 3DP-Ag-containing scaffolds[16].

Tumor prosthesis: In orthopaedic oncology, peri-prosthetic infection rates from 9% to 29%. Due to the immunosuppressive environment, this group of patients is more prone to infection than arthroplasty patients. Gosheger *et al*[29] demonstrated a superior antimicrobial effect with a silver-coated mega prosthesis (7% infection rate) than titanium prosthesis (47% infection rate) in a rabbit model. Ag coated group showed fewer signs of inflammation as measured by ESR, CRP, and neutrophil count. In sarcoma patients, Hardes *et al*[30] observed 17.6% of infection in the non-silver coated mega prosthesis group than 5.6% of infection in silver coated mega prosthesis group. About 38.5% of cases of amputation in the non-silver-coated mega prosthesis group were due to deep infections whereas no case of amputation was reported in the silver-coated mega prosthesis group. Hence, silver-coated mega prosthesis reduces the risk of further infection in oncology cases as they are already in an immunocompromised state. However, large-scale blinded controlled trials have to prove the safety and efficacy of infection prevention with the silver-coated prosthesis in orthopaedic oncological cases.

External fixator pins: Pin tract infections mount for 42% of orthopaedic infections which results in loosening of the implant, fracture non-union, and osteomyelitis. An in-vitro study demonstrated a 3-log step reduction of *S. epidermidis* biofilm producers when incubating the stainless steel pins coated with AgNP compared with titanium and copper pins for 20 h (9). Wassall *et al*[31] revealed the antimicrobial effects of Ag in Ag-coated pins with the significant reduction of adhesion of *E. coli, P. aeruginosa*, and *S. aureus* when compared with normal stainless steel pins. Loosening of external fixator pins was less frequently found with Ag-coated pins. Hence silver inhibits microbial adhesion by inhibiting the formation of the glycocalyx on the surface of the pins.

Osteomyelitis and infected non-union: Ag ionophoresis act as an adjunct treatment option for osteomyelitis and infection in non-union of fractures. The continuous inflow of electrically driven Ag into the infective foci curbs the infection and promotes the environment for tissue regeneration. At the end of 3 mo follow-up, radiographic and histological analysis revealed neo-osteogenesis in a 6 mm critical bone defect in the femoral diaphysis of rats managed with bone graft with BMP-2 coupled with AgNP and poly lactic-co-glycolic acid (PLGA) scaffold injected with 10 CFUs of vancomycin-resistant MRSA[32]. Microbial elimination with 2% Ag NP coupled with composite bioscaffold resulted in fracture union.

Bone cement: Alt *et al*[33] proved that nanosilver-coated cement produced a high index of antimicrobial activity against *S. epidermidis*, MRSE, and MRSA. Tiopronin, a stabilizing agent, coupled with AgNP in bone cement expressed a good antimicrobial efficacy without displaying any cement-related cytotoxicity[34]. AgNP coated bone cement resulted in antibacterial activity against MRSA and decrease the formation of polymer debris in joint replacement[35].

TOXICITY OF AGNP

Though nanotechnology poses a greater advantage in clinical applications, a considerable note of precautions and toxic effects are observed with AgNP. The interaction of AgNP with biological media leads to Ag agglomeration and dissolution. Doping of Ag into NP results in the induction of toxic responses. The failure of protective coatings on NPs to prevent aggregation in biological fluids leads to AgNP instability. In vitro and *in vivo* AgNP studies demonstrated the induction of lung fibroblasts, genotoxicity, chromosomal aberrations, DNA damage, and apoptosis of cells. There is only limited evidence for carcinogenicity in any biological tissues.

The interaction of human alveolar basal epithelial cells with AgNP results in the generation of reactive oxygen species, reduction of mitochondrial membrane potential and cellular viability, and enhance cellular apoptosis. Exposure to higher concentrations of AgNP in human cell lines induces not only cellular apoptosis but also induces cellular morphology and genetic mutations. The toxicity of AgNP has been demonstrated in microbes ranging from bacteria, viruses, fungi, and algae. AgNP molecules penetrate the skin and blood tube of zebrafish larvae in aggregate form whereas it induces heat shock, oxidate stress, and DNA damage in *Drosophila melanogaster*.

AgNP technology is associated with developmental abnormalities in zebrafish embryos, cytotoxic, and genotoxic effects with systemic immunosuppression. AgNP-mediated cytotoxicity with 10 μg/g is observed on primary human MSCs and osteoblast cells[36]. In zebrafish, AgNP induced neurotoxicity and persistent abnormal behavior[36]. Cytotoxicity of AgNP depends on the particle size of Ag. Literature has documented the cytotoxic effects of Ag of 24 nm causing an intrinsic pro-inflammatory response and apoptosis of surrounding cells[36].

Drake *et al*[37] and Lansdown[38] have done an extensive review of the exposure-related health effects of silver and its related compounds in health. The evidence of toxic effects and complications of AgNP in human studies is limited. Silver represents occupational health hazards like argyria in long-term exposure[37]. The critical oral dosage of silver varies for every individual. The accumulation of silver and nanosilver particles occur in the liver, spleen, kidney, nails, and mucous membranes[39]. With the topical application of Ag, the risk of percutaneous absorption is very low as the epidermis is a relatively impenetrable barrier[40]. Munger *et al*[41] performed a cross-over time exposure study with oral AgNP (5-10 mm) and demonstrated no change in metabolic, hematologic, physical, or morphological findings. However, the toxicity of AgNP in humans is understudied.

Due to the increase of AgNP usage in the market, governmental regulations in the United States [Environment Protection Agency on the nanomaterials regulation], European Union [European Strategy for Nanotechnology], and Canada [Health Canada and Environment Canada] have been implemented[42]. These agencies mentioned that the size of AgNP must be ranging from 1–100 nm in at least one spatial dimension[42]. No specific occupational exposure limits have been laid by these governmental agencies on AgNPs. Global organizations focus on the safety and sustainability of AgNPs in the market for optimal benefits in the community.

RECENT ADVANCES IN AGNP TECHNOLOGY

With the introduction of new fabricating methods, the toxic effects of AgNP are minimized in the microenvironment[43]. Doping of copolymers and growth factors with AgNPs is more effective in hastening wound healing. Green-synthesized AgNPs are cheaper and eco-friendly for the desired environment. The phytochemicals to be doped with AgNPs have to be characterized and seek appropriate regulatory approvals before commercializing the product for preclinical and clinical studies[44,45]. The addition of electrospun nanofibers along with AgNP offers a great advantage in curbing the infection along with debridement and antibiotics. Once the wound is healed, such electrospun nanofibers provide a naïve extracellular matrix in the newly regenerated tissues[46].

With the evolution of 3-D printing technology, the fabrication of scaffolds with Ag coating prevents infections in complex orthopaedic cases[47,48]. 3D scaffolds with porous structures are ideal for loading biomolecules and ions for targeting the desired site. Doping of AgNP into scaffolds with antimicrobial activity and biocompatibility properties in musculoskeletal tissues aids in curbing infection and promoting tissue regeneration as depicted in Figure 2.

3D bioprinting technology dispenses “bio-inks” which contain cells with regenerative potential, scaffolds doped with metal/ion nanoparticles, and biomicromolecules in a temporospatial controlled fashion[49,50]. Such bio-inks with antimicrobial properties aim at uprooting the infection and facilitating the regeneration of tissues. Damle *et al*[51] proved the proliferation and differentiation of mesenchymal stromal cells when doped with AgNPs which gave further insights in

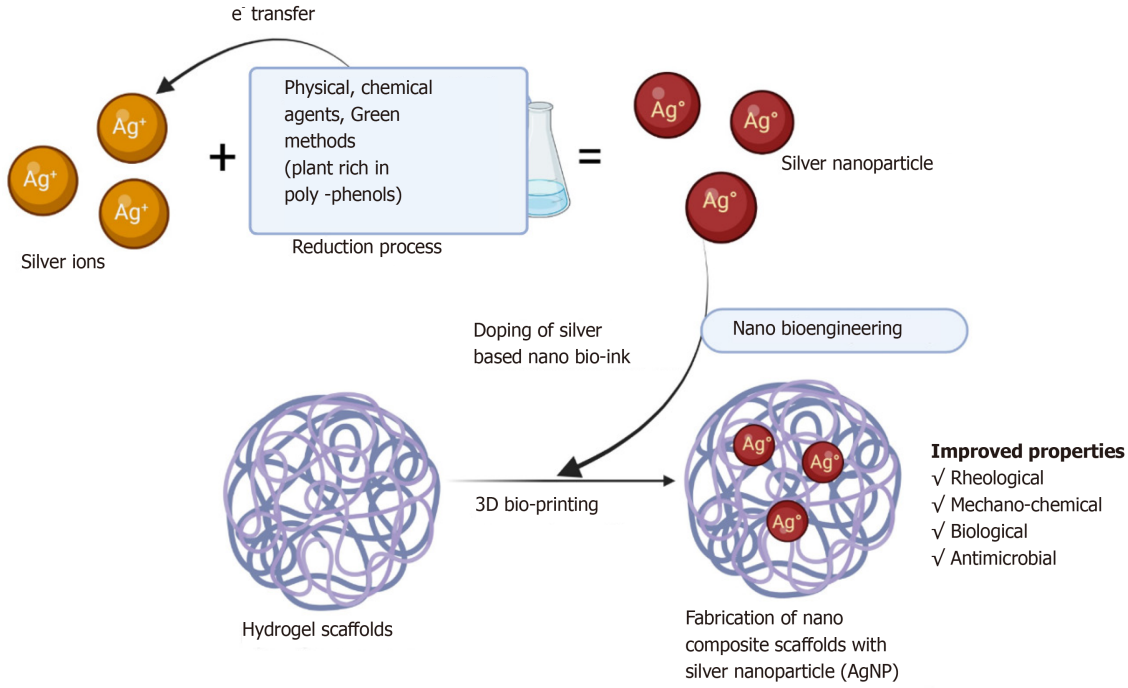

Figure 2 Doping of silver nanoparticles in scaffolds.

osseous tissue engineering. The concept of "Smart Coating" depends on light responsiveness, temperature responsiveness, pH responsiveness, and piezo responsiveness for improving osseous integration, inhibting biofilm formation, and preventing post-operative complications associated with orthopaedic infections[52].

CONCLUSION

In orthopaedics, AgNP technology has the potential to reduce implant-related orthopaedic infections. Doping AgNP with scaffolds and bio-inks must adhere to the regulatory guidelines to avoid toxicity in clinical applications. With the evidence of preclinical studies, large-scale blinded controlled trials on AgNP in orthopaedic infections have to be assessed for further validation.

FOOTNOTES

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ORIGINAL ARTICLE

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Formation process of extension knee joint contracture following external immobilization in rats

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Abstract

BACKGROUND

Current research lacks a model of knee extension contracture in rats.

AIM

To elucidate the formation process of knee extension contracture.

METHODS

We developed a rat model using an aluminum external fixator. Sixty male Sprague-Dawley rats with mature bones were divided into the control group (n = 6) and groups that had the left knee immobilized with an aluminum external fixator for 1, 2, and 3 d, and 1, 2, 3, 4, 6, and 8 wk (n = 6 in each group). The passive extension range of motion, histology, and expression of fibrosis-related proteins were compared between the control group and the immobilization groups.

RESULTS

Myogenic contracture progressed very quickly during the initial 2 wk of immobilization. After 2 wk, the contracture gradually changed from myogenic to arthrogenic. The arthrogenic contracture progressed slowly during the 1st week, rapidly progressed until the 3rd week, and then showed a steady progression until the 4rd week. Histological analyses confirmed that the anterior joint capsule of the extended fixed knee became increasingly thicker over time. Correspondingly, the level of transforming growth factor beta 1 (TGF-β1) and phosphorylated mothers against decapentaplegic homolog 2 (p-Smad2) in the anterior joint capsule also increased with the immobilization time. Over time, the cross-sectional area of muscle fibers gradually decreased, while the amount of intermuscular collagen

and TGF-β1, p-Smad2, and p-Smad3 was increased. Unexpectedly, the amount of intermuscular collagen and TGF-β1, p-Smad2, and p-Smad3 was decreased during the late stage of immobilization (6-8 wk). The myogenic contracture was stabilized after 2 wk of immobilization, whereas the arthrogenic contracture was stabilized after 3 wk of immobilization and completely stable in 4 wk.

CONCLUSION
This rat model may be a useful tool to study the etiology of joint contracture and establish therapeutic approaches.

Key Words: Knee joint; Immobilization; Contracture; External fixator; Rats

Core Tip: Current research lacks a model of knee extension contracture in rats. The study elucidated the formation process and therapeutic strategies of knee extension contracture. To this end, we developed a rat model using an aluminum external fixator. The results showed that the myogenic contracture was stabilized after 2 wk of immobilization, whereas the arthrogenic contracture was stabilized after 4 wk of immobilization. This rat model may be a useful tool to study the etiology of the joint contracture and establish therapeutic approaches.

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INTRODUCTION

Knee contracture is currently one of the most common clinical diseases and is characterized by joint capsule fibrosis and a restricted range of motion (ROM) secondary to periarticular intermuscular connective tissue hyperplasia[1]. The signature pathology of joint contracture is the proliferation of myofibroblasts (active fibroblasts) and the deposition of proteins in the extracellular matrix in the joint capsule and intermuscular connective tissue[2]. The most common cause of knee contracture is prolonged immobilization, which is clinically used as an acute treatment for musculoskeletal disease to relieve knee pain and reduce inflammation[3,4]. Knee contracture is unsightly and has adverse effects on function and quality of life, affecting daily activities such as ascending and descending stairs, walking, and toileting. Furthermore, knee contracture is very difficult to treat[5]. Despite a large amount of rehabilitation, conservative treatment, and even surgical treatment, it is difficult to completely restore the joint mobility, and this loss of mobility seriously decreases the quality of life of patients and adversely affects the distribution of medical resources in society[6,7]. It is therefore very important to investigate the mechanisms leading to knee contracture.

The contracture mechanism has been explored in many studies. As early as 1993, a rat flexion contracture model was successfully established by fixing the tibia and fibula in complete flexion (150) for up to 7 wk without damaging the joints [8]. In recent years, various immobilization methods have been introduced to create flexion contracture models by fixing the animal knee joint at about 150 of flexion, including hook buckle (a hook-and-loop fastener) immobilization and helix (spiral wire) immobilization[9,10]. By contrast, extension contracture models are rare. However, the extension contracture model is of clinical relevance because it better mimics fracture and bed-associated immobilization than the flexion contracture model.

According to the general international standard, the neutral position of the knee joint is the straightened or extended position, which is defined as 0. The functional position of the knee joint is from 15 to 20 of flexion, while the ROM of the normal knee is 120 to 150 for flexion and 5 to 10 for overextension. Knee injury usually requires immobilization in a straightened or functional position, but this type of immobilization may result in limited knee flexion motion (knee extension contracture); therefore, knee extension contracture is the most common type of knee contracture. Different fixation methods have different effects on muscles. If the muscle is fixed under the condition of being lengthened, its atrophy and the decrease of muscle contraction force will be less, and the ratio of fast and slow muscles of biceps femoris, which is often selected as the detection index of flexion knee contracture model, is also different from that of quadriceps femoris; however, the current literature describes several animal knee contracture models, most of which involve flexion knee contracture. The structure of the knee joint of rats is similar to that of humans and is easier to obtain compared to other animals. Thus, it is necessary to establish a convenient and reliable rat model of knee extension contracture.

In the present study, we studied the process of knee extension contracture formation during external fixation of the knee in a straightened position in a rat model that we developed. To the best of our knowledge, this is the first report of a rat model of knee extension contracture.

MATERIALS AND METHODS

A rat model of knee extension contracture

Male Sprague-Dawley (SD) rats (age 8 wk and weight 350 g +) were used in this experiment. Aluminum splints (6061; Longkai, Suzhou, China), sponge (33 d; Changzhou, China), and woodworking (BND-2815; Bonida, Guangdong, China) were prepared. The rats were kept under the same conditions without intervention for 2 wk before the experiment (free diet, day and night balance, temperature 20-25 ℃, humidity 50% ± 5%). Each rat was placed on the operating table in the supine position and fixed. The fixing device and fixing schematic diagram is shown in Figure 1. Figure 2A shows the results of applied fixation. Figure 2B shows the anterior X-ray of the rat knee joint, while Figure 2C shows the lateral X-ray of the rat knee joint. Immobilization was performed under general anesthesia achieved with an intraperitoneal injection of 10% chloral hydrate (0.03 mL/kg). A patent application has been made for the self-made aluminum splint (Patent No. ZL202120470158.0).

Measurements of the knee joints of 8-wk-old male rats (n = 15) revealed that the average thigh width was 3.23 cm ± 0.21 cm (range 6.38 ± 0.41 to 7.21 cm ± 0.43 cm) and the average calf width was 4.86 cm ± 0.27 cm (range 2.34 ± 0.13 to 5.11 cm ± 0.36 cm). In accordance with the anatomical characteristics of the rats, the immobilization device was shaped using a wire cutting process with an aluminum plate and bonded with a 0.5-cm-thick sponge on the skin to prevent excessive immobilization. The shape of the aluminum plate is shown in Figure 1. The fixation device placed the knee joint in the straightened position and ensured complete external immobilization of the knee joint. The animal experiments described in this study were authorized by the Experimental Animal Ethics Committee of Anhui Medical University (No. LLSC20221126).

Grouping and specimen collection

Sixty rats were randomly divided into 10 groups (n = 6 in each group). The control group did not do any intervention. while the immobilization groups had the left hindlimb fixed for 1 d (immobilization-1 d group), 2 d (immobilization-2 d group), 3 d (immobilization-3 d group), 1 wk (immobilization-1 wk group), 2 wk (immobilization-2 wk group), 3 wk (immobilization-3 wk group), 4 wk (immobilization-4 wk group), 6 wk (immobilization-6 wk group), and 8 wk (immobilization-8 wk group). All groups were reared in the same environment, and the ROM of the knee joint was measured on the same day as the 8-wk-fixed group after controlling the fixed time. The rats in the appropriate group were euthanized by an excessive intraperitoneal injection of 10% chloral hydrate. After euthanasia, the fixed left hindlimb of the rat was removed at the hip joint. The skin was separated, and the knee mobility was measured using the measurement device designed for this experiment (Figure 3). Then the muscles were separated. The rectus femoris was divided into two parts: one part was frozen at -80 ℃ for protein molecular weight detection, while the other part was fixed in 4% paraformaldehyde for Sirius red staining. Knee mobility was measured after the separation of the muscles. The anterior joint capsule was divided into two parts: one part was frozen at -80 ℃ for protein molecular weight detection, while the other part was fixed in 4% paraformaldehyde for hematoxylin and eosin (H&E) staining. During the experiment, the rats were free to move within the cage with the immobilization device attached.

Measurement of joint mobility

A joint mobility meter was used to measure the joint motion of the left knee of 60 SD rats (Figure 3). The Kirschner wire was penetrated from the femoral neck parallel to the femur. Fixed the cruzi needle by magnetic suction removable metal clamp. The distal tibia was secured to the turntable with disposable plastic ties. The digital force gauge was secured to the slide. On the base of the equipment was a rope attached to the groove of the turntable and a digital dynamometer. The turntable moved when the drive wheel was turned to indirectly turn the tibia while the femur was stationary. The applied force was displayed on the screen of the digital force meter, and the angular change between the femur and tibia (the disk radius, the force arm) was constant and was calculated according to the scale of the turntable. Therefore, the force moment and the force size showed a linear relationship. The moment size and the angle also had a corresponding relationship. The applied torque was calculated by multiplying the force by the constant radius of the disk. Knee ROM was measured with 5.3 N-cm as the standard torque. This torque brings the knee close to its physiological limit but does not damage the soft tissue[11-13]. The mobility of each left knee was measured three times by two researchers, giving six measurements. The knee ROM before and after myotomy was measured to yield the total, myogenic, and arthrogenic contracture using a previously described method[14]. (1) Degree of total contracture = ROM before myotomy (knee joint in the control group)-ROM before myotomy (knee joint in the immobilization group); (2) degree of arthrogenic contracture = ROM after myotomy (knee joint in the control group)-ROM after myotomy (knee joint in the immobilization group); and (3) degree of myogenic contracture = degree of total contracture-degree of arthrogenic contracture. A patent application has been made for the self-made joint mobility meter (Patent No. ZL202120996643.1).

Histological evaluation

Specimens used for joint mobility assessment were used to evaluate the histology of the knee joint. After the ROM measurements, the left rectus femoris and anterior knee joint capsule were fixed in 4% paraformaldehyde (pH 7.4) at 4 ℃ for approximately 36 h. The specimens were embedded in paraffin. The rectus femoris specimens were cut into 5-μm coronal sections, while the joint capsule specimens were sectioned into 5-μm sagittal sections.

Sirius red staining

Rectus femoris sections were stained with Sirius red solution for 1 h (2610-10-8; Solarbio Life Science, Beijing, China) and rinsed with running water to remove the surface dye. Nuclei were stained with Mayer's hematoxylin solution for 8 to 10

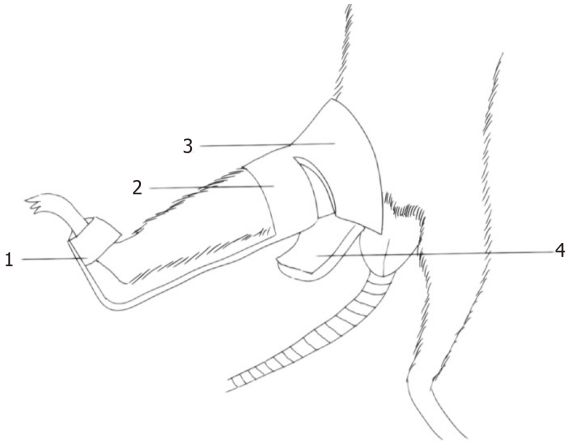

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Figure 1 Knee joint fixation device. Immobilize the back of the rat's distal foot to prevent the rat's lower limb from slipping out of the immobilization device. Immobilize the periphery of the rat knee joint. Above the knee joint of the rat is an inverted conical structure, and this design fixes the periphery of the femur of the rat. Appropriate bending under the rat femur provides a lever fulcrum action. (1) Immobilize the back of the rat's distal foot to prevent the rat's lower limb from slipping out of the immobilization device. (2) Immobilize the periphery of the rat knee joint. (3) Above the knee joint of the rat is an inverted conical structure, and this design fixes the periphery of the femur of the rat. (4) Appropriate bending under the rat femur provides a lever fulcrum action.

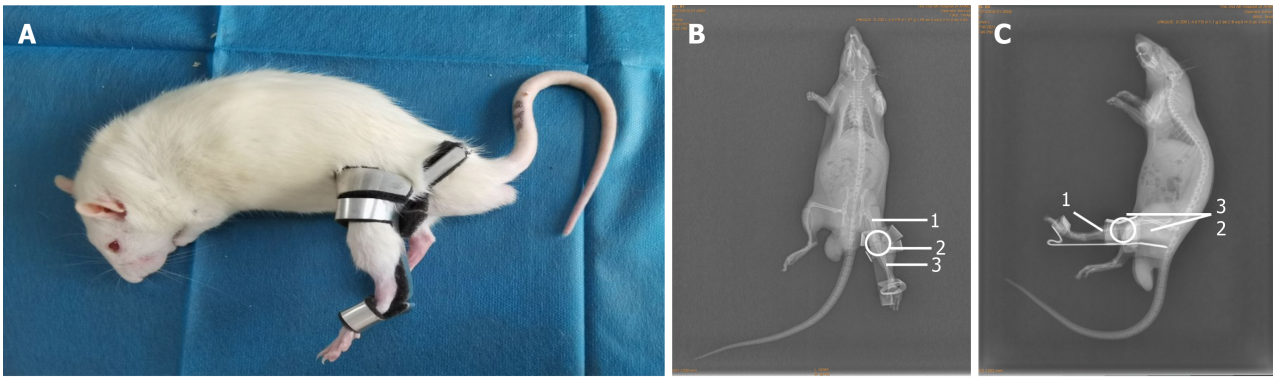

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Figure 2 Fixed schematic diagram. A: Fixed picture; B: X-ray orthotopic slice of rat knee joint after immobilization; C: X-line lateral tablet of rat knee joint after immobilization. [1]Femur; [2]Knee; [3]Tibia.

min and flushed with running water for 10 min. Sections were then conventionally dehydrated and sealed with neutral gum. The muscle collagen fiber density and muscle fiber cross-sectional area for each region were assessed using ImageJ software version 1.53a (National Institutes of Health, Bethesda, MD, United States, available at https://imagej.nih.gov/ij/). Histological analysis was performed on six rats in each group, with three slides for each rat.

H&E staining

The joint capsule sections were stained with H&E using the following steps. (1) Paraffin sections were dewaxed and then placed in xylene I for 10 min, xylene for 10 min, anhydrous ethanol I for 5 min, anhydrous ethanol for 5 min, 95% alcohol for 5 min, 90% alcohol for 5 min, 80% alcohol for 5 min, 70% alcohol for 5 min, and finally washed with distilled water; (2) Sections were stained with harris hematoxylin for 3-8 min, rinsed with tap water and differentiated with 1% ethanol hydrochloride for several seconds, and then rinsed with tap water again. The sections were returned to blue with 0.6% ammonia and rinsed with running water; (3) Sections were stained in eosin solution for 1-3 min; (4) To attain the dehydration seal, the sections were placed in 95% alcohol I for 5 min, 95% alcohol II for 5 min, anhydrous ethanol I for 5 min, anhydrous ethanol II for 5 min, xylene I for 5 min, and xylene II for 5 min; the sections were then removed from the xylene to dry and were sealed with neutral gum; and (5) Microscopic examination, image acquisition, and histological analysis were performed on six rats in each group, with three slides for each rat.

Immunohistochemistry

The following steps were used to prepare the articular capsule sections by immunohistochemistry. (1) Paraffin sections were dewaxed in the same way as H&E staining; (2) The 3% hydrogen peroxide was dropped onto the slice tissue, incubated at room temperature for 15 min, and washed with phosphate-buffered saline (PBS) for 3 times, 3 min each time; (3) After wiping the slide dry, the diluted normal goat serum was added and the slide was sealed at room temperature for

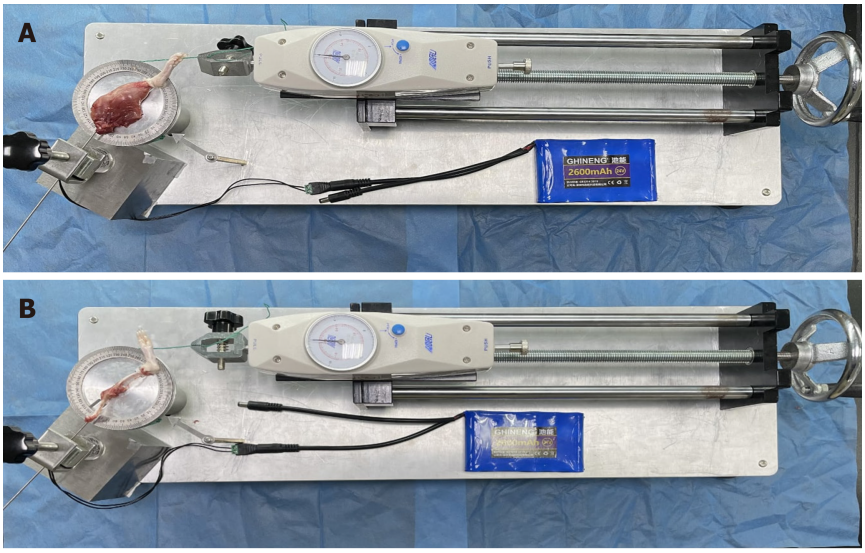

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Figure 3 Joint mobility meter. A: Peeling range of motion (total contracture) measurement; B: Measuring range of motion after muscle separation (arthrogenic contracture).

30 min; (4) The first antibody was added and incubated in a wet box at 4 ℃ overnight (15 h); (5) After PBS washing, the sections were dried with absorbent paper, and streptavidin-horseradish peroxidase conjugate labeled goat anti rabbit/mouse secondary antibody was added and incubated at 37 ℃ for 30 min; (6) After PBS washing, the PBS solution was removed and 3,3'-diaminobenzidine color developing solution was freshly prepared and added to each slice; (7) Mayer's hematoxylin re-staining was performed; and (8) Finally, dehydration and sealing, microscopic examination, image collection and histological analyses were performed the same way as H&E staining.

Proteomics analysis of muscle and joint capsule

Protein immunoblotting (western blotting) was performed as follows. Total protein was extracted from the retained muscle and joint capsule samples. When 50-60 mg rectus femoris muscle was taken, the total tissue protein was extracted with 600 mL radio immunoprecipitation assay (RIPA) reagent (Tris-HCl [pH 7.4], 150 mmol/L NaCl, 1 mmol/L ethyleneiamineetraacetic acid, 1% Triton X-100, 1% sodium deoxycholate, 0.1% sodium dodecyl sulfate [SDS], and 1 mmol/L PMSF), and a protease inhibitor was added to the RIPA. Total proteins were separated by SDS-polyacrylamide gel electrophoresis and transferred to the polyvinylidene difluoride (PVDF) membrane. The PVDF was washed and immersed in 5% skim milk for 4 ℃ overnight. Membranes were incubated with anti-rat monoclonal antibody (1:10000-50000, cell signaling, United States) for 2 h at room temperature, and then washed three times with a Tris-buffered saline with 0.1% Tween 20 (TBST) solution (10 min/wash). The washed PVDF membrane was incubated with horseradish peroxidase-labeled goat anti-rat immunoglobulin G antibody (1: 10000-50000; Cell Signaling, Danvers, MA, United States) for 1 to 2 h at room temperature, washed with TBST (as described above), and then detected with enhanced chemiluminescence light-emitting liquid colored with energy autoexposure. The developing bands were analyzed by IPP software.

Statistical analysis

The results are expressed as the mean ± standard deviation. One-way analysis of variance was used to test the difference between groups. $P < 0.05$ was statistically significant. Statistical analyses were performed using IBM SPSS statistics software, version 22 (IBM Corp., Armonk, NY, United States).

RESULTS

Three rats in the immobilization-6 wk group experienced slippage of the immobilization device in the 2nd week of immobilization; the immobilization device was fixed the same day as the slippage occurred, and there was no further slippage until the end of the immobilization period. There was no death, lower limb necrosis, or other complications in any group.

Total contracture, myogenic contracture, and arthrogenic contracture

After 1 wk of immobilization, the degree of total contracture significantly differed between the control group and the immobilization groups (all $P < 0.05$). Compared with the immobilization-1 d, -2 d, and -3 d groups, the degree of total contracture was significantly greater in the immobilization-1 wk, -2 wk, -3 wk, -4 wk, -6 wk, and -8 wk groups (all $P < 0.05$). Total contracture degree was not significantly different between certain adjacent immobilization groups, *i.e.* between the immobilization-1 d and -2 d, immobilization-2 d and -3 d, immobilization-3 wk and -4 wk, immobilization-4

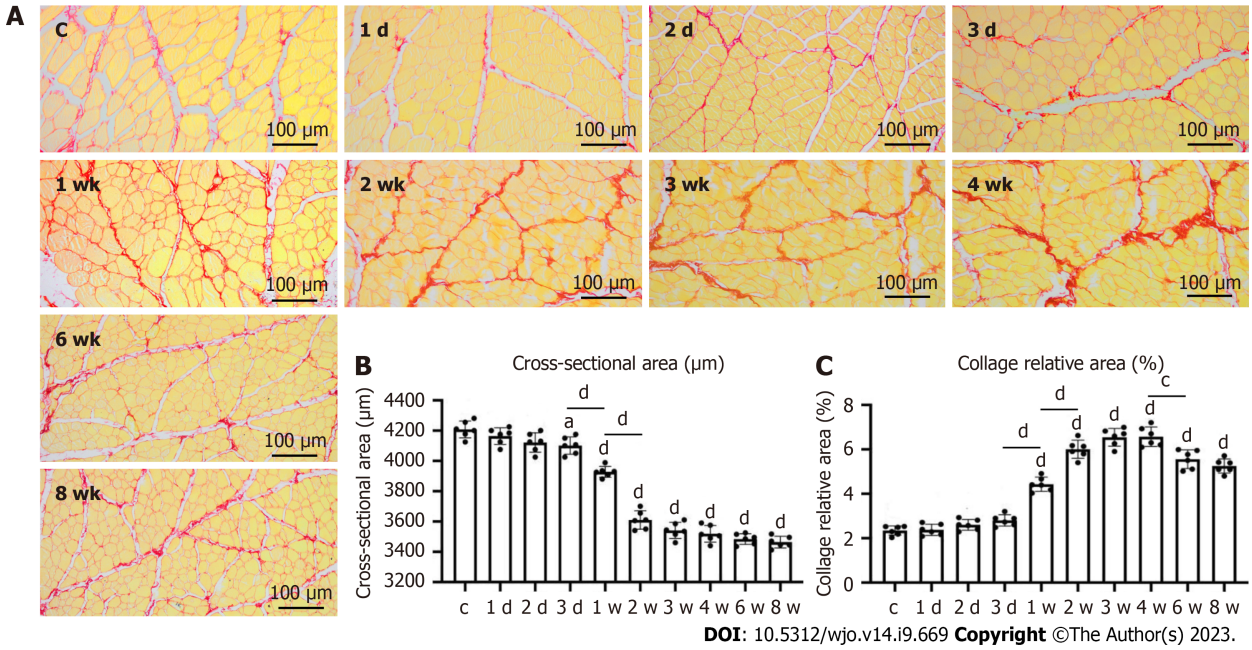

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Figure 4 Sirius red staining findings. A: Morphological changes of rectus femoris after Sirius red staining, group C (control), 1 d, 2 d, 1 wk, 2 wk, 3 wk, 4 wk, 6 wk, and 8 wk; B and C: Cross-sectional value of rectus femoris fibers. $^{a}P < 0.05$; $^{c}P < 0.001$; $^{d}P < 0.0001$.

wk and -6 wk, and immobilization-6 wk and -8 wk groups. The degree of total contracture was increased with the immobilization time (Table 1).

The degree of myogenic contracture was significantly greater in the immobilization-1 wk group than the immobilization-3 d group ($P < 0.05$). The degree of myogenic contracture also significantly differed between the immobilization-1 wk and -2 wk groups ($P < 0.05$), but not between any other adjacent immobilization groups ($P > 0.05$). The results suggested that myogenic contracture occurred after 1 wk of immobilization and gradually stabilized after 2 wk of immobilization, whereas the subsequent joint contractures were mostly arthrogenic (Table 1).

After 1 wk of immobilization, the degree of arthrogenic contracture was significantly greater in the immobilization groups than the control group ($P < 0.05$). The degree of arthrogenic contracture significantly differed between the immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk, and immobilization-2 wk and -3 wk groups (all $P < 0.05$), but not between the other adjacent groups ($P > 0.05$). The results suggested that arthrogenic contracture progressed from 1 to 3 wk of immobilization. However, the progression amplitude of the arthrogenic contracture began to weaken after 3 wk of immobilization, after 4 wk, the arthrogenic contracture is basically stable (Table 1).

Histological evaluation of the Sirius red-stained sections

Compared with the control group, the mean diameter of the rectus femoris was significantly decreased with the duration of immobilization in all immobilization groups except the immobilization-1 d and -2 d groups ($P < 0.05$). From 1 d to 3 wk of immobilization, the proportion of collagen fibers in the rectus femoris of the immobilization groups increased with the fixation time. The proportion of collagen fibers significantly differed between the control group and all immobilization groups except the immobilization-1 d, -2 d, and -3 d groups ($P < 0.05$). The proportion of collagen fibers in the rectus femoris stabilized in the immobilization-4w group, but was decreased in the immobilization-6 wk and -8 wk groups ($P < 0.05$ in all cases; Figure 4).

Evaluation of the hematoxylin-eosin-stained sections and immunohistochemistry

The largest synovial area in the sagittal plane was analyzed. H&E staining showed that the degree of synovial hyperplasia of the anterior joint capsule in the immobilization groups increased with the fixation time, with significant differences between adjacent groups, *i.e.* between the immobilization-1 d and -2 d, immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk, and immobilization-2 wk and -3 wk groups ($P < 0.05$). The degree of synovial hyperplasia of the anterior joint capsule also significantly differed between the control group and all immobilization groups, except the immobilization-1 d group ($P < 0.05$; Figure 5). Immunohistochemistry showed that the change trend of phosphorylated mothers against decapentaplegic homolog (p-Smad2) was consistent with the degree of synovial hyperplasia of the anterior joint capsule, but the percentage of p-Smad2 in each group was significantly different from that in the control group immobilization-2 d ($P < 0.05$; Figure 6).

Protein expression in the muscle and joint capsule

After early joint immobilization, the expression level of transforming growth factor beta 1 (TGF-β1) was significantly increased in the joint capsule and muscles. The expression level of TGF-β1 in the joint capsule was significantly higher in the immobilization-1 wk group than in the immobilization-3 d group. TGF-β1 expression of joint capsule continued to

Table 1 Total, myogenic, and arthrogenic contracture after knee immobilization for various time periods in 60 SD rats (mean ± SD)

Grouping	Quantity	Degree of contracture		
		Total contracture	Myogenic contracture	Arthrogenic contracture
Control	6	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Immobilization-1 d	6	1.1 ± 0.6	0.6 ± 0.4	0.5 ± 0.3
Immobilization-2 d	6	2.4 ± 0.7	1.5 ± 0.4	0.9 ± 0.2
Immobilization-3 d	6	5.9 ± 1.0	4.0 ± 1.0	1.9 ± 0.5
Immobilization-1 wk	6	23.5 ± 2.0[a,b,c,d]	15.9 ± 1.9[a,b,c,d]	7.6 ± 0.7[a,b,c,d]
Immobilization-2 wk	6	51.8 ± 1.8[a,b,c,d,e]	32.7 ± 1.1[a,b,c,d,e]	19.1 ± 1.3[a,b,c,d,e]
Immobilization-3 wk	6	78.7 ± 2.2[a,b,c,d,e,f]	33.9 ± 2.1[a,b,c,d,e]	44.5 ± 1.9[a,b,c,d,e,f]
Immobilization-4 wk	6	79.9 ± 2.8[a,b,c,d,e,f]	34.2 ± 2.2[a,b,c,d,e]	44.9 ± 2.2[a,b,c,d,e,f]
Immobilization-6 wk	6	80.8 ± 3.5[a,b,c,d,e,f]	35.5 ± 2.9[a,b,c,d,e]	45.3 ± 2.9[a,b,c,d,e,f]
Immobilization-8 wk	6	82.5 ± 3.0[a,b,c,d,e,f]	35.9 ± 2.5[a,b,c,d,e]	46.6 ± 2.3[a,b,c,d,e,f]

[a]$P < 0.05$ *vs* control group.
[b]$P < 0.05$ *vs* immobilization-1 d group.
[c]$P < 0.05$ *vs* immobilization-2 d group.
[d]$P < 0.05$ *vs* immobilization-3 d group.
[e]$P < 0.05$ *vs* immobilization-1 wk group.
[f]$P < 0.05$ *vs* immobilization-2 wk group.

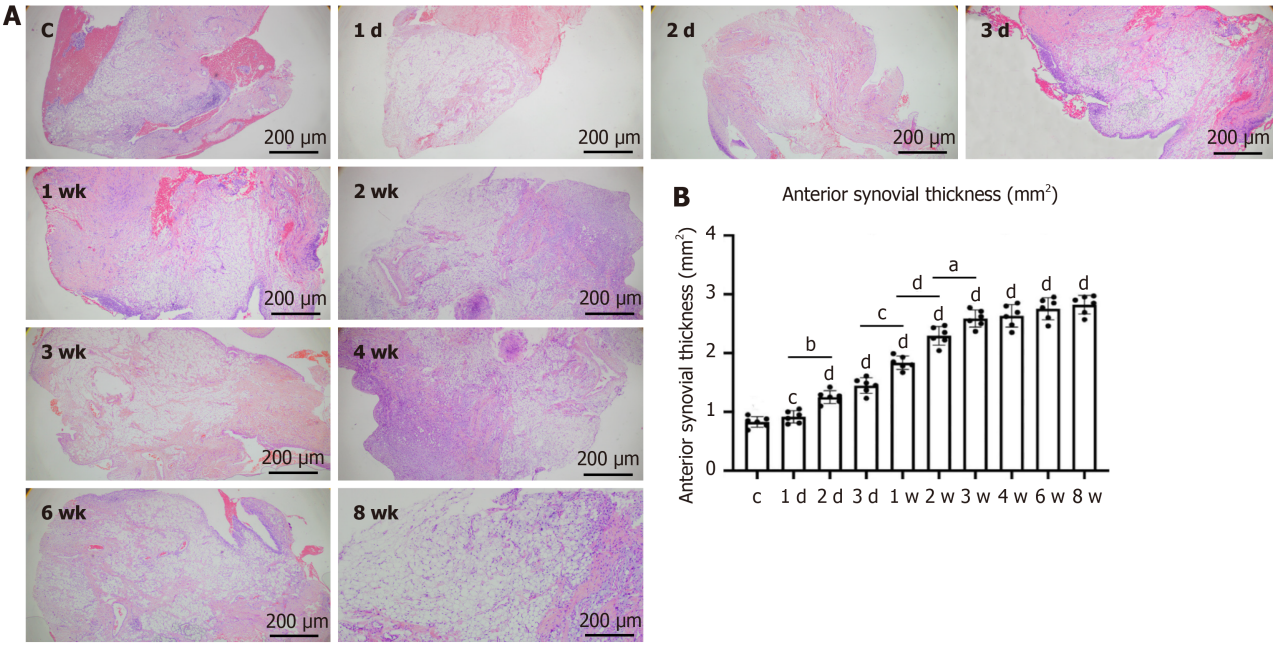

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Figure 5 Hematoxylin and eosin staining findings. A: Morphological changes of the anterior joint capsule; B: The anterior joint capsule thickness value. [a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$; [d]$P < 0.0001$.

increase after immobilization for up to 8 wk. There were significant differences in TGF-β1 levels in the joint capsule between the immobilization-2 d and -3 d, immobilization-1 wk and -2 wk, and immobilization-2 wk and -3 wk groups ($P < 0.05$). The TGF-β1 content of the anterior joint capsule increased with the immobilization time, with a slight downward trend in the immobilization-8w group that did not reach statistical significance ($P > 0.05$). TGF-β1 expression in the anterior joint capsule was significantly increased in the control group compared with the immobilization groups ($P < 0.05$), except the immobilization-1 d and -2 d groups. Western blot analysis showed that the TGF-β1 content in the quadriceps muscle first increased and then decreased. The TGF-β1 content in the muscle significantly differed between the immobilization-2 d and -3 d, immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk, and immobilization-6 wk and -8 wk groups ($P < 0.05$); The contents of Smad2 and Smad3 and TGF-β1 in quadriceps femoris had the same trend of

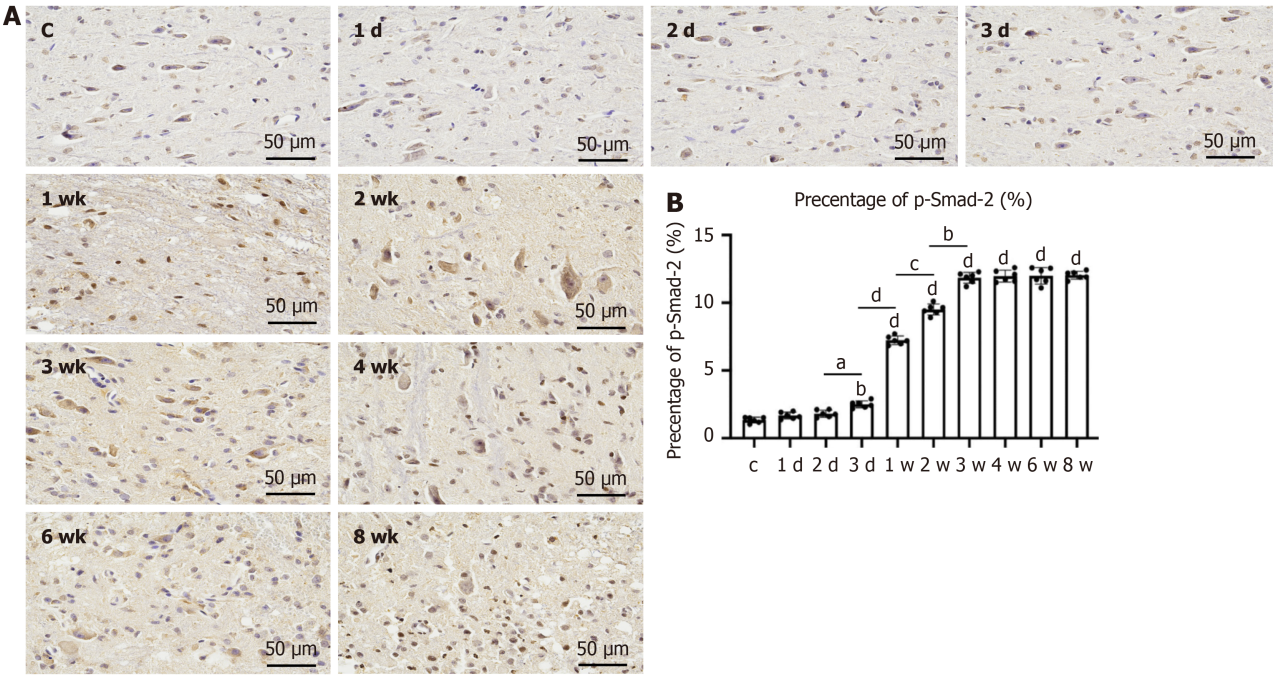

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Figure 6 Immunohistochemistry findings. A: Immunohistochemical staining of the anterior joint capsule; B: Percentage of the anterior articular joint capsule phosphorylated mothers against decapentaplegic homolog 2. [a]*P* < 0.05; [b]*P* < 0.01; [c]*P* < 0.001; [d]*P* < 0.0001.

change, but there were significant differences only between the groups of immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk ($P < 0.05$). In all of the results, with the exception of the fixed-1 d and-2 d groups, there was also a significant difference between the control group and the fixed group ($P < 0.05$) (Figure 7).

DISCUSSION

Joint contracture is a relatively common condition that is mainly caused by fibrosis of the joint capsule and skeletal muscle after long-term immobilization, and shows the pathological features of excessive deposition of collagen and connective tissue components[15]. Numerous animal models have been developed to simulate knee flexion contracture; however, few animal models of knee extension contracture have been reported. A previous study successfully established a model of knee extension contracture in New Zealand white rabbits and reported in detail the characteristics of plaster immobilization and the relevant mechanisms[16]. However, it is beneficial to model knee extension contracture in rats rather than rabbits because of the lower cost of studying the pathogenesis of joint contracture and evaluating therapeutic efficacy. Therefore, the present study described a method to establish a model of knee extension contracture in the rat. We demonstrated that this model had significantly limited knee flexion motion and altered expressions of histological and fibrosis-related proteins in the skeletal muscle and anterior joint capsule.

Wang *et al*[17] directly assessed the muscle limitations of rats with immobilized ankle joints and found that the initial flexion contracture of the knee is mainly due to muscle structures and is reversible and can spontaneously resolve. By contrast, long-term contracture is mainly caused by the joint structures and is irreversible[14]. Such arthrogenic contracture cannot be improved, even by aggressive rehabilitation[18]. Several reports suggest that joint contractures occur within 1 wk of immobilization and progress in a time-dependent manner[19,20]. Chimoto *et al*[21] reported that 2 wk of muscle limitation mainly causes myogenic contracture, while long-term contracture (more than 4 wk of immobilization) results in joint contracture. Therefore, prolonged immobilization for longer than 4 wk should be avoided to prevent irreversible joint contracture[22]. In the present study, myogenic contracture was the predominant type of contracture during the first 2 wk of immobilization. From 2 to 3 wk of immobilization, the joint contracture changed from myogenic to arthrogenic. The contracture initiation time in the present study was consistent with previous studies; however, in contrast with previous studies, the arthrogenic contracture stabilized at 3 wk and completely stable at 4 wk. Arthrogenic contracture is primarily a fibrotic response within the joint capsule. The posterior joint capsule is the main contributor to the formation of immobilization-induced knee flexion contracture, while the anterior joint capsule has the greatest impact on knee extension contracture[21]. The synovial layer of the anterior joint capsule is the widest and most complex in the knee joint[23]. In the present study, the degree of synovial hyperplasia continuously increased with the immobilization time; this may explain why knee extension contracture forms earlier than knee flexion contracture.

In the histologic assessment of the present study, the myofiber cross-sectional area, intermuscular collagen deposition, and extent of hyperplasia in the anterior joint capsule supported the biological findings. As the decreased skeletal muscle mass caused by an imbalance in protein metabolism is characterized by a significantly smaller muscle fiber area[24-26].

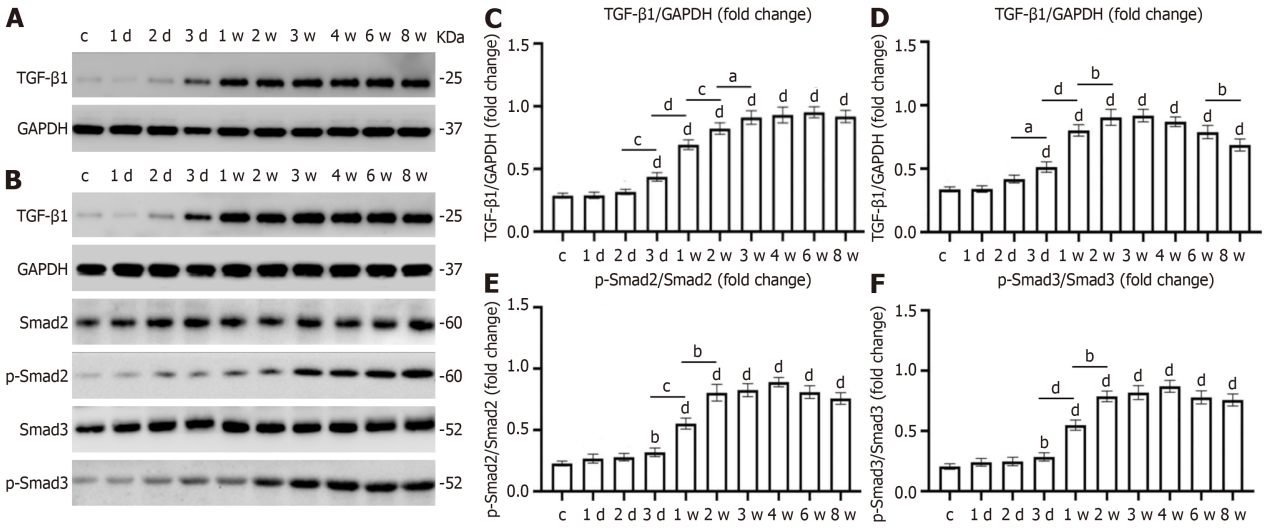

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Figure 7 Western blot findings. A: Changes in the intensity of transforming growth factor beta 1 (TGF-β1) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) bands in the anterior joint capsule; B: Changes in the intensity of TGF-β1/GAPDH, phosphorylated mothers against decapentaplegic homolog 2 (p-Smad2)/Smad2, p-Smad2/Smad2 bands in the quadriceps; C: Graphical representation of the expression level of TGF-β1 in the anterior joint capsule relative to GAPDH; D-F: Graphical representation of the expression level of TGF-β1/GAPDH, p-Smad2/Smad2, p-Smad2/Smad2. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$; $^{d}P < 0.0001$.

The amount of intermuscular collagen deposition was significantly greater in the immobilization-1w group than the control group, but did not significantly differ between the immobilization-2 wk and -3 wk groups. Furthermore, there was significantly less intermuscular collagen deposition in the immobilization-6w group compared with the immobilization-4w group. This indicates that intermuscular collagen deposition began to increase in the 1st week of immobilization, but decreased after 4 wk of immobilization. Previous studies have shown that this may be associated with gradual resolution of the inflammatory and fibrotic response after immobilization[11]. This was demonstrated by the reduction in collagen content and TGF-β1 protein expression over time. The anterior joint synovial proliferation was significantly greater in the immobilization-2 d group than the control group, but did not differ between the immobilization-3 wk and -4 wk groups, indicating that the anterior joint synovial proliferation significantly increased during the first 3 wk of immobilization and completely stabilized from 4 wk onwards. Wang *et al*[27] analyzed changes in the synovial membrane caused by anterior articular capsule fibroblasts, microvasodilation, and congestion due to plaster immobilization. Li *et al*[28] and Yao *et al*[29] reported that intra-articular tissue adhesion does not completely cover the cruciate ligament in and around the knee, but originates from synovial fibrosis. The proliferation of intra-articular synovial tissue was responsible for the limited ROM found in the present study.

To further characterize the altered fibrosis of skeletal muscle and the joint capsule, we evaluated the expression of the TGF-β1 and p-Smad protein. There are three subtypes of TGF-β family: TGF-β1, TGF-β2, and TGF-β3. A large number of studies have demonstrated that the expression of TGF-β1 is the most important in fibrosis changes. TGF-β1 can cause differentiation, proliferation and extracellular matrix production, promote the transformation of fibroblasts to myofibroblasts, cause the deposition of collagen and increase the expression of alpha smooth muscle actin (α-SMA), and then cause tissue fibrosis[30,31]. Zhang *et al*[32] found that the expression level of TGF-β1 in the posterior joint capsule was significantly increased *in vivo* experiments. *In vitro* experiments showed that the expression level of TGF-β1 was increased, and the expression of α-SMA and type I collagen was also increased. Mao *et al*[33] applied a TGF-β inhibitor to treat a traumatic rat knee joint contracture animal model and found that after the activity of TGF-β was inhibited, the degree of joint contracture was alleviated, while the protein expression of collagen type I, collagen type III, α-SMA, and p-Smad2 was decreased. Therefore, we used the TGF-β1 and Smad signaling pathway as indicators to prove the formation of contracture. The aggravation of contracture enhances the fibrosis response, characterized by increases in profibrotic genes and proteins (*e.g.*, cytokine TGF-β1 genes, type I and type III collagen genes and proteins), leading to increases in collagen density and joint capsule thickness[34]. Hildebrand *et al*[35] reported the increased expression of type I and III collagen, TGF-β1, p-Smad2, and p-Smad3 in a rabbit post-traumatic flexion contracture model compared with control joint cysts. The increased mRNA levels of TGF-β1 may be related to collagen deposition inside and outside the articular capsule. Joint capsule fibrosis may be associated with the development of joint contracture. Similarly, the present study showed that the expression of fibrosis-related genes increased with prolonged immobilization, but the expression of TGF-β1, p-Smad2, and p-Smad3 in the rectus femoris decreased slightly after 3 wk of immobilization and was significantly decreased at 8 wk. The altered expression levels of TGF-β1 may be due to hypoxia or a reduction in collagen turnover or degradation rates[36]. Among several other roles, one of the adaptive responses of hypoxic cells is the upregulation of hypoxia-inducible factor 1 alpha (HIF-1α). The expression of TGF-β1 and HIF-1α is significantly upregulated during the transformation of fibroblasts to myofibroblasts, leading to the promotion of vascular endothelial growth factor (VEGF) gene expression[37]. The HIF-1α signaling pathway in turn regulates angiogenesis by inducing VEGF expression, thereby improving circulation and reducing the inflammatory response[38].

In the present study, ordinary gypsum and polymer gypsum were initially used to establish the extended knee contracture model. However, the rats inevitably gnawed the gypsum and there was also gypsum slippage. In the process of switching to an aluminum splint, we found that the knee joints of the rats could not be wrapped when fixed because the proximal lower limbs were short and strong. The present shape of the external immobilization device was determined after multiple improvements. The immobilization device comprised of aluminum plate pressurized at the distal end on the back of the foot that was plantarflexed at 60. After the first proximal rectangular aluminum plate was used to fix the knee joint, the second inverted trapezoidal aluminum plate was wrapped around the knee to ensure that the knee was completely immobilized. Although this immobilization method is simple, the pressure strength must be carefully controlled. A pressure that is too high will easily cause poor limb circulation in rats. As aluminum is easy to shape, we were able to adjust the tightness of the external immobilization to resolve any swelling. Tokuda *et al*[39] successfully created a model of flexion contracture outside the knee joint; however, the external immobilization device used in the present study had less effect on the overall activity of the rats and better reflected the clinical situation in which the knee joint is usually fixed in extension after injury, leading to limited knee flexion after long-term immobilization. Therefore, to more closely mimic the clinical situation, we chose to create a model of knee extension contracture.

We demonstrated that the present model is as reliable as other animal models in reproducing the features of human joint contracture, including limited joint mobility, changes in the joint and muscle histology, and changes in the expression of fibrosis-associated proteins in the joint capsule *vs* muscle. The advantage of the present model is that it is easy to replicate because it does not require complex surgical procedures, the tools are easy to use, and the rat anesthesia and immobilization can be performed in a very short period of time. We described the detailed process of establishing a rat model of knee extension contracture, with photographs. The model closely replicates joint contracture caused by complications of immobilization, enabling researchers to investigate the etiology of joint contracture and establish new treatments. This model is a reliable tool, as described earlier. Contractures caused by long-term fixation are mainly caused by joint structure and are irreversible. Moreover, the mechanism by which movement after fixation may exacerbate joint contracture has not been fully explored[40]. As the external fixator is easy to shape and can be removed at any time. Therefore, this model can be used to study the prevention and treatment of knee extension contracture in rats, at the same time, it is possible to change the dressing and keep the wound dry during the fixation of traumatic knee joint contracture.

The present study had some limitations. First, in this model, the ankle joint and the knee joint were inevitably fixed together. Because the lower limb of the rat is shaped like a cone, the ankle joint was plantarflexed at 60 and fixed with the knee joint to prevent slippage of the aluminum splint. Second, the longest immobilization time in the present study was 8 wk. We plan to explore the continuous longer-term changes in fibrosis-related proteins in a future study. Finally, the state of the extension contracture after the removal of the external fixator was also studied and will be reported.

CONCLUSION

The results in this study suggest that the myogenic contracture is stabilized after 2 wk, whereas the arthrogenic contracture is stabilized after 3 wk and completely stable in 4 wk.

ARTICLE HIGHLIGHTS

Research background

There is currently no research on establishing a model of knee joint extension contracture in rats.

Research motivation

The extension contracture model is of clinical relevance because it better mimics fracture and bed-associated immobilization than the flexion contracture model.

Research objectives

Clarify the formation process of knee joint extension contracture in rats.

Research methods

Verify the formation process of extension contracture by observing pathology, detecting fibrotic proteins, and measuring joint range of motion.

Research results

All results show that the myogenic contracture tends to stabilize after 2 wk, and the arthrogenic contracture tends to stabilize after 3 wk and completely stable in 4 wk.

Research conclusions

The extension contracture model is of clinical relevance because it better mimics fracture and bed-associated immobilization than the flexion contracture model.

Research perspectives

This rat model may be a useful tool for studying the etiology of joint contracture and establishing new treatment methods.

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FOOTNOTES

Author contributions: Zhou CX conceived the study, participated in its design and coordination, and drafted the manuscript; Wang F participated in the design of the study and performed the statistical analyses; Zhou Y participated in its design and coordination, and helped to draft the manuscript; Fang QZ drew the pictures in the manuscript; Zhang QB performed the statistical analysis in the revised manuscript; All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Comparative study *in vivo* of the osseointegration of 3D-printed and plasma-coated titanium implants

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Abstract

BACKGROUND

Total hip arthroplasty is a common surgical treatment for elderly patients with osteoporosis, particularly in postmenopausal women. In such cases, highly porous acetabular components are a favorable option in achieving osseointegration. However, further discussion is needed if use of such acetabular components is justified under the condition of normal bone mass.

AIM

To determine the features of osseointegration of two different types of titanium implants [3-dimensional (3D)-printed and plasma-coated titanium implants] in bone tissue of a distal metaphysis in a rat femur model.

METHODS
This study was performed on 20 white male laboratory rats weighing 300-350 g aged 6 mo. Rats were divided into two groups of 10 animals, which had two different types of implants were inserted into a hole defect (2 × 3 mm) in the distal metaphysis of the femur: Group I: 3D-printed titanium implant (highly porous); Group II: Plasma-coated titanium implant. After 45 and 90 d following surgery, the rats were sacrificed, and their implanted femurs were extracted for histological examination. The relative perimeter (%) of bone trabeculae [bone-implant contact (BIC%)] and bone marrow surrounding the titanium implants was measured.

RESULTS
Trabecular bone tissue was formed on the 45th day after implantation around the implants regardless of their type. 45 d after surgery, group I (3D-printed titanium implant) and group II (plasma-coated titanium implant) did not differ in BIC% (83.51 ± 8.5 *vs* 84.12 ± 1 .73; P = 0.838). After 90 d, the BIC% was higher in group I (87.04 ± 6.99 *vs* 81.24 ± 7.62; P = 0.049), compared to group II. The relative perimeter of the bone marrow after 45 d did not differ between groups and was 16.49% ± 8.58% for group I, and 15.88% ± 1.73% for group II. Futhermore, after 90 d, in group I the relative perimeter of bone marrow was 1.4 times smaller (12.96 ± 6.99 *vs* 18.76 ± 7.62; P = 0.049) compared to the relative perimeter of bone marrow in group II.

CONCLUSION
The use of a highly porous titanium implant, manufactured with 3D printing, for acetabular components provides increased osseointegration compared to a plasma-coated titanium implant.

Key Words: Rats; Hip arthroplasty; Femur; Porosity; 3-dimensional printing; Microscopy

Core Tip: The use of porous titanium materials was shown to be the most favorable solution for osseointegration for total hip arthroplasty, especially in the case of osteoporosis. Is the use of highly porous acetabular components justified under the condition of normal bone mass? We conducted a study on rats, in which we compared the osseointegration of 3-dimensional (3D)-printed or plasma-coated titanium implants into femoral bone defect by assessing the relative perimeter (%) of bone trabeculae. The highly porous titanium implant, manufactured with 3-dimensional printing, for acetabular components provides increased osseointegration compared to a plasma-coated titanium implant.

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INTRODUCTION

Titanium has long been used for the manufacture of medical implants. Among them, highly porous titanium created using additive technologies [used, in particular, for acetabular component manufacturing for total hip arthroplasty (THA)] was shown to be the most favorable material for osseointegration[1-3]. This is due to the similarity of the structure and biomechanical qualities of this material with bone tissue[4,5]. THA is a common surgical treatment for elderly patients, women are equally represented among THA patients. A common challenge is matching the structure of the material to the structure of the bone, this becomes even more important due to the possibility of osteoporosis[6] or slowing of bone tissue formation due to age changes, endocrine diseases, menopause, hormonal therapy, *etc.*[7,8]. The use of acetabular components with a porous surface formed by plasma spraying has also proven itself in clinical practice[9-11]. Previously, we reported the comparative osseointegration of four types of highly porous materials from which the acetabular components of endoprostheses are made[12]. No established difference was seen between them in healthy rats, in contrast differences were seen in postmenopausal osteoporotic animals[12]. Additionally, an *in vivo* study in sheep also showed that surface modification by chemical treatment of porous titanium can improve osseointegration[13]. It has been shown in clinical settings that the use of porous titanium cups was accompanied by a higher intensity of pain during the first 5 years after THA compared to cups made of titanium with plasma spraying[14]. Conflicting data has been published regarding better primary stability of porous titanium cups compared to plasma sprayed titanium cups[4,15]. The question arises: Is the use of highly porous acetabular components justified under the condition of normal bone mass?

Aim of the study was to establish the features of osseointegration of two different types of titanium implants [3-dimensional (3D)-printed and plasma-coated titanium implants] in a distal femoral metaphisial rat model.

MATERIALS AND METHODS

The study was conducted in compliance with the national guidelines, the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (1986, ETS 123) and Directive 2010/63/EU. The protocol of the study was approved by the local Bioethics Committee (protocol No. 211 dated February 01, 2021).

Experiment design

The experimental study was performed on 20 white male laboratory rats weighing 300-350 g of 6 mo of age (Figure 1A), which were kept under conditions of standard food for rodents, free access to drinking water, and 12-h light day/night. The rats were divided into two groups of 10 animals each depending on the type of implanted titanium material: Group I: 3D-printed titanium implant (highly porous); Group II: Plasma-coated titanium implant (Figure 1A).

Implants

The cylindrical implants (2 mm diameter and 3 mm length) were made from the material of one of the two types of acetabular cups from (AK Medical H.L. Beijing, China): AK 3D ACT Titanium Alloy Trabecular Acetabular Cup[16] or AK A Series Bio-Type Acetabular Cup[17]. The difference between the coatings was in the method of their production and the resulting structure. In particular, the AK 3D ACT Titanium Alloy Trabecular Acetabular Cup is a highly porous titanium cup with open controlled porosity (approximately 80%) manufactured using additive technologies (Figure 1B); AK A Series Bio-Type Acetabular Cup is created by plasma spraying of titanium on the surface of the cup and has closed porosity (Figure 1C).

Surgical intervention

Surgical interventions were performed under aseptic and antiseptic conditions under general anesthesia (aminazine 10 mg/kg and ketamine 50 mg/kg intramuscularly). After preparation of the operative field [shaving the hair on the left knee and thigh, treatment with Kodan® forte antiseptic (Schülke & Mayr GmbH, Germany)], the distal metaphysis of the femur was opened through an anterolateral approach (Figure 1D). In the animal distal femoral metaphysis, a hole defect with a diameter of 2 mm was created with a dental boron, where 3D-printed or plasma-coated titanium implants were installed (Figure 1E and F). After that, the soft tissues and skin were sutured with knotted sutures and treated with Kodan® antiseptic. The condition of the rats after surgery did not necessitate pharmacological treatment.

At 45 and 90 d after surgery, rats were euthanized with a lethal dose of anaesthetic (sodium thiopental, 90 mg/kg intramuscularly) and implanted femurs were removed for histological examination.

Histological examination

Removed femurs with titanium implants were cleaned of soft tissue, then fixed in 10% buffered formalin for 5 d. After fixation, the bones were transferred to 70° ethyl alcohol for dehydration. After a day, three longitudinal sections with a thickness of approximately 0.5 mm were made from each distal metaphysis of the femur in the area of implantation of the titanium cylinders with a diamond saw. The obtained slices were stored in 70° ethyl alcohol and dried with filter paper before taking measurements.

Histomorphometry

Bone sections together with the implant were photographed using an Olympus BX-63 microscope (Olympus, Japan) with × 4 magnification in fluorescent light (U-FBW filter, blue excitation; Olympus, Japan), X-Lite lamp (Olympus, Japan), camera DP73 (Olympus, Japan). The relative perimeter (%) of bone trabeculae [bone-implant contact (BIC%)] and bone marrow around titanium implants were measured using ImageJ software.

Statistical analysis

The obtained results are presented as mean and standard deviation. To detect the influence of the type of titanium material on tissue formation, as well as to detect changes in tissue formation during the experiment (45 and 90 d), Mann–Whitney U test was used. The difference between groups was considered statistically significant if $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics 19.0 software.

RESULTS

Forty-five days after the index surgery, both implant groups, formed spongy bone tissue of the lamellar type, in which lacunae with osteocytes were observed (Figure 2). 90 d after the index surgery, no qualitative changes in the structure of the bone tissue around both types of implants were detected.

Forty-five days after surgery, group I (3D-printed titanium implant) and group II (plasma-coated titanium implant) did not differ in BIC% (Figure 3) (83.51 ± 8.5 *vs* 84.12 ± 1 .73; $P = 0.838$). After 90 d, the BIC% was higher in group I (87.04 ± 6.99 *vs* 81.24 ± 7.62; $P = 0.049$), compared to group II (Figure 3). The relative perimeter of the bone marrow after 45 d did not differ between groups and was 16.49% ± 8.58% for group I, and 15.88% ± 1.73% for group II, respectively. In comparison after 90 d in group I, the relative perimeter of the bone marrow was 1.4 times smaller (12.96 ± 6.99 *vs* 18.76 ± 7.62; $P = 0.049$) compared to the relative perimeter of the bone marrow in group II.

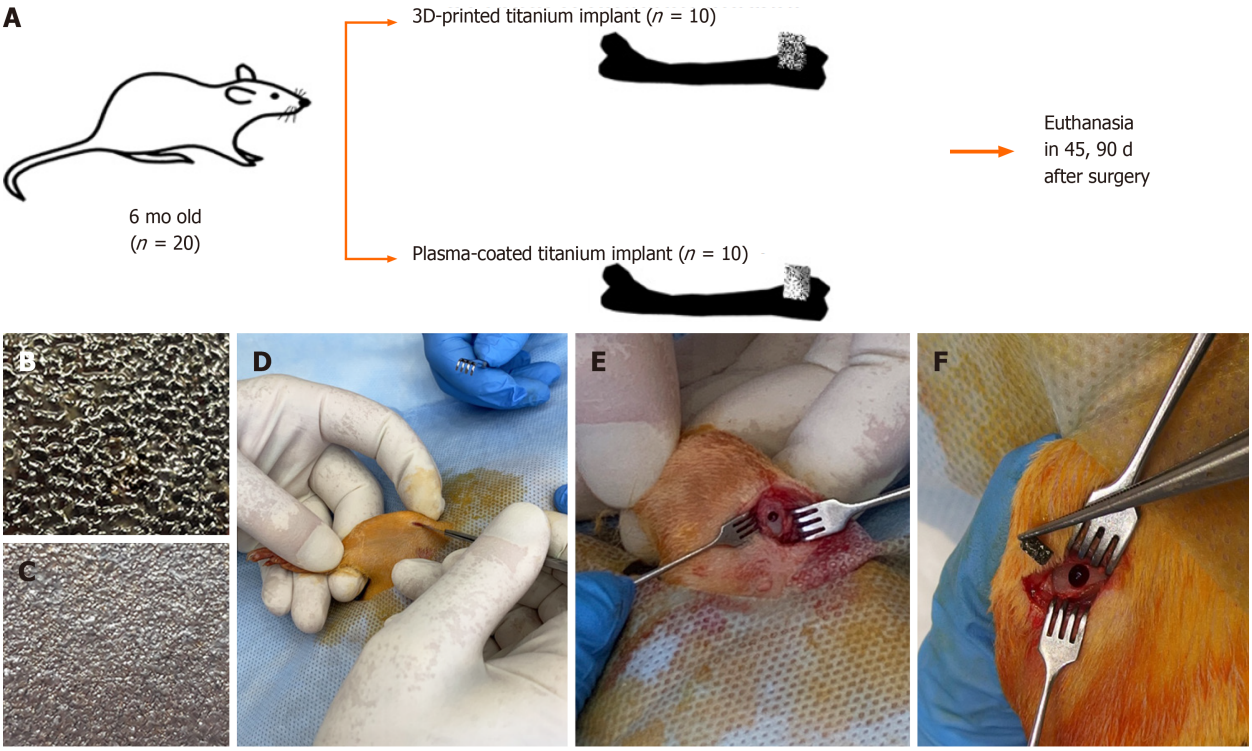

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Figure 1 Design of study with characteristics of implanted material and stages of index surgery. A: Design of an experimental study on rats with a demonstration of the features of the implant materials used; B: 3D-printed titanium implant; C: Plasma-coated titanium implant; D-F: Stages of surgical intervention.

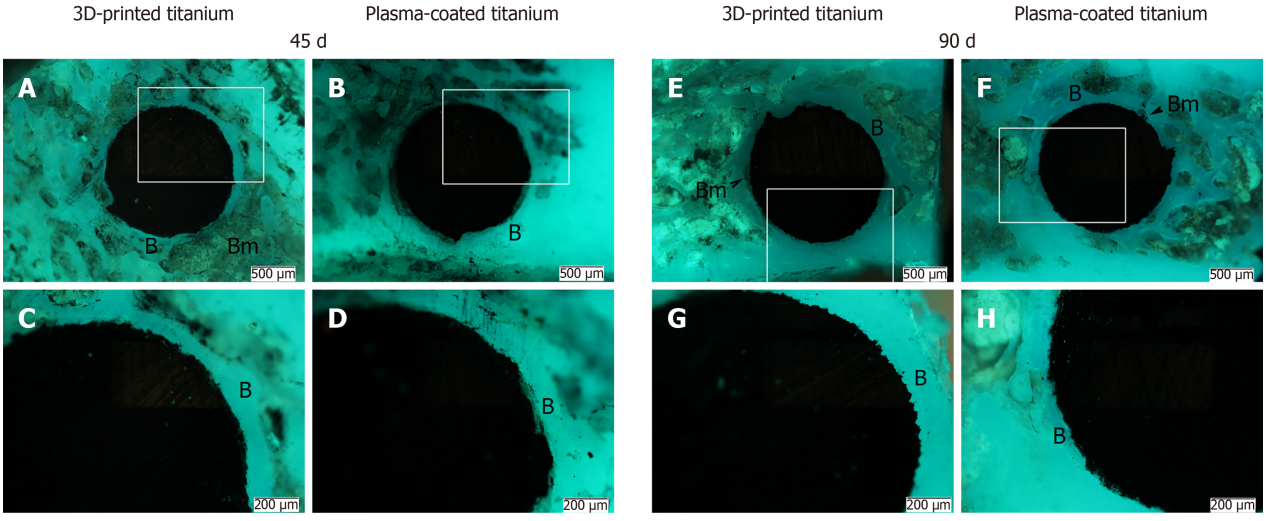

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Figure 2 Fluorescence microscopy of rat femoral sections after index surgery. Titanium implants (black color) with 3D-printed or plasma-coated titanium in the distal metaphysis of the rat femur. Bone trabeculae are formed along the perimeter of implants with areas of bone marrow. White rectangles show fragments of the corresponding photos taken at a higher magnification. Longitudinal sections. A-D: 45 d (*n* = 10) after implantation; E-H: 90 d (*n* = 10). B: Bone trabeculae; Bm: Bone marrow.

During the experimental study (45 d and 90 d after the index surgery), the BIC% indicator and the relative perimeter of the bone marrow did not significantly change in both groups of differing titanium implants (Figure 3).

DISCUSSION

The results of this study show that both types of cylindrical titanium implants (made by 3D printing with controlled open porosity and by plasma spraying with closed porosity) contribute to the formation of bone tissue, with corresponding

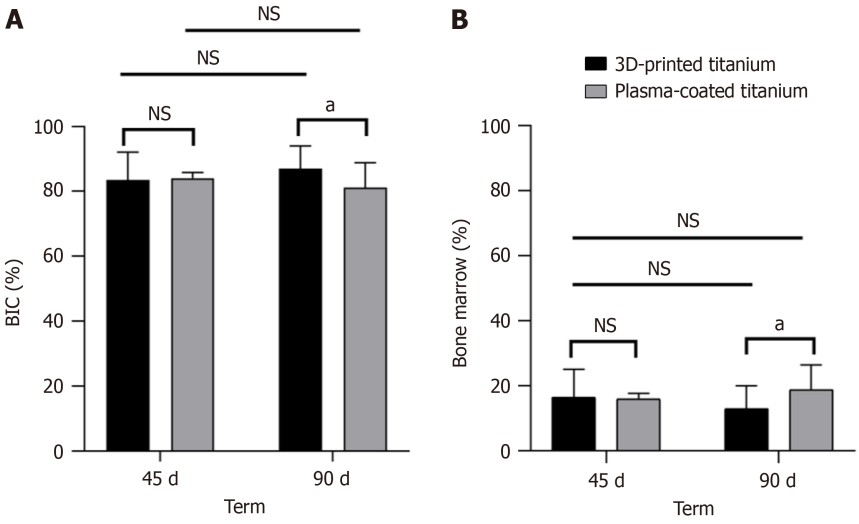

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Figure 3 Bone tissue formation (Bone-implant-contact%; Bone marrow%) around two types of titanium implants. 3D-printed and plasma-coated titanium implants 45 d (n = 10) and 90 d (n = 10) after implantation in the distal metaphysis of the femur of rats. Data are presented as mean ± SD. A: Bone-implant contact (Bone-implant-contact%) is significantly higher at day 90 for the implant with 3D-printed titanium; B: Bone marrow% is significantly lower at day 90 for the implant with 3D-printed titanium. NS: Not significant; $^{a}P < 0.05$.

structure, 45 d after installation in the femoral distal metaphysis in a rat model. The study shown that the BIC% in rats was more than 80% for both types of titanium implants and did not differ significantly between implant groups. The successful formation of bone tissue is primarily related to the chemical composition of the implants[18]. In addition, the surface structure of the implanted samples has an important influence on the osteointegration process. In particular, *in vitro* experiments have shown that cell adhesion and proliferation are slowed down on the rough surface of titanium plasma sprayed implants compared to the smooth surface of an identical titanium alloy[19,20]. However, based on the analysis of bone formation markers (type I procollagen peptide, alkaline phosphatase, osteocalcin, osteoprotegerin), a greater degree of differentiation of cultured cells into osteoblasts on the rough surface of titanium plasma sprayed implants was established[21]. On the other hand, as a result of the comparison of titanium samples with a porous surface (one created using plasma spraying, the other using additive technologies) in the culture of osteoblasts, no difference between them was found either in terms of cell adhesion, nor in the rate of their proliferation and alkaline phosphatase activity[21]. Other researchers[22] have shown both in *in vitro* and *in vivo* experiments the dependence of bone formation on the technology used to create a porous titanium surface. For this, they compared titanium samples with a porous titanium coating created using titanium plasma spray (TPS) and two 3D printing techniques: The powder bed fusion and direct energy deposition (DED). In human osteoblast cultures, after 14 d of cultivation, the largest number of cells and the highest activity of alkaline phosphatase were established in tested DED samples. In an *in vivo* study in rabbits, the best integration at 6 wk after implantation into the distal femoral metaphysis, as determined by BIC%, was found in the DED group, but the difference disappeared at 12 wk[22].

In our study, we observed bone formation around both titanium specimens 45 d after their implantation without statistical difference in BIC%. The time frame in a rat model for bone tissue formation is similar to bone recovery under conditions of a closed fracture, which is reported at 42 d[23].

At 90 d postoperatively, we found a significantly higher BIC% for the 3D-printed highly porous titanium implant group compared to the plasma-coated titanium implant group. This may be due to the fact that in rats, newly formed bone tissue covers titanium implants by the 30th day, but the process of rebuilding the regenerate may last up to the 90th day[24]. Results similar to ours were reported in a sheep model, where two different types of titanium implants, one etched sandblasted and the other a porous surface were, studied. Better results were found for the porous material but only for the final observation period (56 d after index surgery)[25]. In addition, the positive influence of the porous material created with the help of 3D printing was observed, one finding was the proliferation of human 1.19 fetal osteoblast-like cells and calcium production compared to a TPS coated surface in orthopedic spinal implants[26].

In our study, autofluorescence of bone tissue was used, which made it possible to distinguish between bone trabeculae and bone marrow around titanium implants in the rat femoral sections. Bone autofluorescence is associated with the content of type I collagen[27], which is absent in bone marrow. Due to the above mentioned characteristic structures can be distinguished and bone sections can be analyzed without additional staining.

Our study is not without limitations, first of all the conducted research is limited by it's methodological simplicity, which is stipulated by the goal: *In vivo* evaluation to substantiate the utility of the use of porous titanium implants as acetabular components for patients with normal bone mass, as such we can not answer study questions about different bone qualities. At the same time, despite the already known results of effective osseointegration of porous titanium materials compared to smooth ones, there is a paucity of *in vivo* studies comparing porous titanium materials with plasma sprayed titanium acetabular components.

CONCLUSION

The use of a highly porous titanium implant, manufactured using 3D printing, for acetabular components showed a larger amount of bone tissue integration around it, thus it may provide better osseointegration compared to a plasma-coated titanium implant.

ARTICLE HIGHLIGHTS

Research background

Total hip arthroplasty is a common surgical treatment for elderly patients with osteoporosis and further discussion is needed if use of such acetabular components is justified under the condition of normal bone mass.

Research motivation

There is a need to perform studies to compare of osseintegration of two different types of titanium implants [3-dimensional (3D)-printed and plasma-coated titanium implants].

Research objectives

To determine the features of osseointegration of two different types of titanium implants (3D-printed and plasma-coated titanium implants) in bone tissue of a distal metaphysis in a rat femur model.

Research methods

This study was performed in a rat femur model. Histological examination of the femur was carried out by measuring the relative perimeter of bone trabeculae [bone-implant contact (BIC%)] and bone marrow surrounding of 3D-printed titanium implant (highly porous) and plasma-coated titanium implant.

Research results

Trabecular bone tissue was formed on the 45th day after implantation around the implants regardless of their type. Forty-five days after surgery groups with different implants did not differ in BIC%, but after 90 d, the BIC% was higher in 3D-printed titanium implant group.

Research conclusions

The use of a highly porous titanium implant, manufactured with 3D printing, for acetabular components provides increased osseointegration compared to a plasma-coated titanium implant.

Research perspectives

Further research studies on the use of other histological and biomechanical methods will help to determine the optimal materials of acetabular implants in terms of structure and complexity of their manufacture to be used in patients with normal bone mass.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design; Bondarenko S, Maltseva V and Ashukina N wrote the first draft version of the manuscript; Filipenko V supervised the study and performed critical revision of the article; Maltseva V performed data analysis and interpretation; Ivanov G, Lazarenko I and Sereda D performed experimental surgery, collection and interpretation data; Schwarzkopf R performed critical revision of the article; all authors revised and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Sytenko Institute of Spine and Joint Pathology Review Board.

Institutional animal care and use committee statement: All applicable national guidelines for the care and use of animals were followed. The *in vivo* study was approved by the Ethical Clearance Bioethics Committee State Institution (Sytenko Institute of Spine and Joint Pathology NAMS of Ukraine), Kharkiv, Ukraine (protocol number 211 of 01 Feb 2021).

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Epidemiology of shoulder dislocations presenting to United States emergency departments: An updated ten-year study

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Abstract

BACKGROUND

Glenohumeral dislocation is a common injury that may predispose patients to chronic pain and instability. However, there is a paucity of current data available regarding the epidemiological trends of this injury.

AIM

To provide an updated, comparative assessment of the epidemiology of shoulder dislocations presenting to emergency departments in the United States. We also sought to analyze patient demographic risk factors and consumer products associated with dislocation events.

METHODS

Data were obtained from the national electronic injury surveillance system database for glenohumeral dislocations between 2012 and 2021. Incidence, age, sex, and injury characteristics were analyzed using weighted population statistics as well as incidence rates and 95% confidence intervals (CI).

RESULTS

In total, an estimated 773039 shoulder dislocations (CI: 640598-905481) presented to emergency rooms across the United States during the study period. The annual

incidence rate was 23.96 per 100000 persons and the average patient age at the time of injury was 37.1 years. Significantly more male patients sustained dislocations than female patients (537189, 69.5%, *vs* 235834, 30.5%, $P < 0.001$). With regard to associated consumer products, sports and recreation equipment were involved in the highest proportion of incidents (44.31%), followed by home structures and construction materials (21.22%), and home furnishings, fixtures, and accessories (21.21%). Regarding product sub-groups, stairs, ramps, landings, floors was cited in the greatest number of cases (131745).

CONCLUSION

The national annual incidence rate of glenohumeral dislocations throughout the study period was approximately 23.92 per 100000 persons. Male adolescents sustained the highest proportion of dislocations, with a peak incidence in age group 15-20 years, predominantly secondary to participation in sporting and recreational activities. Conversely, women experienced a relatively consistent incidence of dislocation throughout their lifespan. After age 63, the incidence rate of dislocations in females was found to surpass that observed in males.

Key Words: Shoulder dislocation; Epidemiology; United States; Emergency department; Glenohumeral dislocation; national electronic injury surveillance system

Core Tip: Shoulder dislocations occur in a bimodal distribution and are commonly seen in young men and older women. The national incidence of shoulder dislocations presenting to United States emergency departments has remained relatively stable compared to previous epidemiologic studies. Among young patients sustaining shoulder dislocations, sporting and recreational activities are the most involved activities.

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INTRODUCTION

The glenohumeral joint is the most mobile joint in the body, making it particularly vulnerable to dislocation[1]. This physiologic predisposition makes shoulder dislocation a common injury across age groups-especially in young, physically active men[2-5]. Existing studies have estimated the incidence of shoulder dislocation to be 23.9 per 100000 person-years in the general population, with rates as high as 169 per 100000 person-years among young, active, and military populations[3,5-7]. Patients with shoulder dislocations often experience lasting functional impairments and are known to be at high risk for recurrent injury[1,8]. Despite the high incidence of shoulder dislocations experienced in the United States, there is a paucity of current epidemiological data available regarding general population risk factors and etiology.

While young populations have the highest incidence of shoulder dislocation, these injuries have a bimodal age distribution, affecting both the young and elderly at higher rates[6,9]. Unsurprisingly, the etiology of shoulder dislocation varies with patients' age as the activities they routinely engage in change. Older patients classically sustain shoulder dislocations as the result of a fall, whereas younger patients are more likely to experience injury while participating in sporting and recreational activities[6]. Because of these observed differences in the mechanism of injury for shoulder dislocations across age groups, there is an interest in exploring the relationship between consumer products and patient demographics as it relates to shoulder dislocation events.

The purpose of this study is to provide an updated, comparative assessment of the epidemiology of shoulder dislocations presenting to emergency departments in the United States. We also sought to analyze patient demographic risk factors and consumer products as-sociated with dislocation events. We hypothesized that consumer products involved with shoulder dislocations would vary depending on patient age and gender, with male adolescents utilizing sports and recreation equipment representing the highest incidence of dislocations.

MATERIALS AND METHODS

Database and Query

Data for this cross-sectional, epidemiologic study of glenohumeral dislocations that present to United States emergency departments was obtained from the national electronic injury surveillance system (NEISS) database[10,11]. The NEISS database collects de-identified patient demographics, injury characteristics, and associated consumer product information

from approximately 100 emergency departments across the United States. Data was obtained by a hospital coordinator assigned to the facility and acquired from both clinical information and follow-up telephone communication as needed. These data points are then extrapolated to establish national estimates for each category after weighing each hospital. NEISS is managed by the Consumer Product Safety Commission, who have been responsible for collecting this data since 1999. This organization makes annual adjustments by weighting probabilities of each of the included emergency departments, then uses the number of annual emergency department visits to establish their calculated national estimates [12,13].

The NEISS database was queried for a 10-year period between 2012 and 2021. All age groups were included in the study. "Shoulder (30)" was selected for body part and "dislocation (55)" was selected for diagnosis for all queries. Information was further stratified by age, gender, product group, and product sub-group.

Statistical Analysis

When querying data from the NEISS database, 95% confidence intervals (CI) were calculated based on input requests. Following data acquisition, incidence rates were calculated per 100000 persons. Unstable data, characterized by a national estimate of less than 1200, number of cases less than 20, or coefficient of variation exceeding 33%, were excluded from data analysis, based on NEISS database outputs. Sub-group analysis was performed comparing ages over and under 40 years. This comparison essentially split life expectancy in half (currently approximately 79 years) and compared "early life" and "later life" with known bimodal distribution of patient age[14]. Chi-squared tests were used to compare categorical variables between cohorts. A P value < 0.05 was used to determine statistical significance.

RESULTS

In total, an estimated 773039 (CI 640598-905481) shoulder dislocations presented to emergency departments between 2012–2021 across the United States (Table 1). The annual incidence rate was 23.96 per 100000 persons (CI 19.86-28.07). Average age at time of injury was 37.1 +/- 22.0 years. Male patients accounted for a greater proportion of shoulder dislocations than female patients (537189, 69.5%, *vs* 235834, 30.5%, P < 0.001). Young males accounted for the highest proportion of dislocations, with 17.70% of all dislocations occurring in males aged 15-20 years. The incidence rate for this demographic was observed to be 106.91 per 100000 persons (95%CI: 84.24-129.57).

The largest number of dislocations occurred in patients 17 years old (national estimate 30796, 3.98%). The peak age for dislocation was 18 years in males (national estimate 26661, 4.96% of males) and 66 years in females (national estimate 4833, 2.05% of females). Young males experienced a higher dislocation rate and reached a relative plateau around age 40. Conversely, females had a relatively stable rate of dislocations throughout all age groups and the incidence increased in their later decades. The incidence rate of dislocations in females surpassed that of males at approximately age 63 years. The overall rate per year of shoulder dislocations by gender and age is seen in Figure 1.

The NEISS database divides consumer products into broad categories, which were analyzed to determine overall injury patterns (Table 2). Sports and recreation equipment were associated with 44.31% (365348) of dislocations, followed by home structures and construction materials (21.22%), and home furnishings, fixtures, and accessories (21.21%).

In an analysis of sub-groups, stairs, ramps, landings, floors were associated with the greatest number of dislocations (131745, 14.0%), with a predominance noted among patients ≥ 40 years (9.6% for ≤ 39 years, 28.4% for ≥ 40 years, P < 0.001) and females (12.0% for males, 28.6% for females, P < 0.001). Among sport and recreational activities, most dislocations occurred during basketball (56600) followed by football (45167). A more throughout breakdown of this information is seen in Table 3.

Specific analysis of males aged 15-20, previously identified as having the highest incidence of dislocation, was undertaken (Table 4). In this group of young males, 82.88% (113421) of dislocations were associated with sports and recreation equipment[3,6]. Specifically, basketball (18.60%) and football (18.59%) were involved in the greatest number and percentage of dislocations. Eight of the top ten subcategories for this age group involved sports and recreation equipment.

DISCUSSION

This study represents a current analysis of the epidemiology of shoulder dislocations presenting to emergency departments in the United States from 2012-2021. The national annual incidence rate throughout the study period held was approximately 23.92 per 100000 persons. Male adolescents sustained the highest proportion of dislocations, with 17.70% of all dislocations occurring in males aged 15-20 years, predominantly resulting participation in sports and recreation equipment. Conversely, women experienced a relatively consistent incidence of dislocation throughout their lifespan. After age 63, the incidence rate of dislocations in females surpassed that observed in males.

The findings of this study align with the existing literature. We observed an annual incidence rate of 23.92 per 100000 throughout the study period. Similarly, Zacchilli *et al*[6] noted an incidence of 23.9 per 100000 person-years in a study analyzing NEISS data between 2002 and 2006. Of note, a study by Owens *et al*[3] reported a much higher incidence rate of dislocations among United States Military Academy cadets at 169 per 100000 person-years, although their study was comprised of primarily young, physically active males. Additionally, other studies have reported dislocation rates among young, physically active patients to be as high as seven times greater than that observed in the general population[6,9]. These findings agree with the results of our analysis, which noted male adolescents to account for the greatest number of

Table 1 Total weighted national electronic injury surveillance system estimates, rate per year, national incidence, and demographics, for all United States shoulder dislocations between 2012 and 2021

	National estimate	95%CI
Total	773039	640598-905481
Rate per year	77304	64060-90548
Incidence per 100000	23.92	19.86-28.07
	Mean	St. Deviation
Age	37.1	22.0
Gender	National estimate	Percent
Male	537189	69.5%
Female	235834	30.5%

CI: Confidence intervals.

Table 2 Total weighted national electronic injury surveillance system estimates for all United States shoulder dislocations between 2012 and 2021, by consumer product categories

Consumer product category	National estimate	Percent of cases
Sports and recreation equipment	365348	44.31%
Home structures and construction materials	174975	21.22%
Home furnishings, fixtures, and accessories	174883	21.21%
Personal use items	32235	3.91%
Packing and containers, household	15511	1.88%
Home communication, entertainment and hobby	13940	1.69%
Yard and garden	8943	1.08%

shoulder dislocations presenting to emergency departments.

The current study found an estimated total reported cases of 136844 men 15-20 years old, which made up for 17.70% of the total cases reported in this study, with an annual incidence of 106.91 per 100000. These results are higher to those of similar studies in other countries which found men 16-20 years old to have an incidence of 80.5 per 100000 in the United Kingdom and 98.3 per 100000 in Canada[15,16]. Studies have attributed this difference in rates of injury to the prevalence of competitive contact sports played among men within this age range in the United States and Canada (American football and ice hockey) compared with their peers in the United Kingdom[15]. Further, it was observed that in this population, 113421 (82.88%) of the injuries occurred while using sports and recreational equipment. This finding is consistent with prior studies that have analyzed the incidence of this injury among young athletes and military populations[3,4,17,18].

During our study period, women were found to account for less than one third of dislocations presenting to emergency departments and previous studies have reported a similarly low incidence of this injury in women when compared to men[7,15,16]. However, the incidence of shoulder dislocation in women was noted to surpass that of men after the age of 63. This aligns with existing data demonstrating a higher dislocation rate in women after the sixth decade[7,15]. While this discrepancy is poorly understood, we hypothesize that it may be due to a combination of biological differences between men and women as they age, such as muscle bulk and tendon strength, as well differences in the rate of falls between sexes[19,20]. Interestingly, over 60% of dislocations events in female patients were associated with home furnishings, fixtures, or structures. This suggests a need for separate preventative measures and strategies for older female patients from the already established sports-related strategies directed at young males. Further research is necessary to fully understand underlying differences in risk between patient demographics and may assist in the development of preventative measures aimed at decreasing the burden of shoulder dislocations associated with falls in the elderly[21].

Of note, there were too few recorded cases of shoulder dislocation in children younger than 12 years to provide national estimates, suggesting that this is a relatively rare injury among this demographic. One existing study reporting on the epidemiology of pediatric shoulder dislocation in Italy demonstrated an incidence of 0.3 per 100000 inhabitants less than age 14[22]. The low incidence of shoulder dislocation in pediatric patients may be explained by skeletal immaturity as the mechanisms of injury generally associated with dislocation are more likely to cause proximal humerus fractures or physeal injury in patients whose physis has not yet closed[23].

Table 3 Total weighted national electronic injury surveillance system estimates for all United States shoulder dislocations between 2012 and 2021, for the top ten product sub-groups, with subgroup analysis for age ≤ 39 and ≥ 40 years, and gender

Rank	Product sub-group	National estimate	≤ 39	Percent (%)	≥ 40	Percent (%)	Male	Percent (%)	Female	Percent (%)
1	Stairs, ramps, landings, floors	131745	45193	9.6	86551	28.4	64235	12.0	67510	28.6
2	Beds, mattresses, pillows	76778	45200	9.6	31579	10.4	48119	9.0	28660	12.2
3	Basketball	55226	53619	11.4	1607	0.5	51081	9.5	4145	1.8
4	Football	43158	42172	9.0	[1]	[1]	42006	7.8	[1]	[1]
5	Exercise and equipment	39052	26388	5.6	12665	4.2	26836	5.0	12216	5.2
6	Bicycles and accessories	32789	15733	3.4	17040	5.6	28600	5.3	4189	1.8
7	Clothing, all	26832	12714	2.7	14118	4.6	13653	2.5	13180	5.6
8	Ladders, stools	22372	4930	1.1	17442	5.7	17529	3.3	4842	2.1
9	Bathtub and shower structures	21640	8861	1.9	12779	4.2	11076	2.1	10564	4.5
10	Chairs, sofas, and sofa beds	21193	8143	1.7	13050	4.3	10667	2.0	10526	4.5
Total		773039	468458		304566		537189		235834	

[1]Estimates denoted by have at least one of the following unstable characteristics and were not returned: Estimate is less than 1200, number of cases is less than 20, coefficient of variation exceeds 33%.
$P < 0.001$ age groups *vs* gender groups.

Table 4 Total weighted national electronic injury surveillance system estimates for shoulder dislocations among males aged 15-20 years between 2012 and 2021, including the top ten product sub-groups

		National estimate	95%CI
	Total	136844	107830-165857
	Rate per year	13684	10783-16586
	Incidence per 100000	106.91	84.24-129.57
Rank	Product sub-group	National estimate	Percent
1	Basketball	25448	18.60%
2	Football	25435	18.59%
3	Beds, mattresses, pillows	7314	5.34%
4	Exercise and equipment	6350	4.64%
5	Miscellaneous sports	5941	4.34%
6	Soccer	5772	4.22%
7	Skateboards, scooters, hoverboards	5771	4.22%
8	Stairs, ramps, landings, floors	5627	4.11%
9	Swimming activity, pools, equipment	5440	3.98%
10	Baseball/softball	5163	3.77%

CI: Confidence intervals.

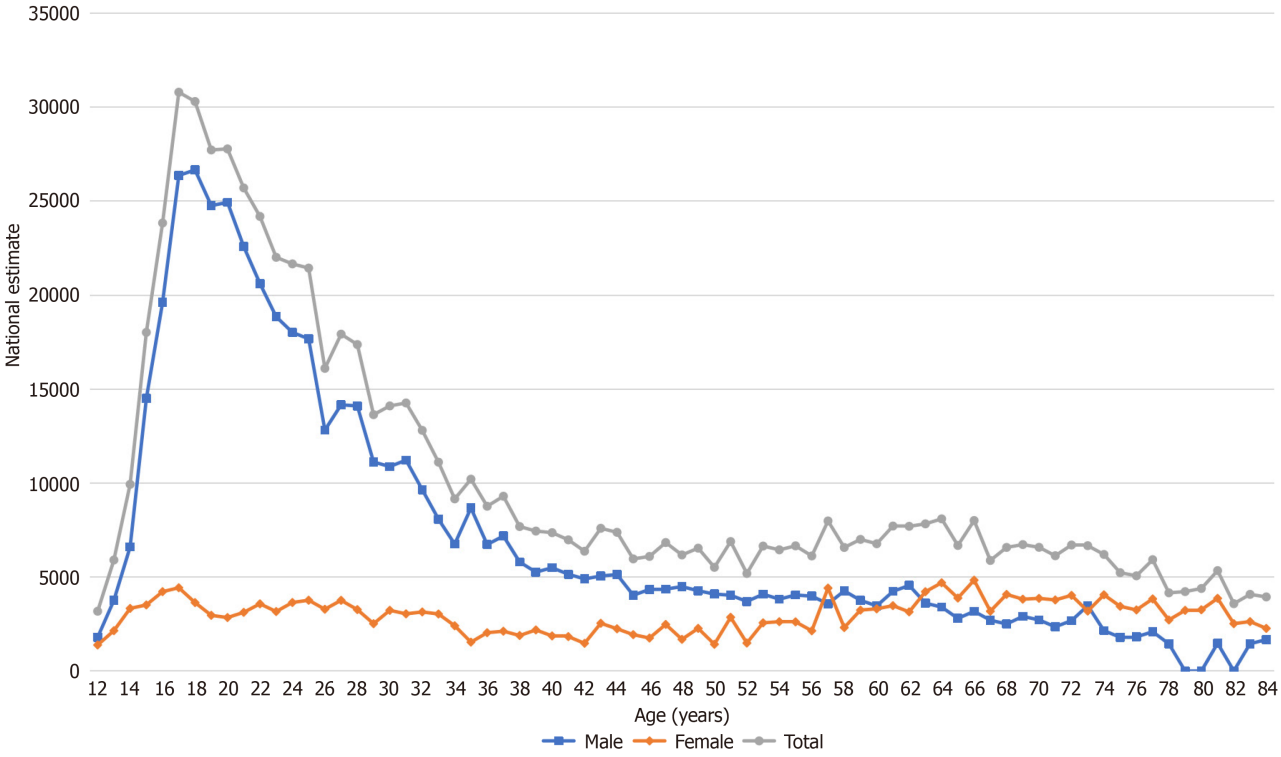

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Figure 1 Total weighted national electronic injury surveillance system estimates per year for all United States shoulder dislocations between 2012 and 2021, by age in years and gender. There was insufficient data to provide national estimates for ages < 12 and > 84 years, as well as males ages 79, 80, and 82.

This study was not without its limitations. As with any database, the scope of this study is limited to variables obtained by data collectors and does not include patients who presented to primary care, urgent care, or sports medicine clinics. Because the provided totals are weighted estimates based on a probability sample of emergency room visits, the numerical estimates could be subject to sampling bias and therefore may not represent the true incidence of injury in the defined study population. Additionally, it is possible that errors were made while coding these injuries and their associated consumer products within the NEISS. Furthermore, logging products into broad categories relies on the coder's judgment and this carries bias. Due to the nature of the NEISS database, we were unable to retrieve more detailed information regarding specific consumer products associated with injury, nor where we able to retrieve exact mechanism of injury. Lastly, the database did not differentiate between anterior and posterior shoulder dislocations, nor did it indicate whether dislocation events were primary or recurrent. It is possible that the presence of patients with multiple recurrent dislocations may contribute to a falsely elevated incidence rate[6].

CONCLUSION

The national annual incidence rate throughout the study period was approximately 23.92 per 100000 persons. Male adolescents sustained the highest proportion of dislocations, with peak incidence occurring in age 15-20 years, predominantly secondary to participation with sports and recreation equipment. Conversely, women experienced a relatively consistent incidence of dislocation throughout their lifespan. After age 63, the incidence rate of dislocations in females was found to surpass that observed in males.

ARTICLE HIGHLIGHTS

Research background

This research was conducted to examine temporal trends regarding shoulder dislocations in the Untied States.

Research motivation

Shoulder dislocations are common among all populations, especially young men, and understanding the epidemiology is important for orthopedic surgeons.

Research objectives
To provide and updated assessment of the epidemiology of shoulder dislocations in the United States.

Research methods
Emergency department within the United States was collected using the national electronic injury surveillance system database between 2012 and 2021, and epidemiologic data was collected and analyzed for shoulder dislocations.

Research results
The national annual incidence of shoulder dislocations in the United States was approximately 23.92 per 100000 persons, with a predominance of dislocations occurring in male adolescents between the ages of 15-20.

Research conclusions
There is a bimodal distribution of shoulder dislocations in the United States. A large portion of male adolescent sustain these injuries between the ages of 15-20 secondary to participation in sporting events. Conversely, women have a relatively consistent incidence of dislocations in their lifespan with an increase in their later decades of life.

Research perspectives
Future studies should help create measures to help lower the incidence of shoulder dislocations in at risk population, particularly adolescent males participating in sports.

FOOTNOTES

Author contributions: Patrick CM performed the majority of the research, collected data, analyzed data, and contributed to the manuscript; Snowden J and Eckhoff MD contributed equally to this work by performing research, and contributing to the manuscript and background research; Green CK and Scanaliato JP oversaw manuscript revisions and project design; Dunn JC and Parnes N designed the research study, coordinated the research team, and oversaw final manuscript revisions; All authors have read and approve the final manuscript.

Institutional review board statement: All data used in the following manuscript are deidentified and available online through the United States Consumer Product Safety Commission.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: United States

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ORIGINAL ARTICLE

Retrospective Study

Sclerotherapy as a primary or salvage procedure for aneurysmal bone cysts: A single-center experience

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Abstract

BACKGROUND

Aneurysmal bone cysts (ABC) are benign cystic bone tumors of an osteolytic and locally aggressive nature. As an alternative to the primary treatment of choice, which consists of curettage with bone grafting, alternative treatment methods with promising results have been described. At our department, we have, in recent years, used percutaneous sclerotherapy with polidocanol. The objective of this study was to identify the healing rate and safety of sclerotherapy with polidocanol.

AIM

To identify the efficacy and safety of sclerotherapy with polidocanol in primary and recurrent ABC.

METHODS

Twenty-two consecutive patients (median age 12.5 years; range 1-27) with 23 ABCs treated with sclerotherapy with polidocanol from 2016-2021 were included retrospectively. Eleven patients (48%) had undergone different forms of previous treatment with recurrence. Under general anesthesia and fluoroscopic guidance, repeated percutaneous injections of 4mg polidocanol/kg body weight were performed. Through review of the electronic medical records, the following were identified: healing and recurrence rate, number of treatments, gender, age, comorbidity, location of the tumor and side effects / complications, as well as any previous surgery for ABC. The median length of radiographic follow-up was 19.5 mo.

RESULTS

All ABCs except one (96%) showed healing or stable disease after a median of 4 (range 1-8) injections. Complete clinical and radiographic healing was observed in 16 cysts (70%), while partial radiographic healing with resolution of pain was seen in 6 cases (26%) and considered as stable disease. The cyst that failed to heal had

previously undergone curettage twice with recurrence. One patient with a large pelvic ABC experienced, right after two injections, a sudden drop in blood pressure, which could quickly be reversed. One patient with a juxtaphyseal ABC in the femoral neck showed a minor limb length discrepancy because of deformity. Beyond that, no complications were observed.

CONCLUSION

Percutaneous sclerotherapy with polidocanol appears to be a safe alternative for treatment of aneurysmal bone cysts. In our series of both primary and recurrent cysts, it showed the ability to achieve healing or stable disease in 22 of 23 cases (96%). Further studies are needed to decide if this provides a long-lasting effect.

Key Words: Aneurysmal bone cyst; Bone tumor; Sclerotherapy; Polidocanol; Healing rate; Complications

Core Tip: This retrospective study presents the first outcomes after implementation of sclerotherapy for aneurysmal bone cysts (ABC) at our department. Compared to other series, 48% of our cohort consisted of patients with recurrent ABC after previous treatment or failed surgery. Sclerotherapy showed a high potency to achieve healing or stable disease and a low rate of adverse events in both treatment groups. We can recommend it as standard treatment both for primary and recurrent ABC, keeping in mind that randomized multicenter studies would be needed to provide evidence for the superiority of one treatment method.

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INTRODUCTION

Aneurysmal bone cysts (ABC) are rare benign bone tumors, usually affecting children and adolescents[1]. Patients mostly present with pain, with or without swelling, and sometimes with a pathological fracture.

Radiologically, these lesions are expansile and osteolytic and can be locally aggressive (Figure 1). On magnetic resonance imaging (MRI), fluid-fluid levels are diagnostic, and soft tissue expansion can be seen. It is the gold standard to verify the diagnosis with biopsy.

The traditional treatment, curettage and bone grafting, has shown high rates of morbidity and recurrence[1-4]. As a result of that, several other treatment options have been explored: embolization, radiotherapy, wide excision and sclerotherapy with different agents and more[5-9]. In recent years, percutaneous sclerotherapy, especially with polidocanol, alcohol or doxycycline, has shown promising results with similar recurrence rates and low morbidity compared to open surgery[10-17]. There are several series published with polidocanol as primary treatment, but to our knowledge, there are no larger reported series on polidocanol as a salvage procedure. In our series, 48% of the cysts were treated with polidocanol for failed surgery or recurrence after previous treatment.

In this study, we present our experience with percutaneous polidocanol treatment for primary and recurrent ABC with focus on healing rate, recurrence and complications.

MATERIALS AND METHODS

In this single-center retrospective study design, all patients treated for ABC with percutaneous sclerotherapy from 2016-2021 were included. In 2016, sclerotherapy was introduced as standard therapy for primary and recurrent ABCs at our institution. Through review of the electronic medical records, the following data was identified: healing and recurrence rate, number of treatments, gender, age, comorbidity, location of the tumor, side effects and complications, as well as any previous surgery for ABC. Twenty-two patients with a combined number of 23 ABCs were identified. The various characteristics are shown in Table 1. Imaging at first presentation included conventional radiographs and MRI in all patients. Furthermore, a histological sample was available in all patients, either from previous surgery or collected with open biopsy. In five patients, open biopsy was performed simultaneously with the first sclerosant injection (Figure 2).

Sclerotherapy was performed under general anesthesia. The cyst was punctured percutaneously with a 1.0 or 1.2 mm trocar needle under fluoroscopic guidance. In classic ABC, bloody fluid from the cyst can be aspirated at the beginning of treatment. The cyst was injected with 4 mg Polidocanol (Aethoxysklerol®) per kilogram bodyweight, as described by Brosjö *et al*[10], mixed with contrast agent Iohexol (Omnipaque®). Before injection, the needle with trocar was directed in all cystic areas to break down possible septae. During injection, contrast agent was used to ensure that all parts of the cyst

Table 1 Demographic data and treatment details

Patient-ID	Age at presentation	Gender	Location	No. of injections	Ossification	Previous treatment	Follow-up (mo)	Histologic result
1	13	M	Pubic bone	5	Complete	Curettage + bone graft	13	Classic ABC
1	13	M	Sacrum	3	Partial	None	13	Consistent with ABC
2	13	F	Distal fibula	5	Absent	Two curettages + bone graft	37	Classic ABC
3	10	M	Ischium	6	Partial	None	29	Classic ABC
4	6	M	Scapula	7	Partial	None	24	Classic ABC
5	25	F	Proximal femur	3	Partial	Two curettages + bone graft	8	Classic ABC
6	14	M	Ileum	6	Partial	None	16	Consistent with ABC
7	4	M	Distal fibula	3	Complete	None	4	Consistent with ABC
8	12	F	Distal tibia	1	Complete	Curettage + bone substitute	31	Classic ABC
9	16	M	Proximal tibia	4	Complete	Curettage + bone graft	33	Classic ABC
10	6	M	Distal tibia	8	Complete	Triamcinolone injection	47	Consistent with ABC
11	5	F	Proximal fibula	3	Complete	Curettage + bone substitute	38	Classic ABC
12	15	M	Ischium	2	Partial	None	4	Consistent with ABC
13	14	M	Distal fibula	4	Complete	Curettage + bone graft	23	Classic ABC
14	25	M	Acetabulum	1	Complete	Two curettages + bone graft	35	Classic ABC
15	10	F	3. metatarsal	4	Complete	Curettage + bone substitute	19	Classic ABC
16	10	M	Proximal femur	3	Complete	None	26	Classic ABC
17	27	M	Proximal radius	1	Complete	None	11	Classic ABC
18	16	M	Proximal fibula	5	Complete	None	6	Classic ABC
19	18	M	Proximal femur	2	Complete	Three curettages + bone graft	20	Consistent with ABC
20	9	M	Ischium	4	Complete	None	16	Classic ABC
21	7	F	Distal tibia	6	Complete	None	5	Classic ABC
22	1	F	Proximal femur	6	Complete	None	9	Classic ABC

ABC: Aneurysmal bone cysts.

were treated (Figure 3). After injection, the needle was flushed with saline or previously aspirated blood, and after needle removal, pressure was applied at the site for at least two minutes to prevent extravasation.

The procedure was repeated every 4-6 wk, following the example of Brosjö *et al*[10], until satisfactory radiographical and clinical healing of the cyst was seen. Healing was defined as resolution of pain on clinical examination in addition to complete ossification on radiographs (Figures 1 and 4). Partial ossification or stable disease was determined as resolution of pain on clinical examination in addition to thickening of cortex and partial ossification without increase in cyst size on radiographs (Figure 5). The median radiographic follow-up was 19.5 mo (range: 4-47 mo).

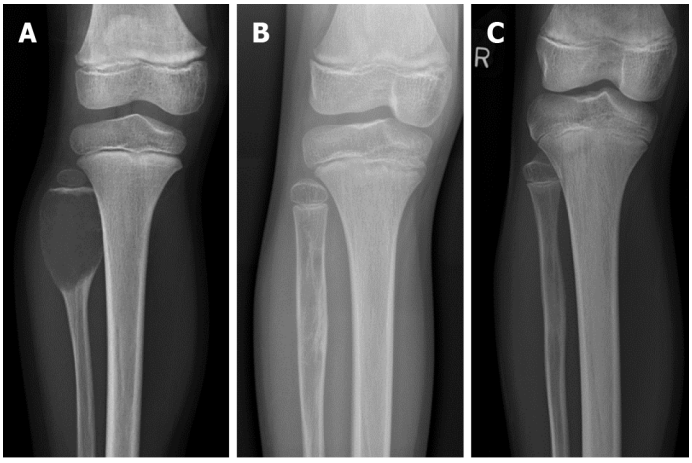

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Figure 1 Radiographs of an aneurysmal bone cyst in the proximal fibula of a 5-year-old girl. A: At presentation; B: After three injections of polidocanol; C: At 38 mo follow-up

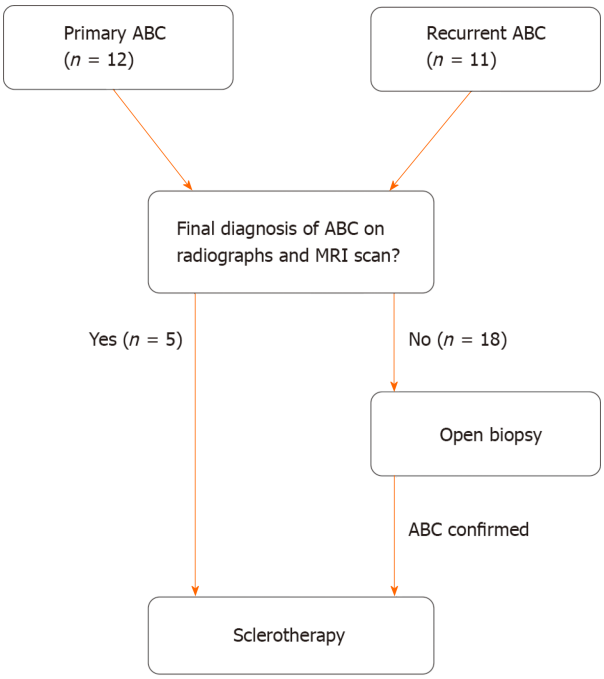

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Figure 2 Flowchart of the algorithm from initial diagnosis to final management. ABC: Aneurysmal bone cysts; MRI: Magnetic resonance imaging.

RESULTS

The summary of the patient characteristics and treatment results is shown in Table 1. The median age at beginning of treatment was 12.5 years (range: 1-27), and males accounted for 68% of patients. Of the 23 cysts, eleven had undergone previous surgical intervention (48%) with subsequent recurrence, wherein ten cysts had been treated with curettage and bone grafting/bone substitute and one with glucocorticoid injection (for details see Table 1). Histopathologically, the diagnosis was confirmed in 17 cases, and in the remaining six cases, the sample was consistent with aneurysmal bone cyst. There were no tumors with an ABC-like area (previously called secondary ABC) or malignancies.

All cysts except one (96%) showed healing or stable disease after a median of four (range: 1-8) injections. Complete ossification was observed in 16 cysts (70%), while partial ossification with complete resolution of pain were seen in six cases (26%), which were considered as stable disease. There were no recurrences in the follow-up period.

The cyst in the distal fibula that failed to heal had previously undergone curettage twice with recurrence. During the course of five polidocanol injections, it showed recurring radiolucency in different parts of the cyst, and the patient displayed persistent pain. Finally, extended curettage with high-speed burring and bone grafting with polidocanol as adjuvant was performed, and the cyst healed without recurrence.

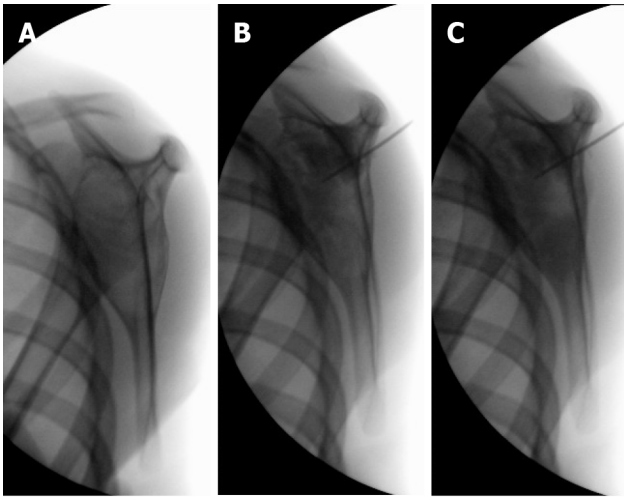

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Figure 3 Intraoperative fluoroscopy images showing sclerotherapy of an aneurysmal bone cyst in the scapula. A: Before injection; B: During injection with polidocanol and contrast agent; C: After injection

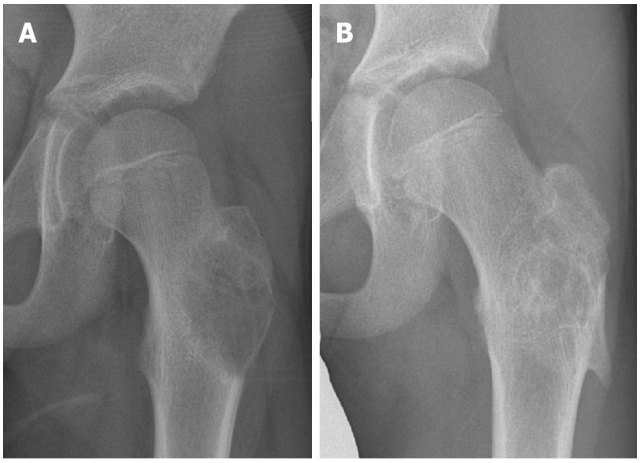

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Figure 4 Radiographs of an aneurysmal bone cyst in the proximal femur showing complete ossification. A: At presentation; B: At 26 mo follow-up after sclerotherapy.

Due to a possible allergic reaction, one patient with a large cyst in the ischium showed a sudden drop in blood pressure to 60 mmHg systolic right after injection of polidocanol/iohexol in two settings, which could quickly be reversed after a bolus of ephedrine and fluid.

One patient with a juxtaphyseal ABC in the femoral neck, who was only 18 mo old at the beginning of treatment, developed a minor limb shortening because of deformity in the trochanteric area at 9 mo follow-up, possibly requiring further orthopedic treatment in the future. Beyond that, no complications, such as skin necrosis or infections, were observed.

DISCUSSION

In this study, we present our experience with percutaneous sclerotherapy of ABC with polidocanol. In our series, 96% of all cysts showed satisfactory treatment response with complete resolution of pain, with 70% showing complete ossification and 26% showing partial ossification without increase in cyst size. There were no recurrences in the follow-up period, but one cyst failed to heal, and treatment was converted to extended curettage and bone grafting with polidocanol as adjuvant. The healing rate of 96% in this study is comparable to the results published in recent literature, with healing rates ranging from 83%-100%[10-13,17-20], except for one study discussed further below. The studies comparing sclerotherapy with polidocanol with curettage found healing rates slightly in favor of sclerotherapy (93.3% *vs* 84.8% and 100% *vs* 82%, respectively) and showed lower morbidity in the sclerotherapy group[11,17].

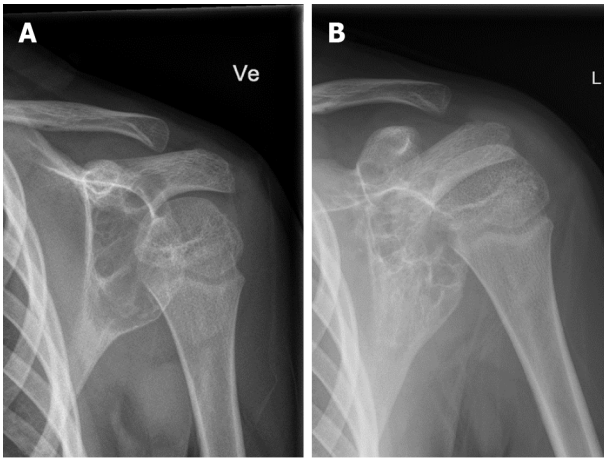

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Figure 5 Radiographs of an aneurysmal bone cyst in the scapula showing partial ossification. A: At presentation; B: At 24 mo follow-up after sclerotherapy.

There is no agreement about the clear definition of successful treatment, or healing, in the literature. As applied in this study, most authors accept the following clinical and radiological signs as successful treatment: Resolution of pain, restoring of function, increasing sclerosis and cortical thickness without increase in cyst size[12,13,17,18].

One study showed less favorable results in both groups: Failure of sclerotherapy with polidocanol and need for further treatment in 34.5% of cases as well as a 38.5% recurrence rate with need for further treatment after intralesional curettage [21]. The authors find a possible explanation for these less satisfactory results in the more accurate cyst size measurement based on MRI scans and higher initial cyst volume in their study compared to similar studies[21]. Furthermore, MRI scans might be more sensitive to detect residual cyst activity (*i.e.*, fluid-fluid levels) than conventional biplanar radiographs, though the clinical importance of this finding remains unclear.

Apart from polidocanol, other sclerosing agents have been used for ABC with promising results. Publications on sclerotherapy with ethanol (in one study combined with Surgiflo®) and doxycycline showed success rates ranging from 68%-100% and 86%-100%, respectively, making them comparable to treatment with polidocanol[14,15,22-25]. At this stage, no sclerotherapy modality has been proven superior, and the treatment choice is usually dependent on regional preference and experience.

The general disadvantage of sclerotherapy is the need for repeated treatments in most cases, which, in this patient age group, usually requires general anesthesia.

Our cohort consisted of 12 primary ABCs and 11 cysts that had undergone previous surgical intervention with subsequent recurrence. To our knowledge, there are no larger reported series on polidocanol as a salvage procedure. In this series, 10 of the 11 recurrent ABCs (92%) showed satisfactory treatment response after sclerotherapy (Table 1).

One recurrent cyst, which had previously undergone curettage twice, failed to heal. Five injections of polidocanol were performed, but the patient showed persistent pain, and radiologically recurrent osteolytic areas were observed in different parts of the cyst. Finally, extended curettage with high-speed burring and bone grafting with polidocanol as adjuvant was performed, and the cyst healed without recurrence. We argue that it can be difficult to address all areas of a recurrent cyst, which in some cases consists of many subcavities. Especially if there are bony septae, it can be challenging to reach a certain subpart of the cyst percutaneously.

There are other described methods for ABC as salvage treatment or in patients where sclerotherapy or open surgery are contraindicated or not feasible. Selective arterial embolization has shown good results and is primarily used in the spine and other anatomically difficult locations, as well as a preoperative adjuvant to surgery. However, it is a technically demanding, operator-dependent procedure with potentially serious side effects due to ischemia, and it requires that a feeding vessel to the cyst can be identified[26,27].

Furthermore, there are pharmacological treatments available as rescue therapy for ABC. In several studies, denosumab, a monoclonal antibody inhibiting osteoclast formation and activity, has been shown to achieve re-ossification of ABC[6, 28-30]. However, serious side effects have been described. Some patients demonstrated severe hypo- or hypercalcemia under or after denosumab treatment[30,31]. Moreover, knowledge regarding the long-term consequences of denosumab on the growing skeleton is lacking so far. A related medical therapy is the use of bisphosphonates, such as zoledronic acid, which also inhibits osteoclast activity. They are widely used to successfully treat and manage various unresectable or metastatic bone tumors. Two smaller studies, with five and eight patients, respectively, have shown positive clinical and radiological effects of bisphosphonates in ABC without adverse events[32,33]. The authors even suggest bisphosphonates as treatment of choice in spinal ABC without neurological deficit or instability[32].

Based on the results of the present study, sclerotherapy with polidocanol might be another alternative salvage procedure to stabilize refractory or recurrent ABC. It can be considered before advancing to salvage treatments with a spectrum of more serious adverse events, as described above. However, further studies with more patients and longer follow-ups are needed to decide whether this is of lasting effect.

There was one adverse event observed in our cohort: A ten-year-old boy with a large cyst in the ischium showed a sudden drop in blood pressure to 60 mmHg systolic right after injection of polidocanol/iohexol in two settings. The reaction could quickly be reversed after a bolus of ephedrine and fluid. This phenomenon has also been described by other authors[18,34]. Like in the present study, it is usually harmless and quickly reversible, but in two cases, severe reactions have been described: One patient developed hypovolemic shock and cardiac arrest needing resuscitation, and the other one presented ventricular tachycardia with a sharp drop in blood pressure[18,34]. Both patients are reported to have recovered completely, but these observations necessitate this procedure only to be performed in a controlled setting with monitoring of vital signs.

Other authors reported minor complications to sclerotherapy, *e.g.*, skin induration, hypopigmentation, minor inflammatory reactions, ulceration or temporary pain[10,12,13,17,19,20]. On the other hand, the studies comparing sclerotherapy to curettage and/or resection found a higher rate of clinically pertinent complications and poorer functional outcomes in the surgery group[11,17,21].

One important limitation of this study is the short radiological follow-up in some patients. The retrospective study design meant that the follow-up was planned individually by the treating surgeon, not following a standard plan. Some patients showing signs of healing and resolution of pain in the first year after treatment were discharged and informed to contact our department again should pain or other symptoms recur. For these patients, our department is the responsible center for treating ABCs. The electronic medical journal showed no contacts to our or other hospitals in the region concerning their previous ABC in the following months and years. Furthermore, it was ensured that the place of residence was still in our region. The authors therefore argue that recurrence with clinical signs most likely would have been detected in these patients.

The other limitations of this study consist primarily of the number of patients, the retrospective study design and the lack of a control group. Randomized multicenter studies would be needed to provide evidence for the superiority of one treatment method for aneurysmal bone cysts.

CONCLUSION

This study supports evidence in the current literature that percutaneous sclerotherapy with polidocanol is an efficient and safe alternative to conventional surgery for the treatment of aneurysmal bone cysts. It can especially be recommended for cysts in difficult anatomic locations where open surgery would cause significant morbidity. Based on the present study, it may also be considered as a salvage procedure for failed surgery or multiple recurrences. Further studies are needed to decide if this provides a long-lasting effect and which of the discussed treatment methods is superior for primary or recurring aneurysmal bone cysts.

ARTICLE HIGHLIGHTS

Research background

As an alternative to the traditional treatment of aneurysmal bone cysts (ABC), which consists of curettage with bone grafting, alternative treatment methods with promising results have been described. At our department, we have been using percutaneous sclerotherapy with polidocanol for primary and recurrent ABC. To our knowledge, this is the first larger series reporting on polidocanol as a salvage procedure.

Research motivation

The main challenge with aneurysmal bone cysts is their locally aggressive nature and a high risk of recurrence. Therefore, there is a need to find evidence for the best available treatment, which optimally shows high efficacy and at the same time low morbidity and low rates of recurrence.

Research objectives

The main objective was to identify the efficacy and safety of sclerotherapy with polidocanol in primary and recurrent ABC. The outcomes of this study, especially regarding recurrent ABC, propose sclerotherapy as a relevant treatment method to be considered.

Research methods

This is a single-center retrospective study, where all patients treated for ABC with percutaneous sclerotherapy from 2016-2021 were included. The data was collected through review of the electronic medical records.

Research results

In our series, sclerotherapy with polidocanol showed the ability to achieve healing or stable disease in 96% of cases (100% in primary ABC and 92% in recurrent ABC). These results support the positive experience with sclerotherapy for primary ABC in the recent literature and open the debate about sclerotherapy as a possible salvage treatment. The median length of radiographic follow-up was 19.5 mo. Further studies with longer follow-up are needed to decide if this provides a long-lasting effect.

Research conclusions

Based on the present study, sclerotherapy with polidocanol may also be considered as a salvage procedure for failed surgery or multiple recurrences. This can be a valuable alternative to other salvage treatment methods, which may have higher morbidity.

Research perspectives

Given the variety of possible treatment methods, future research should focus on randomized clinical trials to identify the gold standard treatment for primary and recurrent ABC.

FOOTNOTES

Author contributions: Weber KS designed and performed the research and wrote the paper. Jensen CL and Petersen MM designed the research, contributed to the analysis and supervised the report.

Institutional review board statement: The study was approved by the Danish Patient Safety Authority and the Data Protection Agency of the Capital Region of Copenhagen.

Informed consent statement: According to the Danish medical law and the institutional review board statement, this retrospective study did not require informed consent from the patients.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Clinical Trials Study

Use of orthotics with orthotic sandals versus the sole use of orthotics for plantar fasciitis: Randomised controlled trial

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Abstract

BACKGROUND

Plantar fasciitis (PF) affects around 10% of the population. Prefabricated orthotics with arch support has been shown to provide symptom relief in PF by decreasing the repetitive stress sustained by the plantar fascia. However, prefabricated orthotics are only effective when shoes are worn, meaning the foot may be left unsupported when it is impractical to wear shoes. Using orthotic sandals in conjunction with prefabricated orthotics may increase PF symptom relief, as they can be worn inside the home, extending the period in which the foot is supported.

AIM

To compare the combined use of prefabricated orthotics and orthotic sandals *vs* the sole use of prefabricated orthotics in the treatment of PF.

METHODS

98 participants with PF were randomised into two groups. The intervention group received the Aetrex L420 Compete orthotics and the Aetrex L3000 Maui Flips (orthotic sandals), whilst the control group received the Aetrex L420 Compete orthotics only. Foot pain was assessed both by the numerical rating scale (NRS) and the pain sub-scale of the foot health status questionnaire (FHSQ). Foot functionality was measured using the function sub-scale of the FHSQ. Symptom change was measured using the global rating of change scale (GROC).

RESULTS

Foot pain scores measured both by NRS and FHSQ pain sub-scale showed statistically significant reductions in foot pain in both groups ($P < 0.05$) at six months. Both groups also reported statistically significant improvements ($P < 0.05$) in function as measured by the FHSQ function subscale and improvement of symptoms as measured by the GROC scale. Between-group analysis showed that the intervention group with the combined use of orthotics and orthotic sandals scored better on all four outcome measures as compared to the control group with the sole use of orthotics. However, the between-group analysis only reached statistical significance on the NRS pain score ($P < 0.05$).

CONCLUSION

Combined use of prefabricated orthotics and orthotic sandals provides a greater decrease in foot pain and improvement in foot function in PF compared to using prefabricated orthotics alone.

Key Words: Plantar fasciitis; Foot diseases; Musculoskeletal pain; Foot orthoses

Core Tip: Plantar fasciitis (PF) is a common cause of heel pain and affects 10% of the population. Prefabricated orthotics provides relief of symptoms by supporting the arch but can only be used with shoes. Using both prefabricated orthotics and orthotic sandals can extend the period of support. This study finds that the combined use of Aetrex L420 orthotics and Aetrex L3000 orthotic sandals and the sole use of Aetrex L420 orthotics provide statistically significant decreases in foot pain and improved foot function in PF. The effect was greater when both the orthotic and orthotic sandals were used in combination.

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INTRODUCTION

Plantar fasciitis (PF) is the most common cause of heel pain, affecting 10% of the population[1]. Despite the name "fasciitis", which suggests inflammatory causes, the condition is indicated to result from degeneration of the plantar fascia. Histological findings typically reveal degenerative changes such as localised fibrosis, matrix calcification, collagen necrosis and angiofibroblastic hyperplasia. Hence, the term plantar fasciopathy may be preferred[2]. PF is most commonly found in individuals between 40 and 70 years old and is more frequent in women than in men[1,3]. Both physically active and sedentary populations can develop the condition, and risk factors consist of, among others, a recent increase in running, prolonged standing activities, tightness of the gastrocnemius, obesity, pes cavus or pes planus foot types, and the use of footwear that is either unsupportive or that alters foot kinematics[1]. Although the exact aetiology of the condition remains unclear, mechanical overload is thought to contribute to its development[4]. Studies have shown that excessive tensile forces on the fascia cause microscopic changes[5]. Disparity in leg length and tightness of the gastrocnemius contribute to increased tensile loading of the fascia, which heightens the pressure on the longitudinal arch [6]. This may result in microscopic tears and degeneration in the fascia. Symptoms include sharp pain following palpation of the medial plantar calcaneal region and heel pain during the first steps of the day or following extended periods of inactivity[4]. The resulting pain from PF can cause activity limitation and considerable disability, negatively impacting overall quality of life[7].

PF is a self-limiting condition, with most cases resolving within 6 to 18 mo[8]. However, some reports suggest that up to 49% of PF patients are symptomatic for 1.5 to 5 years following the onset of symptoms, and an estimated 2 million people worldwide will receive treatment for the condition annually[9,10]. However, there is currently no standardised treatment method for the condition, with very few studies providing high-quality analysis across different treatment modalities[11]. Furthermore, many studies use treatment methods in combination, making it difficult to determine which is the most beneficial as a stand-alone modality.

Gastrocnemius contracture is an evident contributor to PF[12], and so stretching techniques such as calf-stretching and plantar-fascia-specific-stretching are frequently prescribed. However, a systematic review of the literature found only very low-quality evidence to support their use over sham stretching[13]. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used in the treatment of PF. Long-term use of NSAIDs, defined as consumption of three or more times a week for more than three months[14], is not without risk of complications, including gastrointestinal bleeding, nephrotoxicity, and dependency[15]. A 2015 systematic review evaluated the literature investigating the efficacy of various taping techniques, including calcaneal and low dye taping, in the treatment of PF. The review found that taping, in general, is beneficial in treating the condition. However, all studies included in the review only assessed short-term

effects, so no evidence was available regarding long-term outcomes[16]. Probe *et al*[17] assessed the effects of the combined use of Achilles stretching exercises, shoe recommendations and anti-inflammatory medications, with and without the addition of night splints, on PF symptoms. They found that the addition of night splints provided no statistical difference in improvements.

Orthotics have been found to decrease foot pain and increase function in PF patients compared to other non-interventional methods[18]. Such benefits from orthotics result from evened weight distribution across the plantar area and arch, shock absorption, and enhanced proprioception[19,20]. The arches of the foot are maintained not just by bony contours but also by the soft tissues that surround the structure. During weight bearing, the arches are depressed and lengthened. The repetitive lengthening whilst weight bearing has been implicated as one of the causative mechanisms of PF[21]. A contoured orthotic which provides mechanical support to the foot prevents repetitive deformation whilst weight bearing and thereby can provide symptom relief and prevent relapse of PF[21]. However, a recent systematic review and meta-analyses of orthotics for plantar heel pain have reported low-quality evidence due to the high risk of bias in studies[22]. Another systematic review and meta-analyses suggest that conclusions have been drawn from low-quality trials and future high-quality trials are required[23].

Like orthotic insoles, orthotic sandals may offer improved arch support and even weight distribution. Research has shown that the use of orthotic sandals and flip-flops with moulded footbeds can have significant effects on the symptoms of PF, including foot pain, function, and foot health[24,25]. The combined use of orthotics and orthotic sandals may be appropriate, as they are both non-invasive and complement each other. Although PF is self-limiting, it is painful and disabling during periods of activity, and hence symptom relief is essential. Unfortunately, orthotics can only be used when donning shoes. Utilising orthotic sandals in conjunction with prefabricated orthotics may enhance symptom relief in PF, as orthotic sandals can be used when donning shoes may not be practical, as whilst at home and indoors. The pain and symptoms from PF is also most severe early in the morning on waking. It may be more feasible to get into orthotic sandals rather than into shoes and orthotics as one takes the first step in the morning. To our knowledge, no research has been conducted into the effects of the combined use of prefabricated orthotics and orthotic sandals in the treatment of PF.

Hence the aim of this study is to identify if the combined use of prefabricated orthotics and orthotic sandals is superior to the use of orthotics only in the treatment of PF. The clinical significance for health providers and patients is that though PF is a self-limiting disorder, symptom relief is required during the active phase of the disease. As most cases of PF only require symptomatic treatment, it is needless to burden the overstretched healthcare system to treat this disorder. This trial hopes to identify a method by which patients can safely and reliably choose a non-invasive treatment modality to address plantar heel pain.

MATERIALS AND METHODS

This study is a non-blinded randomised control trial (RCT) and was conducted over a period of 17 mo between July 2021 and November 2022 through an independent musculoskeletal clinic. The participants were volunteers who responded to social media advertisements about the study. The primary objective is to investigate whether the combined use of prefabricated orthotics and orthotic sandals *vs* the sole use of prefabricated orthotics is more beneficial in decreasing foot pain and increasing foot functionality in PF. The Wales Research Ethics Committee (REC) 5 provided ethical approval on April 14, 2021 by REC reference: 21/WA/0099 and IRAS project ID: 297181. Reporting of the study conforms to the CONSORT statement (CONSORT 2010 statement)[26].

Sample size calculation

A sample size calculation was performed using a target of a one-point change in the numerical rating scale (NRS) pain score (SD 1.6) (the primary outcome), with 80% power and a significance level of 5%. A 20% drop-out rate was allowed. This led to a required sample size of 52 per group, resulting in a total sample size of 104 study participants.

Participants

Participants were recruited from mainland United Kingdom including England, Scotland, Wales and Northern Ireland on a voluntary basis through social media advertisements. Potential participants were provided with a participant information sheet by post or email.

PF whose ICD-10-CM diagnosis code is M72.2[27], is diagnosed both from history and examination findings. The study was designed during the coronavirus pandemic when non-urgent and non-acute cases were diverted to telephone or online consultations. In telephone and online consultations, a physical clinical examination is not possible. To accommodate the restrictions of the lockdown and social distancing the study was designed to diagnose PF only from history and without the advantage of physical examination. To be included in the study, participants had to state that their pain was in the medial-inner aspect of the heel and that the pain was most severe in the morning upon waking. If a potential participant stated otherwise, they were disqualified from participating in the trial. Participants then had a telephone consultation with the lead investigator, a consultant orthopaedic surgeon who has 20 + years of experience post certificate of completion of speciality training.

Inclusion criteria required participants to be aged between 18-75 years old and to have experienced symptoms of PF for at least two months. Participants were excluded if they had received any treatment other than analgesia within the last 12 mo, had any history of foot surgery, and had any congenital or acquired foot abnormalities that would prevent the use of normal footwear. Participants were informed that they could withdraw from the study at any time without needing to give a reason. Participants were then given the opportunity to raise any questions they had about the study. Subse-

quently, participants agreeing to enrol in the trial were asked to provide informed written consent, either online *via* legalesign.com, or by post.

Randomisation

Following recruitment, participants were randomised into one of two groups using an allocation ratio of 1: 1, the intervention group, or the control group. Randomisation was achieved by opening sealed, opaque envelopes, which either contained labels stating, "O and F", denoting orthotics and flips (sandals) and corresponding to the intervention group or "O Only", denoting orthotics only and corresponding to the control group. An individual independent of the research team then randomly selected an envelope, the contents of which assigned the participant to their group. Blinding of participants or researchers was not possible due to the nature of the study.

Intervention

Participants in the intervention group received both the Aetrex L420 Compete orthotics (Figure 1) and the Aetrex L3000 Maui Flips (Figure 2) by post according to their shoe size. Participants in the control group received the Aetrex L420 Compete orthotics only. Participants were instructed to use the devices where possible for a period of 6 mo.

Data collection

Basic demographic information and baseline data were collected upon recruitment. The outcome measures used in this study were foot pain by NRS and foot health status questionnaire (FHSQ), foot functionality (by FHSQ) and change in PF symptoms [by global rating of change scale (GROC)]. Data for all outcomes were collected *via* questionnaires upon initial recruitment, then at three weeks, six weeks, three months, and six months. Participants completed this questionnaire online at smartsurvey.co.uk or as a paper copy provided *via* post, depending on their preference.

Primary outcome measure

The primary outcome measure was to measure the change of foot pain between baseline and 6 mo follow-up using an 11-point NRS, which ranged from zero, denoting "no pain", and ten, denoting "extremely severe pain". The minimal clinically important difference (MCID) on the NRS scale is a 1.7 score change of the median[28].

Secondary outcome measures

Foot pain was also scored along with foot functionality using the "foot pain" and "foot functionality" sub-scales of the FHSQ. For these sub-scales, 5-point likert scales ranging from "no problems, pain or limitations" to "severe problems, pain or limitations" were provided. A dedicated FHSQ programme (https://www.fhsq.org/) was then utilised to calculate an overall score between 0 and 100, depending on the participants' answers, with 0 representing "the worst foot health" and 100 representing "the best foot health". The MCID for the FHSQ pain subscale is 13 points and for the FHSQ function subscale is 7 points[29]. Change in symptoms was assessed using the GROC, an 11-point scale from -5 to + 5, with "-5" representing "very much worse", "0" representing "no change" and "+5" representing "completely recovered".

A data monitoring committee consisting of patients, an independent doctor not part of the research team, and a medical statistician was implemented during the study to ensure that the data collected was legitimate and reliable and to observe for any significant adverse outcomes.

Statistical analysis

NRS for pain: Wilcoxon signed-rank test was used to assess the within-group statistical significance of changes from baseline to 6-mo follow-up of the NRS pain scale. The Mann-Whitney U test was used to assess the between-group statistical differences for the two groups from baseline to six months.

FHSQ pain and function sub-scales: The paired T-test was used to assess the within-group statistical significance of changes from baseline to 6-mo follow-up of the FHSQ pain and function sub-scale. The independent sample t-test was used to compare the between-group differences.

GROC: Wilcoxon signed-rank test was used to assess the within-group statistical significance of changes from 3 wk to 6-mo follow-up on the GROC scale. The Mann-Whitney U test was used to assess the between-group statistical differences for the two groups from 3 wk to six months. The statistical methods of this study were reviewed by an independent statistician from the department of data health sciences, University of Liverpool.

RESULTS

One hundred and four participants were recruited for this RCT. Of these 104 participants, six were not included in the final analysis (drop-out rate = 5.7%), leaving a total of 98 participants to be included in the analysis. In the intervention group (orthotics and orthotic sandals) 1 participant failed to respond and 1 discontinued as the orthotic was uncomfortable. In the control group 2 participants failed to respond, 1 passed away due to unrelated reasons and 1 discontinued as the orthotic did not fit in the shoe. Ninety-eight of the 104 complied with the treatment giving a compliance rate of 94.2%. Details of participant flow through the study, including the number of withdrawals and reasons, are provided in Figure 3. Fifty of the 98 participants included in the analysis were randomly allocated to the intervention group and 48 to the control group. Data collection began in July 2021 and ended in November 2022.

Figure 1 Aetrex L420 Compete orthotics. This orthotic was provided to participants in both the intervention and control group. Copyright ©Aetrex, Inc.

Figure 2 Aetrex L3000 maui orthotic sandals. This orthotic sandal was provided only to participants in the intervention group. Copyright ©Aetrex, Inc.

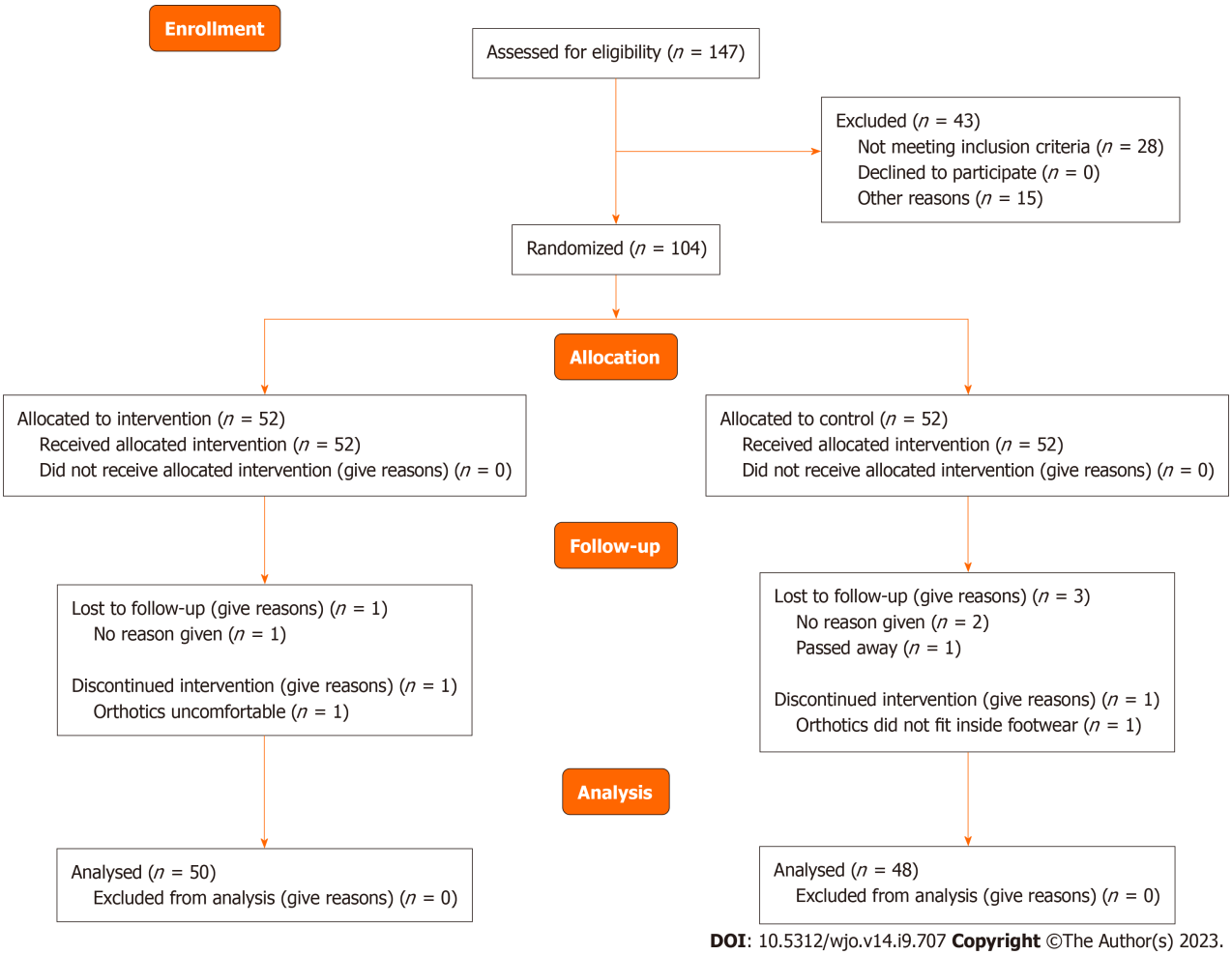

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Figure 3 CONSORT flow diagram.

The baseline demographics of the participants in the intervention and control groups are shown in Table 1. The participants' ages ranged from 29 to 71 years old (mean age = 48.81). Participants in the intervention group with the combined use of orthotics and the orthotic sandals were, on average, slightly younger (mean age = 48.44) than participants in the control group with the sole use of orthotics (mean age = 49.19). Participants in both the intervention group (94%) and the control group (91.6%) were predominantly female. Results for all outcome measures are provided in Table 2. All outcomes were collected at baseline, 3 wk, 6 wk, 3 mo and 6 mo, aside from the GROC, which was collected at all time points except baseline.

At 6 mo, there was a statistically significant improvement in foot pain by the NRS in both groups. Median change of pain was 6 [interquartile range (IQR) 3.25, $P < 0.001$] in the interventional group with the combined use of orthotics and orthotic sandals and 4 (IQR 4.75, $P < 0.001$) in the control group with the sole use of orthotics. Between-group analysis with the Mann-Whitney U test showed statistically significant improvement ($P = 0.003$) in the interventional group with the combined use of orthotics and orthotic sandals as compared to the sole use of orthotics.

Mean pain scores on the FSHQ subscale improved significantly during the six-month period in the interventional group by 51.49 points [95% confidence interval (CI): 44.52 to 58.46, $P < 0.001$] and in the control group by 42.07 points (95% CI: 35.20 to 48.94, $P < 0.001$). Between-group analysis showed that though the mean pain score improved more in the intervention group with the combined use of orthotics and orthotic sandals as compared to the control group with the sole use of orthotics, it did not reach statistical significance ($P = 0.07$).

Foot functionality, measured using the function sub-scale of the FHSQ, improved during the six-month period in the interventional group by 41.50 (95% CI: 34.44 to 48.56, $P < 0.001$) and in the control group by 37.64 (95% CI: 30.19 to 45.09, $P = 0.001$). Between-group analysis showed that there was again greater improvement of function in the intervention group with the combined use of orthotics and orthotic sandals as compared to the control group with the sole use of orthotics, the improvement was not significant ($P = 0.46$).

The findings for the GROC scale demonstrated statistically significant improvement in symptoms over time for both groups (Median improvement in intervention group 2 ($P < 0.05$) *vs* Median improvement in control group 2 ($P < 0.05$). Between-group analysis showed that there was again greater improvement of symptoms in the intervention group with the combined use of orthotics and orthotic sandals as compared to the control group with the sole use of orthotics, but the improvement was not significant ($P = 0.093$).

Figures 4-7 show how the study outcomes varied for each group over time. Figures 4, 5 and 6 show that, for both the intervention group with the combined use of the orthotics and orthotic sandals and the control group with the sole use of orthotics, the greatest improvements in foot pain reported *via* NRS and FHSQ pain sub-scale and foot functionality reported *via* the FHSQ function sub-scale, were between baseline and 3 wk. Following the 3-wk period, there was a slower but sustained improvement in both groups. Additionally, for these three outcomes, the rate of initial improvement between baseline and week 3 was greater for the intervention group with the combined use of the orthotics and orthotic sandals than the control group with the sole use of orthotics. Figure 7 shows the median change in GROC scale scores for each group over time. At each time point that data were collected, a greater improvement in symptoms was reported by the intervention group with the combined use of the orthotics and orthotic sandals than by the control group with the sole use of orthotics.

DISCUSSION

This article presents the results from a RCT. The study investigated whether the combined use of prefabricated orthotics and orthotic sandals provided enhanced symptom relief from PF in comparison to the sole use of orthotics.

The main findings show that both the intervention group with the combined use of orthotics and orthotic sandals and the control group with the sole use of orthotics experienced significant decreases in foot pain at 6 mo as assessed *via* both the NRS and FHSQ pain sub-scale. Decreases in foot pain on both measures were significantly greater in the intervention group with the combined use of orthotics and orthotic sandals, as compared to the control group with the sole use of orthotics. However, between-group differences in pain scores reached statistical significance only on the NRS pain score ($P < 0.05$). Foot function, as assessed by the FHSQ function sub-scale, also showed statistically significant improvement in both the intervention and control groups at 6 mo. Similarly, there was greater improvement in foot function in the intervention group with the combined use of orthotics and orthotic sandals compared to the control group with the sole use of orthotics but it did not reach statistical significance. At 6 mo, the GROC showed a statistically significant improvement in each of the two groups but between-group analysis did not reach statistical significance.

Baldassin *et al*[30] evaluated the effectiveness of both prefabricated and customised insoles on PF in 142 symptomatic adults. The study employed the visual analogue score (VAS) and the foot function index (FFI) to compare pain and function at baseline, 4 wk, and 8 wk. Results showed that both the use of prefabricated and customised orthotics significantly reduced pain and improved function at 8 wk. However, no significant difference was found between the two groups, suggesting that the costlier customised orthotics were not superior to prefabricated orthotics.

Conversely, other studies have had mixed results. Landorf *et al*[7] conducted an RCT containing 136 participants who were randomised into one of three groups to receive either prefabricated foot orthotics, custom foot orthotics or sham orthotics (placebo). Like the current study, this employed the FHSQ to evaluate pain and function. Findings revealed that, at 3 mo, both prefabricated and custom orthotics significantly improved function. However, no continued significant effects were observable at 12 mo for any outcome in either group. This lack of continued significant improvement at 12 mo may have been caused by the self-limiting nature of PF, in which spontaneous resolution of symptoms may occur with the passage of time. Nevertheless, the findings did show that prefabricated orthotics are effective in the period when

Table 1 Table of participant demographics

	Intervention group orthotics and orthotic sandals (%)	Control group orthotics only (%)	Both groups (%)
Sex			
Male	3 (6.0%)	4 (8.3%)	7 (7.1%)
Female	47 (94.0%)	44 (91.7%)	91 (92.9%)
Age (year)			
20-29	1 (2.0%)	0 (0.0%)	1 (1.0%)
30-39	4 (8.0%)	10 (20.8%)	14 (14.3%)
40-49	21 (42.0%)	13 (27.1%)	34 (34.7%)
50-59	20 (40.0%)	18 (37.5%)	38 (38.8%)
60-69	4 (8.0%)	6 (12.5%)	10 (10.2%)
70-79	0 (0.0%)	1 (2.1%)	1 (1.0%)
Mean age	48.44	49.19	48.81
Total	50	48	98

the symptoms of PF are potentially most severe. Furthermore, results indicate that more cost-effective prefabricated orthotics obtain similar results to the costlier custom orthotics.

Wrobel *et al*[18] conducted a RCT to compare the use of custom foot orthoses (CFO), prefabricated foot orthoses (PFO) and sham insoles for the treatment of PF. Outcomes measured were first-step pain, end-of-day pain, Revised FFI short form (FFI-R), and a short form health survey. Following 3 mo of orthoses/sham insole use, the results showed that both the CFO and PFO groups demonstrated significant improvements in morning and evening pain. All groups, including the sham orthotics group, also reported significant improvements in FFI-R pain and short form health survey at 3 mo.

Costa *et al*[31] evaluated the efficacy of flip-flop sandals, adapted with insoles, on pain and function in PF patients. Sixty-six participants were randomised to receive either a pair of adapted flip-flop sandals with custom insoles or a pair of un-adapted plain sandals. Participants were instructed to use the flip-flops for at least 4 h a day for 12 wk. Data regarding first-step pain, as assessed by VAS, and function, as assessed by the FFI, were collected at baseline and 12 wk. Results showed that the group with the adapted flip-flop sandals with custom insoles had significant improvements with first-step pain and function compared to the un-adapted plain sandals group.

In addition, Chuter *et al*[25] investigated the effects of sandals with a moulded footbed on pain and function in PF. Results showed that, after 12 wk of intervention, there were significant improvements in the primary outcome of foot pain, also measured using FHSQ. In further agreement with our study findings, secondary outcomes of function and pain measured using VAS also improved significantly.

Vicenzino *et al*[24] compared the effects of a contoured sandal, a flat flip-flop and contoured in-shoe orthotics for plantar heel pain. The study contained 50 participants who had experienced plantar heel pain for at least 4 wk. Like our study, this used a GROC scale to determine change in symptoms. The lower extremity function scale (LEFS) was also used to assess function. Findings showed that participants who had been provided with the contoured sandals were 68% more likely to experience symptom improvement using the GROC compared to those who used the flat flip-flop. The contoured sandal group was also 61% more likely to report improvements on the LEFS. No significant differences were observed between the effects of the contoured sandals and the contoured in-shoe orthotics. The findings of these investigations, along with the findings of our study, suggest that the use of orthotic sandals is effective in the treatment of PF.

In our study, the intervention group with the combined use of orthotics and orthotic sandals reported greater improvements on all measures than the control group with the sole use of orthotics. However statistical significance in between-group differences was only reached on the NRS pain scale. We hypothesise that these enhanced benefits were due to the extended periods of support to the feet, and consequent symptomatic relief, provided by the orthotic sandals. Prior to this study, the combined use of prefabricated orthotics and prefabricated orthotic sandals for PF had not been investigated. Nevertheless, studies have assessed the effects of sandals whose weight-bearing surface is contoured like an orthotic on PF as an independent intervention.

The current study investigated the long-term benefits of the intervention, with final data collection at 6 mo. In comparison, other studies only investigated short-term symptom relief, such as 8 wk[25], and 12 wk[26]. The natural history of PF is that most cases resolve spontaneously within 6 to 18 mo[8], and hence symptom relief is required during the active or symptomatic phase of the study. This study demonstrates that both the combined use of orthotics and orthotic sandals or the sole use of orthotics alone can be beneficial for relieving symptoms of PF when it is most symptomatic. In addition, both orthotics and orthotic sandals are drug-free and non-invasive modality to treat PF. Hence it has a lower cost burden and decreased long-term risk profile than other treatment strategies. The combined use of orthotics and orthotic sandals were better on all outcome measures as compared to the sole use of orthotics but between group differences only reached statistical significance on the NRS pains scales.

Table 2 Table of analysis for all outcomes

	Intervention group (orthotics and orthotic sandals)							Control group (orthotics only)							Between-group sig.[test]
	Baseline	3 wk	6 wk	3 mo	6 mo	Change	Sig.[test]	Baseline	3 wk	6 wk	3 mo	6 mo	Change	Sig.[test]	
Foot pain NRS (IQR)	7 (2)	5 (4)	4 (2)	2 (3)	1.5 (3)	-6 (3.25)	$P < 0.001$[a]	8 (3)	5 (3)	4 (3)	4 (4)	3 (3)	-4 (4.75)	$P < 0.001$[a]	$P = 0.003$[b]
Foot pain FHSQ (SD)	28.48 (16.32)	56.50 (20.83)	66.83 (17.23)	74.98 (18.51)	79.98 (15.80)	51.49 (25.15)	$P < 0.001$[c]	29.17 (19.70)	49.57 (19.34)	57.93 (20.23)	62.79 (21.96)	71.24 (18.98)	42.07 (24.79)	$P = 0.001$[c]	$P = 0.07$[d]
Foot function FHSQ (SD)	46.13 (21.47)	71.5 (22.13)	79.25 (17.83)	82.63 (16.72)	87.63 (14.86)	41.50 (24.94)	$P < 0.001$[c]	43.10 (23.68)	65.48 (21.82)	71.74 (23.31)	75.56 (22.80)	80.73 (21.95)	37.64 (26.34)	$P = 0.001$[3]	$P = 0.46$[d]
Symptom change GROC (IQR)		1 (2)	2 (2)	3 (2)	4 (2)	2(2)	$P < 0.001$[a]		1 (2)	1.5 (3)	2 (2)	3 (3)	2 (3)	$P < 0.001$[a]	$P = 0.93$[b]

[a]Wilcoxon Signed Rank Test.
[b]Mann-Whitney U Test.
[c]Paired T-test.
[d]Independent sample T-test.
NRS: Numerical rating scale; FHSQ: Foot health status questionnaire; GROC: Global rating of change score; IQR: Interquartile range.

The findings of this study contribute to existing literature surrounding the use of orthotics and orthotic sandals in the treatment of PF. By combining the use of prefabricated orthotics and prefabricated orthotic sandals, this study has taken a novel approach. To our knowledge, no study has previously been conducted into the combined effects of prefabricated orthotics and orthotic sandals. We wish to propose that the combined use of orthotics and orthotics sandals resulted in greater improvement due to the increased time that the foot is supported.

Strengths and limitations

A strength of this study is the inclusion of participants with a wide age range of 18-75 years old. This increases the generalisability of our findings to the wider population of patients with PF. The cohort recruited for this trial is similar to other studies in terms of mean age and female predominance[30,31], and reflects global prevalence[3,32].

However, as participants were recruited voluntarily through social media adverts, the sample may not be representative of the general population. This might have limited our participants to individuals who use the computer, internet and social media whilst excluding a large segment of the population that do not use digital media.

In addition, the study design was drafted in the periods of national lockdowns due to the coronavirus pandemic. It was not known for how long the national lockdowns would last and therefore the protocol and the study design were created to accommodate social distancing by introducing telephone/virtual consultation with the lead author on inclusion into the study. The telephone/virtual consultation and the lack of a physical examination could have led to both over and under-diagnosis of PF in the study population.

In this study, both groups showed significant improvements in foot pain, foot function and symptoms. Significant improvements in control groups may be associated with factors such as regression to the mean and Hawthorne effects [31]. Due to the nature of this study, blinding participants to group allocation was not possible. Therefore, participants in

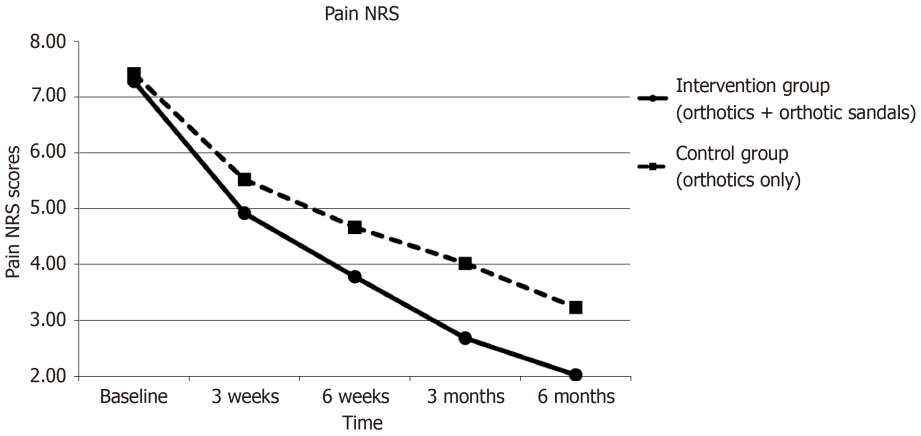

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Figure 4 Foot pain over the last week, measured by numerical rating scale, across time from baseline to 6 mo. NRS: Numerical rating scale.

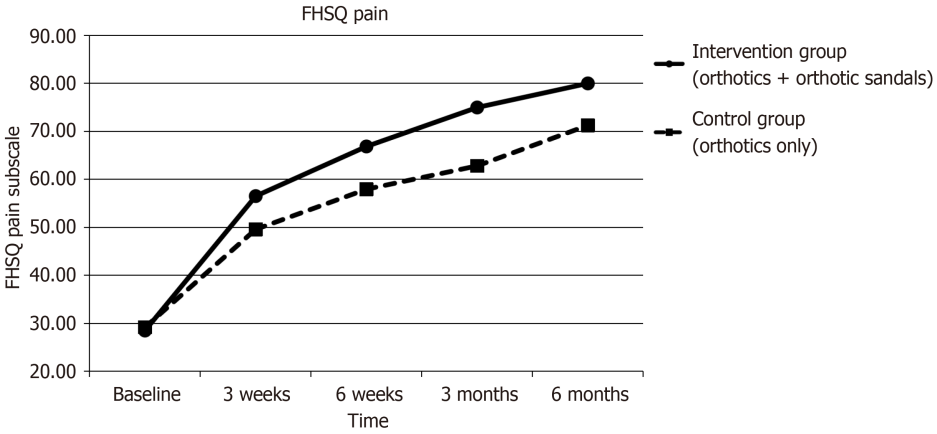

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Figure 5 Foot pain, as assessed by the foot health status questionnaire, across time from baseline to 6 mo. FHSQ: Foot health status questionnaire.

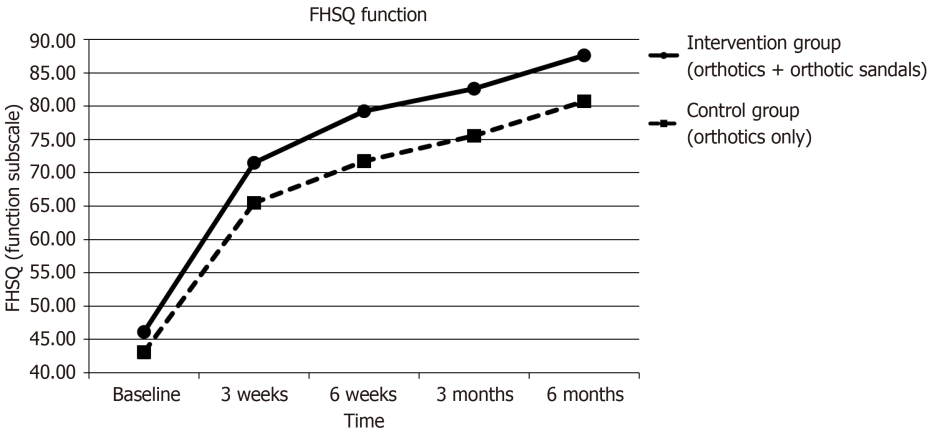

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Figure 6 Foot function, as assessed by the foot health status questionnaire, across time from baseline to 6 mo. FHSQ: Foot health status questionnaire.

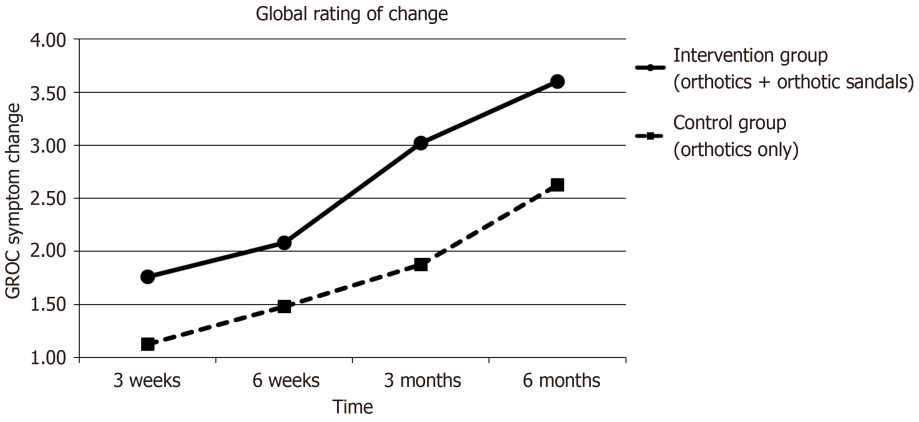

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Figure 7 Symptom change from week 3 to month 6, as assessed by the global rating of change score scale. GROC: Global rating of change score.

the intervention group may have expectations that the combined use of orthotics and orthotic sandals would improve pain and functionality. In future studies, the use of a sham orthotic placebo may be beneficial in reducing bias. However, a sham intervention should provide as little an effect as possible whilst being perceived as equally credible compared to the real intervention[33]. Hence, a sham orthotic should not provide the same mechanical benefits as the real orthotics, and yet participants should expect both to provide similar effects. This may be difficult when attempting to blind participants, as they may detect the sham as a fake, causing their results to be influenced by the nocebo effect. Mitigating this would depend greatly on the design of the sham orthotic to convince the participants that the sham they receive is credible. However, inconsistencies have been found in the construction, blinding and biomechanical validation of sham orthotics in research. Therefore, the quality and reliability of the findings from studies which utilised sham orthotics have been questioned[34]. NRS was selected as the outcome measure to score pain, and though this has been shown to be valid, reliable and appropriate when used for the assessment of pain[35], it is still subjective and therefore has the potential for bias.

In future studies, it would be valuable to collect data on how long each participant has been experiencing plantar heel pain before the study commenced. PF is a self-limiting condition that spontaneously resolves within 12 mo in 75% of cases[36]. Therefore, a natural improvement would be expected regardless of intervention. Hence, data on the duration of participants' pre-study PF would have allowed for this to be factored into the analysis. In addition, monitoring of how often each participant wore orthotic devices would be advised in future studies to determine study compliance and reveal the effect on outcomes. This study was not designed to collect information on risk factors for PF, such as structural foot abnormalities, activity levels, high body mass index *etc.* Future studies may find a correlation between the prevalence of these risk factors and their influence on PF symptom control when using orthotics and orthotic sandals. The current study also did not collect data on concurrent or past treatments like physiotherapy and exercises. This could also be considered in future studies.

However, the main purpose of the study was to empower patients to choose a non-invasive and over-the-counter treatment to address PF or plantar heel pain without the need to seek professional help and thereby reduce the burden on the health care system.

CONCLUSION

The within-group results of this study indicate that both the combined use of prefabricated orthotics and orthotic sandals, as well as the sole use of prefabricated orthotics, significantly improved pain and function in PF in all the four outcome measures utilised in this study. Between-group analysis showed that the combined use of orthotics and orthotic sandals provided better benefits than the sole use of orthotics in all four outcome measures, but the improvement was statistically significant only for foot pain on the NRS scale.

ARTICLE HIGHLIGHTS

Research background

Prefabricated orthotics with arch support provides symptom relief in plantar fasciitis (PF) but are only effective when shoes are worn. Hence, the foot may be left unsupported when it is impractical to wear shoes, such as in the morning or evening at home. Utilising orthotic sandals in conjunction with prefabricated orthotics may enhance symptom relief for PF patients, as they can be worn inside the home, thereby extending the period in which the foot is supported. Prefabricated orthotics and orthotic sandals have been investigated as treatment methods for PF independently, but not in

combination.

Research motivation

PF affects around 10% of the population. The resulting pain can cause activity avoidance, disability, and reduced quality of life. However, the natural history of PF is that it resolves naturally with time. Unfortunately, it remains symptomatic during the active phase and requires intervention for pain relief and symptom improvement. As most cases of PF spontaneously resolve with the passage of time, it is needless to burden the already overburdened healthcare system to address this disorder. This trial sought to identify the superiority between two drug-free and non-invasive treatment modalities to address plantar heel pain which can be used as a self-help measure by patients.

Research objectives

To compare the combined use of orthotics and orthotic sandals *vs* the sole use of orthotics in the treatment of PF.

Research methods

104 participants were randomly assigned to the intervention group, who received both prefabricated orthotics and orthotics sandals, or the control group, who received prefabricated orthotics only. Participants were instructed to use the devices as much as possible. Data were collected at baseline, three weeks, six weeks, three months, and six months. Foot pain was assessed using an 11-point numerical rating scale (NRS). Foot pain and functionality were assessed using the foot pain and foot functionality sub-scales of the foot health status questionnaire (FHSQ). The global rating of change score (GROC) was provided at three weeks, six weeks, three months and six months to assess PF symptom change. A series of Wilcoxon signed-rank tests, Mann-Whitney U tests, Paired T-tests and independent sample t-tests were performed for analysis.

Research results

Foot pain scores significantly improved in both groups, as assessed and measured by the NRS and FHSQ pain sub-scale. Significant improvements in function by the FHSQ function subscale and changes in the level of symptoms by the GROC scale were also observed in both groups. The combined use of orthotics and orthotic sandals showed superior outcomes on all four measures but only reached statistical significance on the NRS pain scales.

Research conclusions

This study provides evidence that both the combined use of orthotics and orthotic sandals and the sole use of orthotics alone, improve pain and function significantly in PF patients. Between-group differences show that the combined use does provide a greater decrease in foot pain compared to using orthotics alone.

Research perspectives

Though this study provides evidence that the combined use of prefabricated orthotics and orthotic sandals improves foot pain in PF patients more than the use of prefabricated orthotics alone, it was not without limitation. Hence, future research should aim to address these limitations, including collecting data on participants' duration of PF symptoms on enrolment, and risk factors for the condition.

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FOOTNOTES

Author contributions: Ampat G supervises the research team and acquired the funding; Ampat G and Sims JMG conceptualised the study and were involved in protocol development and gaining ethical approval; Ampat G and Sims JMG were involved in participant recruitment and data acquisition; Amoako-Tawiah P, Love H, Chacko Madathilethu J, LaCourse J, Fortune AE, and Sims JMG wrote the manuscript; All authors reviewed and edited the manuscript and approved the final draft.

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Clinical trial registration statement: This registration policy applies to prospective, randomized, controlled trials only.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: George Ampat and Jonathan M G Sims are employees of Talita Cumi Ltd, which has a commercial relationship with Aetrex Worldwide, Inc. 414 Alfred Avenue Teaneck, NJ 07666, United States. All other authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Observational Study

Relationships among body weight, lipids and bone mass in elderly individuals with fractures: A case-control study

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Abstract

BACKGROUND

The prevalence of osteoporosis and low bone mass is steadily rising each year. Low body weight is commonly linked to diminished bone mass and serves as a robust predictor of osteoporosis. Nonetheless, the connection between body mass index (BMI), bone mineral density, and lipid profiles among the elderly remains elusive.

AIM

To examine the association between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and delve into the interplay between lipid metabolism and bone health.

METHODS

The study included 520 patients aged ≥ 65 years (178 men and 342 women). Age, sex, weight, and height were recorded. Femoral neck bone mineral density and T scores were determined using a dual-energy X-ray absorptiometry scanner. Blood calcium (Ca), phosphorus (P), albumin (ALB), alkaline phosphatase (ALP), aspartate aminotransferase, alanine aminotransferase, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were measured. Patients were classified by sex (male and female), age (65-79 years and ≥ 80 years), and T score (normal bone mineral density, osteopenia and osteoporosis).

RESULTS

Age, sex, BMI, and ALP and TG levels were independent risk factors for osteoporosis. For the 65-79- and ≥ 80-year-old groups, females presented lower T scores than males. Ca, P, ALB, ALP, TC, HDL and LDL levels were significantly different between men and women in the 65-79-year-old group. In addition, BMI and TG levels were significantly decreased in osteoporotic patients compared with patients with normal bone mass. TC levels declined in 65- to 79-year-old male and female osteoporosis patients. In the group of women aged ≥ 80 years, osteoporotic patients showed significantly increased ALP levels. Furthermore, we found positive correlations between BMI and TG levels in the male and female patient groups. However, we found no significant differences in ALB, Ca, P, HDL and LDL levels in osteoporotic patients compared to patients with normal bone mass.

CONCLUSION

Osteoporotic patients showed significantly decreased BMI and TG levels compared with those with normal bone mass. BMI showed positive correlations with TG levels in male and female patients. These results indicate correlations between BMI and bone mass and between lipid profiles and bone mass.

Key Words: Osteoporosis; Weight loss; Elderly patients; Body mass index; Lipid profiles

Core Tip: Older age, female gender, low body mass index (BMI), and low triglycerides (TG) were identified as overall independent factors for osteoporosis. Furthermore, low total cholesterol represented a gender-unspecific risk factor for osteoporosis in elderly patients aged 65-79 years, and high alkaline phosphatase represented a specific risk factor for osteoporosis in elderly male patients aged 80+ years. In addition, positive correlations were found between BMI and serum TG levels, suggesting an interaction between bone and fat metabolism that may have an impact on the development of osteoporosis and would provide a new strategy for the treatment of osteoporosis.

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INTRODUCTION

The incidence of osteoporosis and low bone mass is progressively rising on an annual basis. Osteoporosis affects over 33% of individuals aged 50 years or older in China[1]. Osteoporosis is marked by diminished bone mineral density (BMD) and compromised bone microarchitecture, resulting in reduced bone mass and heightened bone fragility, thereby elevating the susceptibility to fractures[2]. Numerous factors contribute to osteoporosis, encompassing age, sex, lifestyle, and various medical conditions[3]. Alongside the T score, dual-energy X-ray absorptiometry (DXA) is deemed a pivotal and extensively employed technique for osteoporosis diagnosis[4]. Typically, osteoporosis is classified based on the T score, following the World Health Organization (WHO) guidelines: Normal bone density (≥ -1.0), osteopenia (-1.0 to -2.5), and osteoporosis (≤ -2.5)[5,6].

Recently, numerous studies have examined osteoporosis risk factors, including body mass index (BMI), serum lipid profiles, serum calcium (Ca) and phosphorus (P), serum albumin (ALB), alkaline phosphatase (ALP), and serum alanine transaminase (ALT) and aspartate aminotransferase (AST)[7-11].

Previous research has reported a link between obesity and osteoporosis, suggesting that obesity might act as a protective factor against osteoporosis[12,13]. Obese individuals subject their bones to greater mechanical loads, which can be advantageous for bone mass[14,15]. Furthermore, weight loss detrimentally impacts musculoskeletal health[16], and it has been linked to bone loss and identified as a potent predictor of osteoporosis[17]. Elderly women who experienced weight loss demonstrated heightened bone loss in the hip region[18]. Another investigation noted a relationship between weight loss and hip-bone loss among elderly men and women[17]. These findings imply that elderly individuals with lower body weight face greater risks of both osteoporosis and fractures than their counterparts with higher body weight. Additionally, plasma lipid profiles have been demonstrated to undergo alterations in response to weight changes[19]. Assessing BMI provides a straightforward approach to categorizing an individual's weight status and is linked to the proportion of body fat[20].

Nevertheless, the relationship among BMI, bone mass, and lipid profiles remains unexplored in populations with osteoporosis and fragility fractures. Fragility fractures frequently occur in elderly patients with severe osteoporosis, exacerbating the prognosis[21]. The impact of weight gain on enhancing the lipid profile and subsequently mitigating the prevalence of osteoporosis and fragility fractures remains uncertain. This study aimed to examine the interaction between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and further analyze the interrelationship between lipid metabolism and bone health in individuals experiencing fragility fractures.

MATERIALS AND METHODS

Study participants

This retrospective study was conducted at a singular orthopaedic trauma centre during the time span of January 2017 to December 2020. The study meticulously applied specific inclusion and exclusion criteria as delineated below:

Inclusion criteria were as follows: (1) Age exceeding 65 years at the moment of injury; (2) confirmed diagnosis of fractures in the hip, vertebral region, distal radius, or proximal humerus; and (3) hospitalization at our centre.

Exclusion criteria were as follows: (1) Patients afflicted with cancer, thyroid disorders, hypopituitarism, rheumatoid arthritis, chronic renal failure, or renal insufficiency; (2) patients undergoing lipid-lowering, synthetic thyroid, or hormone replacement therapies; or (3) presence of incomplete data.

Our study managed to acquire comprehensive clinical data suitable for analysis. Participants were categorized based on gender (male and female), age groups (65-79 years and ≥ 80 years), BMI ranges (< 18.5, 18.5-24, > 24 kg/m^2), and T scores [normal BMD (≥ -1.0), osteopenia (-1.0 to -2.5), and osteoporosis (≤ -2.5)]. All laboratory data used in this study were obtained from blood samples collected during the initial admission.

Data collection

Age, sex, height, and weight were recorded from patient documents. BMI was calculated using weight and height (kg/m^2). Femoral neck BMD and T scores were determined using a DXA scanner (Hologic Discovery Wi with software version 13.2). According to the WHO classification, the T score was used to define the BMD categories. Serum samples were collected immediately after the patients were admitted, and serum Ca, P, ALB, AST, ALT, ALP, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were analyzed.

Statistical analysis

Data are presented as the mean ± standard deviation (SD). IBM SPSS statistics software (version 26.0, SPSS Inc., Chicago, United States) and GraphPad Prism software (version 8.4.0, GraphPad Software, Boston, United States) were used to analyze the data. After analysing the normality using the Shapiro-Wilk test, data between two groups were evaluated by the *t* test and nonparametric test. For three groups, data were evaluated by one-way ANOVA. Multivariate analysis was performed by multiple linear regression. The Pearson correlation test was used to analyse the association between BMI and TG levels. $^aP < 0.05$, $^bP < 0.01$, $^cP < 0.001$ and $^dP < 0.0001$ indicated significant differences.

RESULTS

In total, 520 patients aged ≥ 65 years were included in our study. A total of 178 male patients were enrolled, including 48 normal, 81 osteopenic and 49 osteoporotic patients. A total of 342 female patients were included in our study, including 37 normal, 103 osteopenic, and 202 osteoporotic patients (Table 1). Age, sex, BMI and ALP and TG concentrations were significantly different among the groups of normal, osteopenic and osteoporotic patients. Moreover, age, sex, BMI and ALP and TG concentrations were independent risk factors for osteoporosis (Table 1).

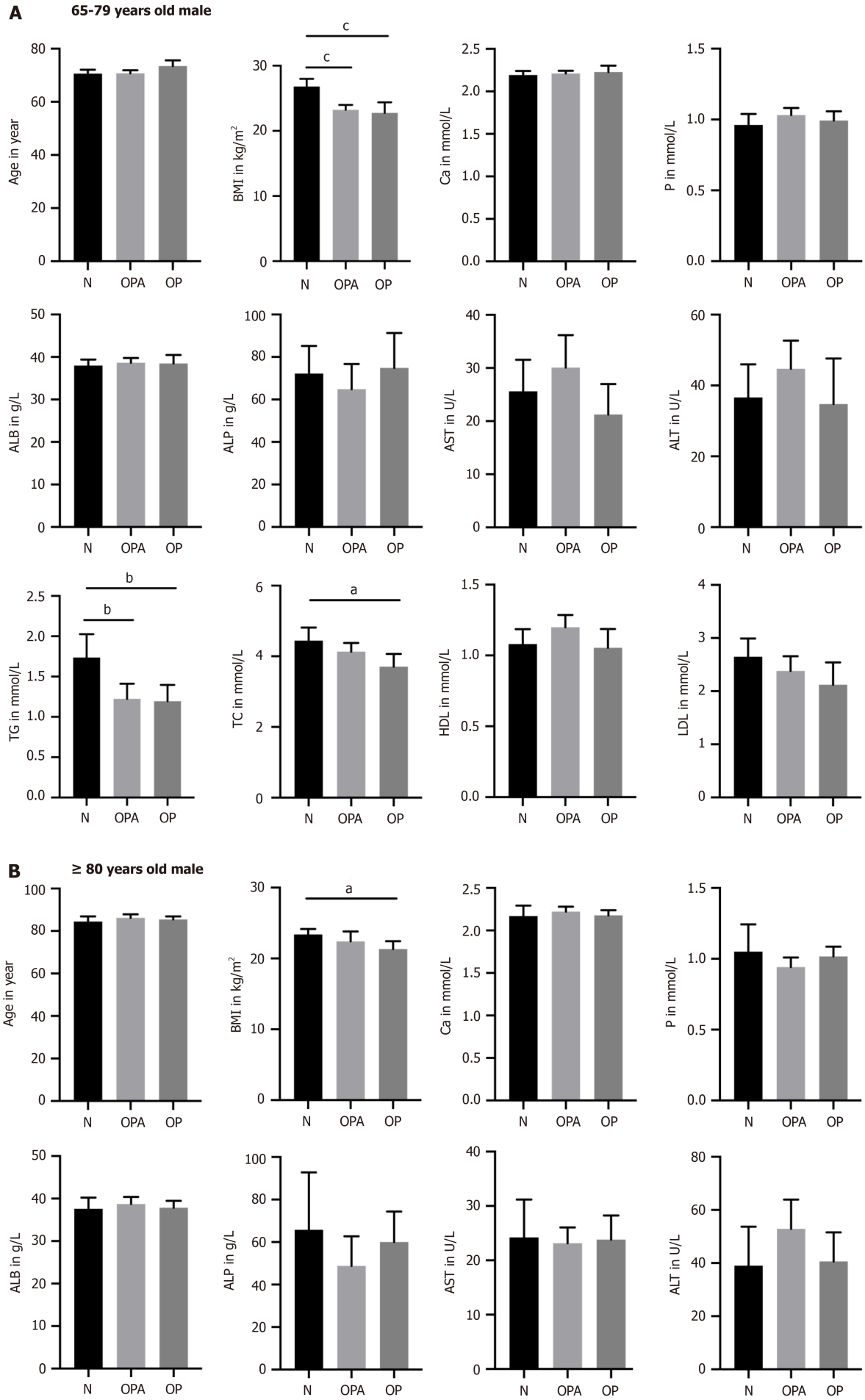
Patients were divided into two groups according to age (65-79 years and ≥ 80 years). To analyze sex differences, a total of 106 men and 188 women were included in the 65- to 79-year age group (Table 2). As shown in Table 2, there were significant differences in the T score and Ca, P, ALB, ALP, TC, HDL and LDL concentrations between male and female patients. However, male patients showed no difference in age, BMI, or AST, ALT and TG concentrations in comparison with female patients.

A total of 72 men and 154 women aged ≥ 80 years were examined in our study. The T score was significantly different in male patients compared to female patients. There were no significant differences in BMI or Ca, P, ALB, ALP, AST, ALT, TG, TC, HDL and LDL concentrations between male and female patients (Table 3).

In the group of 65- to 79-year-old male patients, BMI was lower in osteoporotic patients than in patients with normal bone mass. Furthermore, we found a positive correlation between BMI and T-value in the groups of male patients (Supplementary Figure 1). Moreover, TG and TC levels were also lower in patients with osteoporosis compared to those with normal bone mass. Osteoporotic patients showed no significant differences in Ca, P, ALB, ALP, AST, ALT, HDL and LDL levels compared to patients with normal bone mass. In men aged ≥ 80 years, BMI was significantly lower in osteoporotic patients than in patients with normal bone mass. We also observed decreased TG levels in osteoporotic patients compared to those in patients with normal bone mass. Ca, P, ALB, ALP, AST, ALT, TC, HDL and LDL levels were not significantly different between patients with and without osteoporosis (Figure 1).

In the group of 65- to 79-year-old females, BMI and TG and TC levels were significantly lower in osteoporotic patients than patients with normal bone mass. We also found a positive correlation between BMI and T-value in the groups of female patients (Supplementary Figure 1). Osteoporotic patients also showed no significant differences in Ca, P, ALB, ALP, AST, ALT, HDL and LDL levels compared to patients with normal bone mass. In the group of women aged ≥ 80 years, osteoporotic patients showed significantly decreased BMI and TG levels as well as increased ALP levels. We also did not find significant differences in the Ca, P, ALB, AST, ALT, TC, HDL and LDL levels in osteoporotic patients compared with patients with normal bone mass (Figure 2).

Furthermore, we found a positive correlation between BMI and TG levels in the groups of male patients aged 65-79 and ≥ 80 years. A positive correlation was also found between BMI and TG levels in the groups of 65-79- and ≥ 80-year-old


A
65-79 years old male
Age in year
BMI in kg/m2
Ca in mmol/L
P in mmol/L
ALB in g/L
ALP in g/L
AST in U/L
ALT in U/L
TG in mmol/L
TC in mmol/L
HDL in mmol/L
LDL in mmol/L
N
OPA
OP
B
≥ 80 years old male

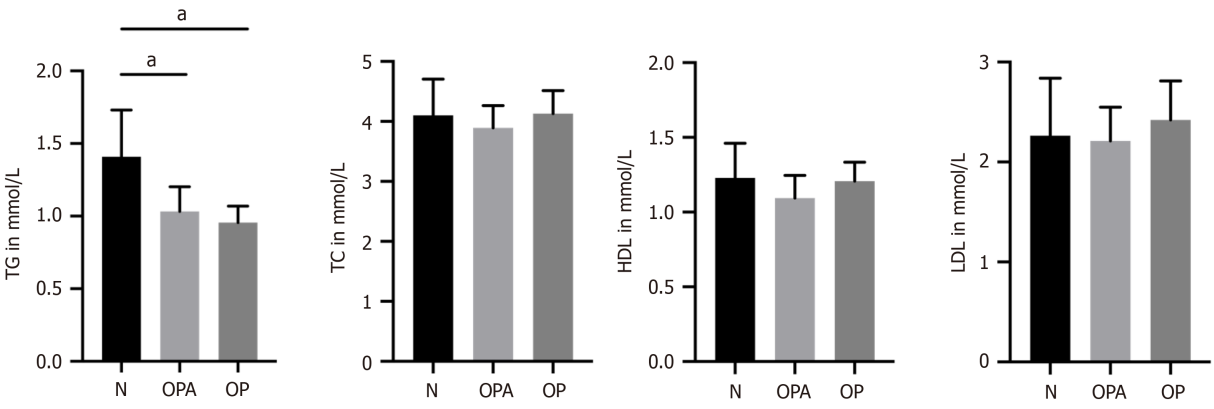


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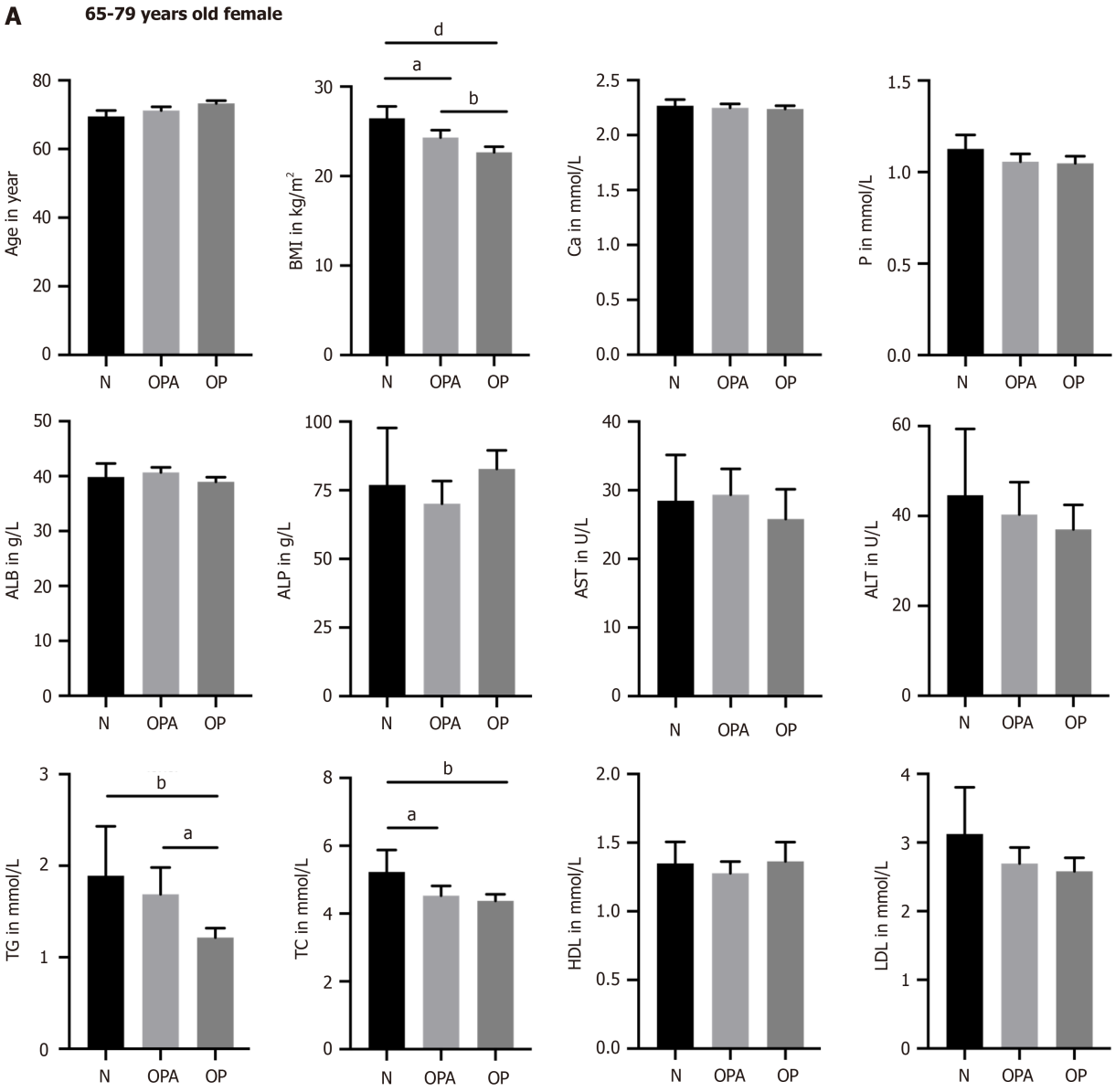
Figure 1 The differences of age, body mass index, calcium, phosphorus, albumin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein in male patients. A: Presented the group of 65-79 years old man; N(N) = 35, N(OPA) = 50, N(OP) = 21; B: Presented the group of ≥ 80 years old man; N(N) = 13, N(OPA) = 31, N(OP) = 28. $^{a}P < 0.05$, $^{b}P < 0.01$ and $^{c}P < 0.001$ as different significance levels. BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; N: Normal bone mass; OPA: Osteopenia; OP: Osteoporosis.



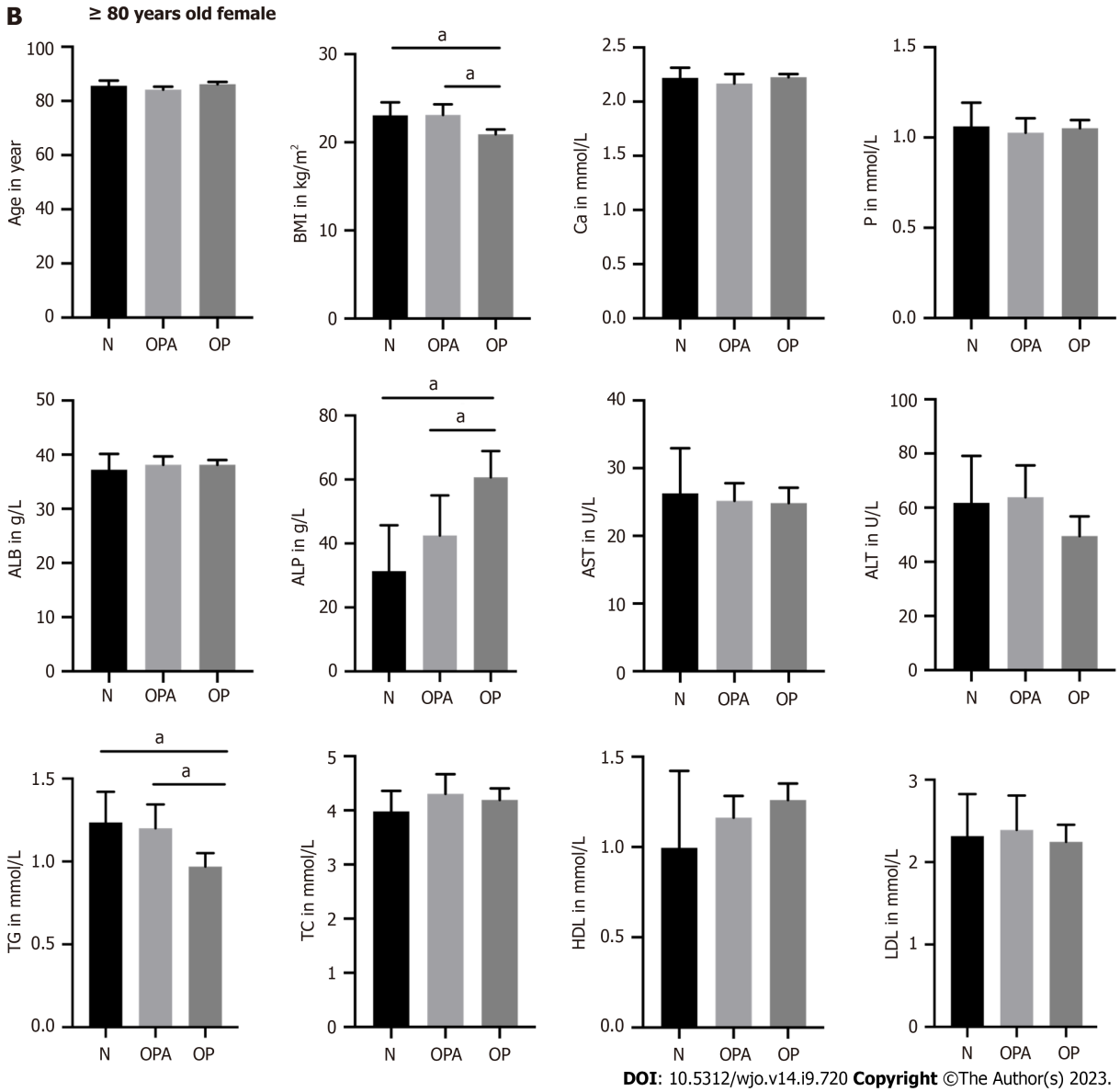


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Figure 2 The differences of age, body mass index, calcium, phosphorus, albumin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein in female patients. A: Presented the group of 65-79 years old female; N(N) = 19, N(OPA) = 65, N(OP) = 104; B: Presented the group of ≥ 80 years old female; N(N) = 17, N(OPA) = 38, N(OP) = 99. [a]*P* < 0.05, [b]*P* < 0.01 and [d]*P* < 0.0001 as different significance levels. BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; N: Normal bone mass; OPA: Osteopenia; OP: Osteoporosis.

female patients (Figure 3).

DISCUSSION

In our study, we analyzed the clinical data of 520 patients aged ≥ 65 years. We found that osteoporotic patients showed significantly decreased BMI and TG levels in comparison with patients with normal bone mass. The number of patients diagnosed with osteoporosis is increasing annually, and previous studies have shown that many factors contribute to osteoporosis, including age, sex, BMI, and Ca, P, ALB, ALP, AST, ALT, TG, TC, HDL and LDL levels.

Previous studies have reported that many factors contribute to osteoporosis[3,22]. In our study, we found that age, sex, BMI, and ALP and TG levels were independent risk factors for osteoporosis. With increasing age, a series of factors are altered, such as a lack of sex steroids, declining levels of growth factors and changes in food intake, exercise and mechanical loading, leading to bone loss. Based on this, we classified the groups according to age. Regarding the relationship between sex and bone mass, previous studies have demonstrated that men tend to have a higher BMD at a later age and a lower rate of bone mass loss than women[23,24], suggesting that bone mass loss differs by sex. In our study, female patients in the 65-79- and ≥ 80-year-old groups presented lower T scores than male patients. The reason for

Table 1 Univariate and multivariate analysis of related factors for osteoporosis

	Univariate analysis				Multivariate analysis		
	Normal (*n* = 85)	Osteopenia (*n* = 184)	Oeteoporosis (*n* = 251)	*P* value	OR	95%CI	*P* value
Age (year old)	75.54 ± 8.22	76.31 ± 8.00	79.72 ± 7.62	< 0.001	-0.04	0.016-0.064	0.001
Gender (*n*)				< 0.001	1.34	0.968-1.720	< 0.001
Male	48	81	49				
Female	37	103	202				
BMI (kg/m^2)	25.46 ± 3.32	23.43 ± 3.32	21.83 ± 3.10	< 0.001	-0.018	-0.373	< 0.001
≤ 18.5 (*n*)	1 (1.18)	9 (4.89)	38 (15.14)	< 0.001			
18.5-24 (*n*)	27 (31.76)	92 (50.00)	148 (58.96)				
≥ 24 (*n*)	57 (67.06)	83 (45.11)	65 (25.90)				
Ca (mmol/L)	2.21 ± 0.16	2.20 ± 0.15	2.22 ± 0.15	0.69			
P (mmol/L)	1.05 ± 0.29	1.02 ± 0.19	1.04 ± 0.20	0.56			
ALB (g/L)	38.21 ± 4.72	39.27 ± 4.26	38.49 ± 4.36	0.09			
ALP (U/L)	64.02 ± 41.37	59.40 ± 38.83	70.89 ± 39.63	0.01	0.01	0.006-0.015	< 0.001
AST (U/L)	26.19 ± 14.73	27.64 ± 15.36	24.83 ± 16.01	0.19			
ALT (U/L)	43.89 ± 30.07	48.50 ± 31.54	42.16 ± 31.87	0.11			
TG (mmol/L)	1.62 ± 0.83	1.35 ± 0.87	1.09 ± 0.47	< 0.001	-0.56	-1.132	< 0.001
TC (mmol/L)	4.48 ± 1.15	4.27 ± 1.06	4.22 ± 1.01	0.16			
HDL (mmol/L)	1.16 ± 0.31	1.21 ± 0.28	1.28 ± 0.44	0.1			
LDL (mmol/L)	2.67 ± 0.93	2.48 ± 0.84	2.40 ± 0.80	0.12			
CHD (*n*)	7	14	27	0.52			

BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHD: Coronary heart diseases.

the differences in bone mass between sexes might be that hormones differ in males and females[23]. Moreover, significant differences were observed in the Ca, P, ALB, ALP, TC, HDL and LDL levels between men and women in the 65- to 79-year-old group. These results indicate that men and women present differences in many factors for osteoporosis. Cui *et al* [7] supported our results in their analysis of 1035 men and 3953 women, where they also showed significant differences in BMI and T scores, as well as in TG, TC, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels, between men and women. According to their and our results, we classified the groups by sex and age (65-79 and ≥ 80 years old).

Previous studies have revealed the correlation among lipid profiles, BMI, and BMD[7,25,26]. In our study, we found that male and female osteoporotic patients showed significantly decreased BMI in the groups aged 65-79 and ≥ 80 years. Supporting our findings, many studies have reported an association between BMI and BMD. Alay *et al*[27] investigated 452 postmenopausal women in an outpatient clinic between 2012 and 2015 and observed that a decreased BMI was related to a lower BMD. In addition, Fawzy *et al*[28] analyzed 101 men and women and found that a decline in BMI was associated with a lower BMD. The possible mechanisms for the association between BMI and BMD might be that weight gain places greater static mechanical loads on the bones and increases various hormone levels, which are beneficial for bone mass and bone remodelling[26,29-31].

Moreover, our study demonstrated that male and female osteoporotic patients presented obviously decreased TG levels in the groups aged 65-79 years and ≥ 80 years. In addition, male and female osteoporotic patients also showed obviously decreased TC levels in the group aged 65-79 years. However, we did not find any significant differences in the HDL and LDL levels between the two groups in our study. Although previous studies have reported the association between serum lipid profiles and BMD, the literature is conflicting. Our study findings were in agreement with those of Cui *et al*[7], who showed that BMI and TG levels were significantly lower in patients with osteoporosis than in those with normal BMD. However, there was no significant difference in TC levels. In a meta-analysis, Chen *et al*[32] selected ten publications and investigated the relationship between lipid profiles (HDL, LDL, TG, and TC levels) and osteoporosis in postmenopausal women, finding significantly higher HDL and TC levels in the postmenopausal osteoporosis group than in the normal BMD group. Although the difference was not significant, postmenopausal osteoporosis patients presented with a lower TG level. Alfahal *et al*[33] also reported a lower TG level in postmenopausal individuals with osteoporosis

Table 2 Male and female patients aged between 65 to 79 years old in related factors for osteoporosis

	Male (*n* = 106)	Female (*n* = 188)	*P* value
Age (year)	71.25 ± 4.39	72.18 ± 4.52	0.095
T-value	-1.51 ± 0.94	-2.5 ± 1.03	< 0.0001
BMI (kg/m^2)	24.33 ± 3.52	23.63 ± 3.37	0.134
≤ 18.5 (*n*)	3 (2.83)	13 (6.91)	0.316
18.5-24(*n*)	48 (45.28)	85 (45.21)	
≥ 24 (*n*)	55 (51.89)	90 (47.88)	
Ca (mmol/L)	2.21 ± 0.13	2.25 ± 0.14	0.027
P (mmol/L)	1.00 ± 0.19	1.06 ± 0.14	0.01
ALB (g/L)	38.40 ± 4.11	39.67 ± 4.21	0.013
ALP (U/L)	69.29 ± 39.15	77.79 ± 35.53	0.032
AST (U/L)	26.86 ± 18.85	27.30 ± 19.34	0.258
ALT (U/L)	40.06 ± 27.97	38.94 ± 28.56	0.953
TG (mmol/L)	1.39 ± 0.73	1.45 ± 0.91	0.727
TC (mmol/L)	4.15 ± 0.95	4.52 ± 1.11	0.005
HDL (mmol/L)	1.13 ± 0.26	1.33 ± 0.45	< 0.001
LDL (mmol/L)	2.42 ± 0.83	2.68 ± 0.86	0.048

BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

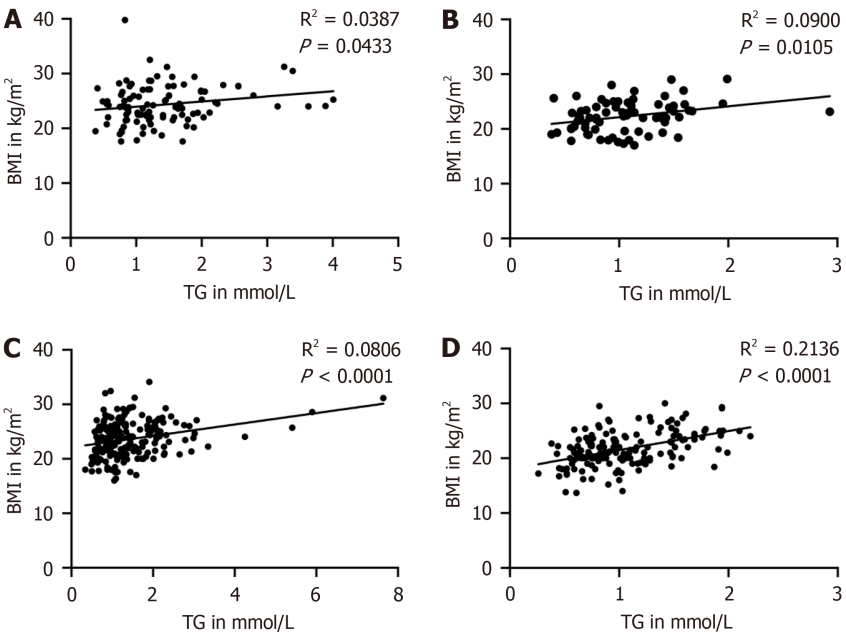

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Figure 3 The correlation between body mass index and triglyceride in male and female patients. A: Presented the group of 65-79 years old male patients; *n* = 106; B: Presented the group of ≥ 80 years old male patients; *n* = 72; C: Presented the group of 65-79 years old female patients; *n* = 188; D: Presented the group of ≥ 80 years old female patients; *n* = 154. *P* < 0.05 as a different significance level. BMI: Body mass index; TG: Triglyceride.

Table 3 Male and female patients aged ≥ 80 years old in related factors for osteoporosis

	Male (*n* = 72)	Female (*n* = 154)	*P* value
Age (year)	85.60 ± 4.08	85.65 ± 33.89	0.839
T-value	-2.06 ± 1.21	-2.94 ± 1.29	< 0.0001
BMI (kg/m^2)	22.34 ± 3.26	21.68 ± 3.12	0.15
≤ 18.5 (*n*)	10 (13.89)	22 (14.29)	0.829
18.5-24 (*n*)	41 (56.94)	93 (60.39)	
≥ 24 (*n*)	21 (29.17)	39 (25.32)	
Ca (mmol/L)	2.20 ± 0.17	2.21 ± 0.19	0.234
P (mmol/L)	1.01 ± 0.28	1.09 ± 0.58	0.092
ALB (g/L)	38.19 ± 4.34	38.04 ± 4.68	0.823
ALP (U/L)	56.21 ± 38.95	52.95 ± 40.44	0.455
AST (U/L)	23.61 ± 9.93	25.08 ± 10.77	0.238
ALT (U/L)	45.61 ± 28.78	54.45 ± 36.12	0.06
TG (mmol/L)	1.07 ± 0.44	1.08 ± 0.49	0.857
TC (mmol/L)	4.03 ± 0.99	4.20 ± 1.03	0.171
HDL (mmol/L)	1.17 ± 0.30	1.21 ± 0.32	0.425
LDL (mmol/L)	2.31 ± 0.78	2.29 ± 0.78	0.926

BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

compared with individuals with normal bone mass individuals. However, Bijelic *et al*[34] evaluated lipid profiles and BMI in 100 postmenopausal osteoporotic patients and patients with normal BMD. They proved that in postmenopausal patients, osteoporosis was associated with LDL, TC, and TG levels. Contrary to our results, they showed increased TG levels in osteoporotic patients compared with those with a normal BMD. The reason might be that, in their study, there were 72 overweight patients in the osteoporosis group and 54 overweight patients in the normal BMD group. However, Alay *et al*[27] did not observe significant differences in HDL, LDL, TG, and TC levels between groups with normal bone mass and osteoporosis. BMI and TG levels were independent risk factors for osteoporosis in our study. Moreover, we also observed a positive correlation between BMI and TG levels in the groups of male and female patients aged 65-79 and ≥ 80 years. These results suggest a positive relationship among BMI, TG levels and BMD.

It has been reported that lipids may be a predisposing factor for osteoporosis and are associated with bone fragility [11], and TG metabolism is considered to be correlated with bone metabolism. Dragojevič *et al*[35] performed a gene expression study by analysing bone tissue from 50 patients with osteoporosis and 62 controls. They reported that osteoporosis patients had decreased osteoblastogenesis, increased osteoclastogenesis, and lower TG metabolism than controls. TGs are considered an important form for the storage of fatty acids. Fatty acids are essential components of all lipids and are involved in producing energy in all vertebrates; fatty acid metabolism plays essential roles in osteoblast and osteoclast function and activities as well as in bone remodelling[36-38]. This could be one explanation for the relationship between serum TG levels and bone remodelling. However, the underlying mechanism between TG metabolism and bone metabolism remains unclear, and more studies should be performed in the future.

In addition, we did not observe significant differences in other factors for osteoporosis, such as Ca, P, AST, ALT and ALB levels, between the osteoporosis and control groups in our study. Regarding the association between serum Ca and P levels and osteoporosis, many studies have shown different results. Our study reported that serum Ca and P levels were normal in postmenopausal women with or without osteoporosis. This may be because the levels of Ca and P in serum may not reflect their storage in bones. Serum Ca and P levels are regulated, and homeostasis is maintained in serum[39,40]. In previous studies, nutrition was reported to be related to osteoporosis, and serum ALB levels were lower in patients with osteoporosis[41,42]. By analysing the serum ALB levels of 15539 individuals, hypoalbuminemia (serum ALB less than 3.5 g/dL) was found to be associated with osteoporosis[42]. However, the mean serum ALB levels were more than 35 g/L in patients with normal bone mass and osteoporotic patients and did not show differences between groups in our study. This might be the reason why serum ALB was not a factor for diagnosing osteoporosis in our study. AST and ALT are liver enzymes, and they were also reported to be associated with osteoporosis. In agreement with our study, Do *et al*[9] selected 7160 subjects to analyse the association between liver enzymes and BMD in Koreans. They also did not show differences in the association of AST and ALT with femur BMD. We discovered that ALP was an independent factor for osteoporosis, and osteoporotic female patients aged ≥ 80 years showed significantly increased ALP levels. Supporting our results, increased serum ALP levels in postmenopausal women indicate high bone turnover and

are helpful for diagnosing osteoporosis[43-45].

This study investigated the interplay between BMI, lipid profile, and bone mass within a population vulnerable to brittle fractures. Our research has several strengths. Firstly, our study utilized blood samples collected from fragility fracture patients upon admission to assess pertinent lipid metabolism markers. Secondly, individuals with fragility fractures frequently experience bone loss or osteoporosis. Our findings introduce a novel perspective for future endeavours in osteoporosis and fragility fracture prevention. Furthermore, our hierarchical analysis provides preliminary results, enhancing the generalizability of our research outcomes.

Nonetheless, our research bears certain limitations. Firstly, being a single-centre study, not all patients had lipid metabolism indicator data available for analysis due to admission discrepancies among fragility fracture patients, which resulted in a significant reduction in sample size. Among patients undergoing DXA assessments, the T-value of the proximal femur was the only site measurement employed for standardization, with lumbar and radius measurements being omitted. Furthermore, follow-up data for the study cohort is absent, impeding outcome comparison. Moving forward, we aspire to extend this discourse through a multicentre, large-sample study. Additionally, we intend to investigate the nexus between BMI, lipid profile, and bone mass *via* prospective studies involving nutritional interventions in patients.

CONCLUSION

In conclusion, osteoporotic patients showed significantly decreased BMI and TG levels in comparison with patients with normal bone mass in our study. These results indicate an association between TG metabolism and bone metabolism and provide a new method for the treatment of osteoporosis.

ARTICLE HIGHLIGHTS

Research background

The increasing incidence of osteoporosis and low bone mass, affecting a significant portion of individuals aged 50 years or older in China, underscores the urgent need to address this public health concern. While obesity's potential protective role and the complex interplay between body mass index (BMI), lipid profiles, and bone health are subjects of recent investigation, their specific impact on populations with osteoporosis and fragility fractures remains relatively unexplored.

Research motivation

The relationship between BMI, bone mass, and lipid profiles in populations with osteoporosis and fragility fractures remains understudied.

Research objectives

This study aims to shed light on the potential impact of weight gain and lipid profiles on bone health in individuals with fragility fractures which may provide a new method for the treatment of osteoporosis.

Research methods

This retrospective study conducted at a single orthopaedic trauma center between January 2017 and December 2020 included participants aged 65 years and above with diagnosed fractures in specific region. Participants' comprehensive clinical data, including gender, age groups, BMI ranges, DXA scores, and laboratory measurements, were collected and analyzed using statistical software. Data were analyzed using IBM SPSS and GraphPad Prism software, employing t-tests, nonparametric tests, one-way ANOVA, multiple linear regression, and Pearson correlation tests ($^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$, $^{d}P < 0.0001$ denoting significance) after assessing normality with the Shapiro-Wilk test.

Research results

In this study involving 520 participants aged ≥ 65 years, distinct gender and age-related disparities were observed in osteoporosis prevalence and associated factors. While a significant divergence in age, sex, BMI, alkaline phosphatase (ALP), and triglyceride (TG) concentrations was noted among normal, osteopenic, and osteoporotic groups, multivariate analysis revealed age, sex, BMI, ALP, and TG concentrations as independent risk factors for osteoporosis. Differential correlations between BMI and bone health parameters, along with lipid profiles, were elucidated across age and gender cohorts. Notably, these findings underscore the intricate interplay between metabolic and skeletal factors in the context of osteoporosis.

Research conclusions

In conclusion, osteoporotic patients showed significantly decreased BMI and TG levels in comparison with patients with normal bone mass in our study.

Research perspectives

These results indicate an association between TG metabolism and bone metabolism and provide a new method for the

treatment of osteoporosis.

FOOTNOTES

Author contributions: Chen XX and Tian CW contributed equally to this work; Chen XX and Tian CW designed the study, including the research questions and methodology; Bai LY, Zhao YK, Zhang C, Shi L, Zhang YW, Xie WJ, Zhu HY, Chen H asisted in study design, contributed to data collection and management; Tian CW performed data analysis, provided critical insights into data interpretation; Rui YF supervised the entire study, provided guidance on research design and took a lead in manuscript writing and revision; All authors have read and approve the final manuscript.

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Data sharing statement: The data presented in this study are available upon reasonable request to qualified researchers for the purpose of academic and scientific collaboration. Requests for data access should be directed to the corresponding author at ruiyunfeng@126.com.

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