frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 26 October 2022
DOI 10.3389/fendo.2022.989648

Check for updates

OPEN ACCESS

EDITED BY
Melissa Orlandin Premaor,
Federal University of Minas Gerais, Brazil

REVIEWED BY
Dominik Saul,
Mayo Clinic, United States
Mengning Yan,
Shanghai Jiao Tong University, China
Nurul 'Izzah Ibrahim,
National University of Malaysia, Malaysia

*CORRESPONDENCE
Dongliang Wang
wang02_73@126.com
Guohui Liu
liuguohui@medmail.com.cn
Yingze Zhang
dr_yzzhang@126.com
Jiacan Su
drsujiacan@163.com

SPECIALTY SECTION
This article was submitted to Bone Research, a section of the journal Frontiers in Endocrinology

RECEIVED 08 July 2022
ACCEPTED 03 October 2022
PUBLISHED 26 October 2022

CITATION
Zhang H, Hu Y, Chen X, Wang S, Cao L, Dong S, Shi Z, Chen Y, Xiong L, Zhang Y, Zhang D, Yu B, Chen W, Wang Q, Tong P, Liu X, Zhang J, Zhou Q, Niu F, Yang W, Zhang W, Wang Y, Chen S, Jia J, Yang Q, Zhang P, Zhang Y, Miao J, Sun K, Shen T, Yu B, Yang L, Zhang L, Wang D, Liu G, Zhang Y and Su J (2022) Expert consensus on the bone repair strategy for osteoporotic fractures in China. *Front. Endocrinol.* 13:989648. doi: 10.3389/fendo.2022.989648

Expert consensus on the bone repair strategy for osteoporotic fractures in China

Hao Zhang[1,2], Yan Hu[1], Xiao Chen[2], Sicheng Wang[3], Liehu Cao[4], Shiwu Dong[5], Zhongmin Shi[6], Yanxi Chen[7], Liming Xiong[8], Yunfei Zhang[9], Dianying Zhang[10], Baoqing Yu[11], Wenming Chen[12], Qining Wang[13], Peijian Tong[14], Ximing Liu[15], Jianzheng Zhang[16], Qiang Zhou[17], Feng Niu[18], Weiguo Yang[19], Wencai Zhang[20], Yong Wang[21], Shijie Chen[22], Jinpeng Jia[23], Qiang Yang[24], Peng Zhang[25], Yong Zhang[9], Jun Miao[24], Kuo Sun[26], Tao Shen[26], Bin Yu[27], Lei Yang[28], Lei Zhang[29], Dongliang Wang[30]*, Guohui Liu[8]*, Yingze Zhang[31]* and Jiacan Su[1,2]*

[1]Institute of Translational Medicine, Shanghai University, Shanghai, China, [2]Changhai Hospital, Naval Medical University, Shanghai, China, [3]Department of Orthopedics, Shanghai Zhongye Hospital, Shanghai, China, [4]Department of Orthopedics, Shanghai Baoshan Luodian Hospital, Shanghai, China, [5]Department of Biomedical Materials Science, Army Medical University, Chongqing, China, [6]Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China, [7]Zhongshan Hospital, Fudan University, Shanghai, China, [8]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [9]Tangdu Hospital, Air Force Medical University, Xi'an, China, [10]People's Hospital, Peking University, Beijing, China, [11]Department of Orthopedics, Shanghai Pudong Hospital, Shanghai, China, [12]Institute of Biomedical Engineering, Academy for Engineering and Technology, Fudan University, Shanghai, China, [13]Department of Advanced Manufacturing and Robotics, College of Engineering, Peking University, Beijing, China, [14]Department of Orthopedics, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China, [15]Department of Orthopedics, General Hospital of Central Theater Command, Wuhan, China, [16]Department of Orthopedic Surgery, People's Liberation Army (PLA), Army General Hospital, Beijing, China, [17]Department of Orthopedics, The Third Affiliated Hospital of Chongqing Medical University, Chongqing, China, [18]Department of Orthopedics, The First Hospital of Jilin University, Changchun, China, [19]Li Ka Shing Faculty of Medicine, Hongkong University, Hong Kong, Hong Kong SAR, China, [20]Department of Orthopedics, The Third Affiliated Hospital of Guangzhou University of Traditional Chinese medicine (TCM), Guangzhou, China, [21]Department of Orthopedics, Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, China, [22]Department of Orthopedics, The Third Xiangya Hospital of Central South University, Changsha, China, [23]Department of Orthopedics, Chinese People's Liberation Army General Hospital, Beijing, China, [24]Department of Orthopedics, Tianjin Hospital, Tianjin, China, [25]Department of Orthopedics, Shandong Province Hospital, Jinan, China, [26]Department of Orthopedics, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [27]Department of Orthopedics, Peking Union Medical College Hospital, Beijing, China, [28]Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China, [29]Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [30]Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, [31]Department of Orthopedics, Third Hospital of Hebei Medical University, Shijiazhuang, China

Osteoporotic fractures, also known as fragility fractures, are prevalent in the elderly and bring tremendous social burdens. Poor bone quality, weak repair capacity, instability, and high failure rate of internal fixation are main characteristics of osteoporotic fractures. Osteoporotic bone defects are

common and need to be repaired by appropriate materials. Proximal humerus, distal radius, tibia plateau, calcaneus, and spine are common osteoporotic fractures with bone defect. Here, the consensus from the Osteoporosis Group of Chinese Orthopaedic Association concentrates on the epidemiology, characters, and management strategies of common osteoporotic fractures with bone defect to standardize clinical practice in bone repair of osteoporotic fractures.

KEYWORDS

osteoporosis, fracture, bone repair, expert consensus, biomaterials

Introduction

Osteoporosis is a systemic bone disease characterized by reduced bone mass, bone microstructure damage, leading to increased bone fragility and susceptibility to fracture (1). The latest epidemiological data showed that the prevalence of osteoporosis in individuals of 40–49 years in China was 2.4% in men and 4.3% in women, the prevalence of osteoporosis in people aged 50–59 years was 4.6% in men and 16.4% in women, the prevalence of osteoporosis in populations 60–69 years reached 5.4% in men and 37.1% in women, and the prevalence of osteoporosis in populations 70–79 years reached 12.3% in men and 67.5% in women (2). The highest prevalence of osteoporosis reached to 79.8% in women older than 85 years old (3).

Osteoporotic fractures, also known as fragility fractures, refer to fractures that occur after minor trauma or in daily activities and are commonly found in the vertebrae, hip, distal forearm, proximal humerus, and distal tibia in elderly (4, 5). Aging of the world populations increased the incidence of osteoporotic fractures in recent years. The prevalence of vertebral fractures in China is about 15% in women over 50 years old and 36.6% in women over 80 years old. The incidence of hip fractures in elder over 50 years old was 83/100,000 for men and 80/100,000 for women in 1990–1992 and 129/100,000 for men and 229/100,000 for women in 2002–2006 (6). It is estimated that the number of osteoporotic fractures in China will be 4.83 million in 2035 and will reach 5.99 million in 2050 (7).

The basic changes in bone structure of osteoporosis are loss of bone mass and reduction of bone density. Specifically, osteoporosis patients are manifested by thinning of the cortex bone, sparseness of cancellous bone, and increased bone fragility. It is difficult to obtain stable compression and fixation of fracture with conventional internal fixation. The implant cannot firmly integrate with bone, which may lead to internal fixation failure (8). Poor osteointegration combined with molecular and cellular defects of osteoporosis increases the risk of internal fixation failure and bone healing (9). Osteoporotic fractures are often accompanied by bone defects due to changes in bone microarchitecture, decreasing deposits of bone mineral and bone matrix components, sparseness of bone trabecular, decreased bone strength, and increased bone fragility (10, 11). To achieve good clinical outcomes, bone implants or bone substitutes are required for osteoporotic bone defect repair and internal fixation augmentation. Appropriate bone grafting provides sufficient biomechanical support for fracture healing and bone repair. In addition, the application of memory alloy-fixation system can improve clinical outcomes in fractures with large bone defect, articular surface collapse, and bone non-union (12–14).

In order to provide a suggestion for clinical treatment of osteoporotic fracture, this consensus is developed by the Osteoporosis Group of the Chinese Orthopaedic Association, in collaboration with the Orthopaedic Specialist Committee of the Chinese Society of Gerontology and Geriatrics, the Traumatic Orthopaedics and Multiple Injuries Group of the Emergency Resuscitation Committee of the Chinese Medical Association, and the Osteoporosis Committee of the Shanghai Society of Integrated Traditional Chinese and Western Medicine.

Bone repair materials in osteoporotic fractures

High porosity and low strength of cancellous bone lead to failure of internal fixation in osteoporosis patients (10). Bone grafting can fill the bone defect to improve biomechanical properties. Current bone repair materials should have at least one of these two roles: (1) bone conductive role, which provides mechanical stability and enhances osteointegration of the implant or (2) bone inducible role, which enhances bone repair by inducing bone remodeling. Clinical bone repair materials are autologous bone, allogeneic bone, and artificial bone.

Autologous bone

Autologous bone graft is the "gold standard" for the treatment of bone defects. Cortical bone can be selected for structural grafting to increase fracture stability. Cancellous bone can be used to fill the bone defect to facilitate fracture healing. Autologous cortical bone grafts have excellent structural integrity and can provide mechanical support in the early stages of fracture healing (15). For osteoporotic proximal humeral fractures, autogenous fibular segment graft combined with locking plate fixation can enhance the support of the internal fixation, against varus stress, reduce the risk of internal fixation failure and humeral head necrosis (16–18). The large surface area of autogenous cancellous bone grafts facilitates vessel reconstruction and bone conduction. Meanwhile, autologous cancellous bone is rich in mesenchymal stem cells (MSCs) and bone inductive factors that promote osteogenesis (19). However, autologous bone still has several disadvantages. Sources of autologous bone are limited. Fibula and iliac bone are common sources of autogenous bone grafting. Trauma, infection, or former bone graft history of donor site may restrict autologous bone application. Obtaining autologous bone is an invasive procedure with risks associated with surgery such as bleeding and infection. These potential complications may cause secondary damage to patients.

Allogeneic bone

Allogeneic bone is a suitable substitute for autologous bone. Allogeneic bone can be obtained from living or non-living donors and preserved in bone tissue bank. Allogeneic cancellous bone grafts are mainly used in spinal fusion enhancement and filling bone defects in patients with osteoporosis. Cortical allografts are primarily used for vertebroplasty to fill bone defects that require immediate loading. Demineralized bone matrix is also a kind of bone graft material for spinal fusion, bone non-union, and bone defects. The integral property of allogeneic bone is similar to autologous bone, triggers endochondral ossification, and, eventually, forms new bone at the implantation site (20). The disadvantages of allogenic are immune rejection and lack of bioactivity. There is a risk of immune rejection of allogeneic bone grafts, which may lead to local redness, swelling even bone resorption. The lack of bioactivity of allogeneic leads a longer duration of bone healing. Those disadvantages are not unacceptable compared with the wide source of homogeneous allogeneic bone and the unrestricted dosage.

Artificial bone material

Calcium sulfate grafts are absorbable synthetic bone substitutes, which could be resorbed within 1–3 months faster than bone grafts (21–23). Calcium phosphate (CaP) ceramics are a family of calcium salt compounds composed of varying proportions of calcium ions and organic phosphates. CaP ceramics have applied as an absorbable ceramic with good bone conductivity (24–27).

Bone cement has been used in the treatment of compressive osteoporotic vertebral fractures. However, the risk of complications caused by bone cement still exists. Indications of bone cement application should be controlled. In addition, the procedure of bone cement should be noticed to prevent leakage. Polymethylmethacrylate (PMMA) bone cement is widely used in clinical practice. PMMA bone cement can stabilize the injured vertebral body rapidly and relieve patients' symptoms. However, PMMA has no bone conductive property and cannot be integrated within the host bone. PMMA cannot conduce adhesion and growth of bone cells after injected into fracture sites. High modulus and stiffness of PMMA can easily lead to local microfracture and compression fractures of adjacent vertebrae (28). Calcium phosphate cement (CPC) is a white powder and a good substitute for bone grafts. CPC is widely used to fill bone defects in fragility fractures. The remodeling process of CPC occurs at the bone-cement interface where deposition of new bone and resorption of CPC occurred simultaneously (29). Zinc, magnesium, copper, and other metal ion can be added in artificial bone materials to promote bone repair in a delicate concentration (30–34). Bioactive composite also showed great prospect in application of bone repair (35–37). Bioactive materials such as biocompatible hydrogel or materials with bioactive factors such as BMP-2, MMP-cleavable peptides were reported in treating large bone defect with good outcomes (38–40). The bioactive materials that carry bioactive factors to create bone organoid may be a new research direction in bone repair (41).

Bone-targeting biomaterials

Bone-targeting materials are mainly divided into two categories: matrix-targeted materials and cell-targeted materials (42). Inorganic hydroxyapatite (HA) is the main component of bone matrix. Matrix-targeted materials select HA high-affinity substances as drugs or drug carriers, mainly include tetracycline and bisphosphonates (43, 44). The cellular components of bone tissue include MSCs, osteoblasts, osteoclasts, and adipocytes (45). Complex functions and the interaction of bone cells need that the drug delivery system has

precise cells targeted ability (46, 47). Advances in cell-targeted materials research used high-cell affinity peptides and nucleic acids as targeting components and growth factors as drug components (48). Recently, several studies reported that several exosomes from special origin are highly bone-targeting *in vivo* and have high drug delivery potential (49–52). Reactive Oxygen Species (ROS) appear in many aging diseases and can be a target in osteoporosis (53). There are many drugs that have bone-targeted function, including many small molecules from traditional Chinese drugs, which were reported could improve osteogenesis in fracture (53–55).

Bone augmentation strategies for common osteoporotic fractures

Proximal humerus fracture

The proximal humerus is a common site for osteoporotic fractures in the elderly. Conservative treatment is the first choice and gold standard for proximal humerus fractures with insignificant fracture displacement (lower than 1 cm). For large displacement fracture, the presence of significant bone loss in metaphysis of the proximal humerus fracture often results in fracture displacement and internal fixation failure after surgery, impedes early exercise of shoulder (56).

Fibular graft and calcium phosphate bone cement are suitable bone strengthen materials for different types of proximal humerus fracture. For varus proximal humerus fractures with defect of medial support, fibular bone grafting of fibular segment is feasible to support the humeral medial screw. Fibular segment graft can fill the bone defect and achieve good mechanical support of the medial cortex, reduce micro-movement of screws, strengthen the stability of the plate screw system, and reduce the incidence of postoperative complication (57, 58). In addition, allogeneic iliac bone and femoral head grafts can also increase bone volume and provide cortical enhancement of internal fixation but are not preferred (59). However, homogeneous fibular segments are of limited origin and are only indicated for severely comminuted proximal humeral fractures that lack medial support. Vascularized fibular graft can also promote bone healing but make second damage to patients so is not preferred.

For valgus-impacted fractures, bone defects occur at the lateral wall of the proximal humerus. The application of calcium phosphate bone cement technique during surgery can increase the strength of the bone and improve the local mechanical strength (60). Injectable calcium phosphate bone cement has certain advantages during operation. Whether to use CPC should consider the degree of bone defect and degree of osteoporosis. CPC and PMMA bone cement can be used as a bone augmentation for most osteoporotic proximal humerus fractures, but its mechanical strength is weaker than that of bone graft. Therefore, for proximal humeral fractures lacking support in the non-medial wall, bone cement injection can effectively enhance the treatment outcome. Proximal humeral fractures lacking medial support is the indication for bone grafting. Fibular graft is recommended, and other methods can be selected depending on the operative situations. Local bone substitute filling plays a positive role in treating valgus-impacted proximal humeral fractures.

Distal radius fracture

Distal radius fracture is the second prevalent osteoporotic fracture (61). Non-operative treatment including closed reduction and immobilize with splint and cast is recommended for a majority of distal radius fracture (62). Osteoporotic distal radius fractures have bone defects, articular surface collapse, fracture displacement after reduction, or secondary fracture need surgical intervention. Autologous iliac cancellous bone filling and inlay support with cortical bone can achieve structural reconstruction and prevent distal articular surface collapse. Stable maintenance of reduction after bone graft prevents loss of distal radius height and fracture re-displacement (63). Homogeneous bone and artificial bone are also an optional selection and avoid second damage (62). CaP injection combined with volar locking plate fixation of distal radius fracture is still controversial and is not preferred in this recommendation (64, 65). Autogenous iliac bone is ideal for effectively restoring the height of the distal radius, providing support to the collapsed cartilage surfaces, and increasing the stability of the internal fixation. Allograft bone and artificial bone may also be an alternative option.

Tibial plateau fracture

Ostesoporotic tibial plateau fracture is not common in elderly. Schatzker types I, II, and III fractures are main fracture type because of low-energy trauma (66). Conservative treatment through cast or orthosis is indicated for patients with small or non-displacement. For patients with significant displacement and acceptable soft tissue condition, plate fixation can promote functional rehabilitation under-weight bearing (67). Although high-energy tibial plateau fracture is not common in osteoporosis patient, late repair and total knee arthroplasty are recommended to protect soft tissue and restore knee function. The goals of surgical treatment are joint surface reconstruction and strong internal fixation. Bone graft assisted locking plate internal fixation has shown good outcome in the treatment of tibial plateau fractures (68). For Schatzker II–VI type tibial plateau fractures with articular surface collapse

greater than 5 mm, calcium phosphate or calcium sulfate injected artificial bone can be used to fill the bone defect to prevent postoperative articular surface collapse and reduce the occurrence of traumatic osteoarthritis. Sufficient artificial bone graft can maintain anatomical reduction and support internal fixation with definite clinical results. However, it is not clear whether artificial bone resorption is coupled with bone formation and whether a bone defect will form after resorption. Therefore, further research is needed. Bone graft combines with locking plate internal fixation therapy is still the mainstream in osteoporotic tibial plateau fractures treatment. Calcium phosphate or calcium sulfate injectable artificial bone can be used as a bone repair material for tibial plateau fractures with large articular surface collapse.

Pilon fracture

The collapse of the distal tibial articular surface in pilon fractures is caused by axial force, and intra-articular damage is severe in patients with osteoporosis (69). The four classical principles of pilon fractures treatment are as follows: restoration of fibular length, reconstruction of tibial articular surface, autologous bone grafting, and application of buttress plates (70). Autologous iliac bone graft or allogeneic bone graft can be used in the treatment of pilon fracture to enhance the mechanical support of the articular surface to increase stability of fracture sites. Bone graft can promote fracture healing and prevent the occurrence of late articular surface collapse. Autogenous iliac bone or allograft bone can be chosen as bone grafting material in treatment of pilon fractures.

Calcaneus fracture

It is still controversial whether bone graft is needed in calcaneus fracture. For Sanders' type II and above calcaneus fracture, bone defects larger than 2 cm^3, articular surface collapse large than 2 mm or difficult to maintain articular surface, bone graft is beneficial if soft tissue conditions allow. Bone graft permits early postoperative weight-bearing rehabilitation and helps to maintain articular surface stability (71, 72). Because calcaneus infection is a disaster for patient, it is generally considered safer to use autologous bone or allogeneic bone (73). The necessity for bone graft in calcaneus fractures remains controversial, and decision is based on the degree of articular surface collapse and bone defect.

Vertebral fracture

Osteoporotic Vertebral Compression Fracture (OVCF) happened within 3 months with significant pain, and an intact posterior wall of vertebra should be treated with vertebroplasty. Percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) are main vertebroplasty in clinic; both of them can restore the height and strength of the compressed vertebral body, improve spinal stability, prevent vertebral collapse, relieve pain, and improve spinal function. PKP has advantages in reducing the occurrence of cement leakage, restoring the height of the vertebral body, and correcting spinal deformity. In severe OVCF with vertebral height less than 1/3 of the original height, PKP is superior to PVP in restoring normal vertebral angle and height (73, 74). There is no consensus on how to choose between these two techniques; decision should be made according to preoperative condition and radiology image (75, 76). The amount of bone cement should be limited to 2–5 ml. Excessive bone cement may increase the risk of cement leakage, but long-term benefits are limited (77, 78). In clinical practice, the amount of bone cement should consider the size of the vertebral body, operative fluoroscopy, and the operator's experiences.

For OVCF with significant spinal cord injury, pedicle screws internal fixation with decompression and reduction is an option in patients without contraindications. There are no uniform criteria whether to use cement reinforcement in pedicle screw fixation. If the bone quality is poor during operative evaluation or screw loosens after nail insertion, cement strengthening techniques are indicated. The reinforced segment may choose 1–2 screws either in cephalad or caudal, and the whether to reinforce screws in the intermediate segment may be decided by operative condition (75, 79).

For most patients with OVCF, PVP or PKP can achieve similar outcomes, but PKP is more suitable for severe compression fractures. Strict operation is required to avoid the risk of cement leakage. Bone cement strengthening technique can be used as an important technique in OVCF internal fixation, which can help reduce incidence of internal fixation failure and loss of reduction.

Rehabilitation aids in osteoporotic fractures

Rehabilitation aids can be a non-operative treatment for osteoporotic fractures and accelerate postoperative rehabilitation. Early exercise and weight-bearing under the protection of aids are important for fracture healing and avoiding deterioration of osteoporosis.

Osteoporotic distal radius fractures need more time to recover and may lead to long-term functional disorders (80). The functional disorders have severe damage to ability and quality of life. Static stretch splints and dynamic stretch splints can lengthen soft tissues and restore range of motion to contracted joints. Those splints can be used to treat persistent wrist stiffness and prevent

bone loss after distal radius fractures and are effective when used in the early stage of rehabilitation (81).

Rehabilitation aids have been widely used in the treatment of osteoporotic foot and ankle fractures. The intrepid dynamic exoskeletal orthosis (IDEO) is a foot and ankle orthosis with energy storage-redistribution function. IDEO is originally designed for the rehabilitation of soldiers with complex lower extremity trauma to cure gait disorders. IDEO is also beneficial for patients with post-traumatic osteoarthritis, mild paralysis, and muscle atrophy (82). Studies have shown that IDEO improves walking speed in patients after pilon fracture and may be helpful for patients with high demand of activity (83). Calcaneus orthosis can be a non-operative treatment of calcaneus fractures without displacement. Full weight bearing can be achieved with the protection of the calcaneus orthosis. The pressure pad can be adjusted to gradually increase the weight bearing on the foot that facilitates early weight bearing and rehabilitation (84). In displaced osteoporotic calcaneus fractures, orthosis can also accelerate postoperative recovery.

The thoracolumbar orthosis provides rigid support and increases intra-abdominal pressure. Orthosis provides a semi-rigid cylindrical support around the spine and distributing the load on the spine. Clinical trials have demonstrated that thoracolumbar orthoses significantly increase trunk muscle strength, improve lung function, reduce kyphosis, and pain in patients with OVCF (84–86). Traditional rigid spinal orthoses are limited due to trunk muscle atrophy and restriction of breath and harmful for patients with osteoporosis (87). Dynamic thoracolumbar orthoses have a lower degree of immobilization based on the biofeedback activation of the low-back muscles and reported good clinical results (88). Although the application of thoracolumbar orthoses as a treatment in vertebral fracture is still contentious, it could be used as an aid in post-operative rehabilitation.

Consensus: Dynamic and static stretch splints are effective for early rehabilitation of distal radius fractures; foot and ankle orthoses have been widely used for foot and ankle osteoporotic fractures, facilitating early weight bearing and rehabilitation training; and dynamic thoracolumbar orthoses can help patients with osteoporotic thoracolumbar fractures to increase muscle strength and reduce pain.

Statement

This consensus is not a clinical treatment standard for osteoporotic fractures in the elderly but only an academic guideline recommendation. Under the constraints of individual patient and actual clinical conditions, the clinical treatment plan varies from person to person. With the development of medical technology, some parts of this consensus will be further improved.

Author contributions

HZ, YH, XC and SW contributed equally to this work. All authors contributed to the article and approved the submitted version.

Funding

National Key Research and Development Program (2018YFC2001500); National Natural Science Foundation of China Major Research Program Key Project (91749204); National Natural Science Foundation of China (81771491); Shanghai Health System Excellent Discipline Leader Program (2017BR011)

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer MY declared a shared parent affiliation with the authors ZS and DW at the time of review.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet* (2019) 393 (10169):364–76. doi: 10.1016/S0140-6736(18)32112-3

2. Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N, et al. Prevalence of osteoporosis and fracture in China: The China osteoporosis prevalence study. *JAMA Netw Open* (2021) 4(8):e2121106. doi: 10.1001/jamanetworkopen.2021.21106

3. Cheng X, Zhao K, Zha X, Du X, Li Y, Chen S, et al. Opportunistic screening using low-DoseCT and the prevalence of osteoporosis in China: A nationwide, multicenter study. *J Bone Miner Res* (2021) 36(3):427–35. doi: 10.1002/jbmr.4187

4. Migliorini F, Giorgino R, Hildebrand F, Spiezia F, Peretti GM, Alessandri-Bonetti M, et al. Fragility fractures: Risk factors and management in the elderly. *Medicina* (2021) 57(10):1119. doi: 10.3390/medicina57101119

5. Halvachizadeh S, Teuber H, Pape H, Allemann F. Principles and current concepts in the surgical treatment of fragility fractures in the elderly. *Best Pract Res Clin Rheumatol* (2019) 33(2):264–77. doi: 10.1016/j.berh.2019.03.018

6. Yu F, Xia W. The epidemiology of osteoporosis, associated fragility fractures, and management gap in China. *Arch Osteoporos* (2019) 14(1):32. doi: 10.1007/s11657-018-0549-y

7. Chen P, Li Z, Hu Y. Prevalence of osteoporosis in China: a meta-analysis and systematic review. *BMC Public Health* (2016) 16(1):1039. doi: 10.1186/s12889-016-3712-7

8. Yaacobi E, Sanchez D, Maniar H, Horwitz DS. Surgical treatment of osteoporotic fractures: An update on the principles of management. *Injury* (2017) 48(Suppl 7):S34–40. doi: 10.1016/j.injury.2017.08.036

9. Grant KD, Busse EC, Park DK, Baker KC. Internal fixation of osteoporotic bone. *J Am Acad Orthop Surg* (2018) 26(5):166–74. doi: 10.5435/JAAOS-D-16-00142

10. von Ruden C, Augat P. Failure of fracture fixation in osteoporotic bone. *Injury* (2016) 47(Suppl 2):S3–10. doi: 10.1016/S0020-1383(16)47002-6

11. Rothberg DL, Lee MA. Internal fixation of osteoporotic fractures. *Curr Osteoporos Rep* (2015) 13(1):16–21. doi: 10.1007/s11914-014-0245-9

12. Chen X, Liu P, Zhu X, Cao L, Zhang C, Su J. Design and application of nickel-titanium olecranon memory connector in treatment of olecranon fractures: a prospective randomized controlled trial. *Int Orthop* (2013) 37(6):1099–105. doi: 10.1007/s00264-013-1878-5

13. Su JC, Liu XW, Yu BQ, Li ZD, Li M, Zhang CC. Shape memory Ni-Ti alloy swan-like bone connector for treatment of humeral shaft nonunion. *Int Orthop* (2010) 34(3):369–75. doi: 10.1007/s00264-009-0726-0

14. Liu X, Xu S, Zhang C, Su J, Yu B. Application of a shape-memory alloy internal fixator for treatment of acetabular fractures with a follow-up of two to nine years in China. *Int Orthop* (2010) 34(7):1033–40. doi: 10.1007/s00264-009-0867-1

15. Roberts TT, Rosenbaum AJ. Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing. *Organogenesis* (2012) 8(4):114–24. doi: 10.4161/org.23306

16. Kim DS, Lee DH, Chun YM, Shin SJ. Which additional augmented fixation procedure decreases surgical failure after proximal humeral fracture with medial comminution: fibular allograft or inferomedial screws? *J Shoulder Elbow Surg* (2018) 27(10):1852–8. doi: 10.1016/j.jse.2018.03.020

17. Chow RM, Begum F, Beaupre LA, Carey JP, Adeeb S, Bouliane MJ. Proximal humeral fracture fixation: locking plate construct +/- intramedullary fibular allograft. *J Shoulder Elbow Surg* (2012) 21(7):894–901. doi: 10.1016/j.jse.2011.04.015

18. Mathison C, Chaudhary R, Beaupre L, Reynolds M, Adeeb S, Bouliane M. Biomechanical analysis of proximal humeral fixation using locking plate fixation with an intramedullary fibular allograft. *Clin Biomech (Bristol Avon)* (2010) 25(7):642–6. doi: 10.1016/j.clinbiomech.2010.04.006

19. Ilan DI, Ladd AL. Bone graft substitutes. *Handb Clin* (2012) 28(4):457–68. doi: 10.1016/j.hcl.2012.08.001

20. Kim JB, Lee DY, Seo SG, Kim EJ, Kim JH, Yoo WJ, et al. Demineralized bone matrix injection in consolidation phase enhances bone regeneration in distraction osteogenesis *via* endochondral bone formation. *Clin Orthop Surg* (2015) 7(3):383–91. doi: 10.4055/cios.2015.7.3.383

21. Hak DJ. The use of osteoconductive bone graft substitutes in orthopaedic trauma. *J Am Acad Orthop Surg* (2007) 15(9):525–36. doi: 10.5435/00124635-200709000-00003

22. Gu Z, Wang S, Weng W, Chen X, Cao L, Wei J, et al. Influences of doping mesoporous magnesium silicate on water absorption, drug release, degradability, apatite-mineralization and primary cells responses to calcium sulfate based bone cements. *Mater Sci Eng C Mater Biol Appl* (2017) 75:620–8. doi: 10.1016/j.msec.2017.02.100

23. Cao L, Weng W, Chen X, Zhang J, Zhou Q, Cui J, et al. Promotion of *in vivo* degradability, vascularization and osteogenesis of calcium sulfate-based bone cements containing nanoporous lithium doping magnesium silicate. *Int J Nanomed* (2017) 12:1341–52. doi: 10.2147/IJN.S124965

24. Tang Z, Li X, Tan Y, Fan H, Zhang X. The material and biological characteristics of osteoinductive calcium phosphate ceramics. *Regener Biomater* (2018) 5(1):43–59. doi: 10.1093/rb/rbx024

25. Scheer JH, Adolfsson LE. Tricalcium phosphate bone substitute in corrective osteotomy of the distal radius. *Injury* (2009) 40(3):262–7. doi: 10.1016/j.injury.2008.08.013

26. Nich C, Sedel L. Bone substitution in revision hip replacement. *Int Orthop* (2006) 30(6):525–31. doi: 10.1007/s00264-006-0135-6

27. Gaasbeek RD, Toonen HG, van Heerwaarden RJ, Buma P. Mechanism of bone incorporation of beta-TCP bone substitute in open wedge tibial osteotomy in patients. *Biomaterials* (2005) 26(33):6713–9. doi: 10.1016/j.biomaterials.2005.04.056

28. Schulte TL, Keiler A, Riechelmann F, Lange T, Schmoelz W. Biomechanical comparison of vertebral augmentation with silicone and PMMA cement and two filling grades. *Eur Spine J* (2013) 22(12):2695–701. doi: 10.1007/s00586-013-2908-0

29. Ooms EM, Wolke JG, van de Heuvel MT, Jeschke B, Jansen JA. Histological evaluation of the bone response to calcium phosphate cement implanted in cortical bone. *Biomaterials* (2003) 24(6):989–1000. doi: 10.1016/s0142-9612(02)00438-6

30. Marx D, Yazdi AR, Papini M, Towler M. *In vitro* osteogenic performance of two novel strontium and zinc-containing glass polyalkenoate cements. *J Biomed Mater Res A* (2021) 109(8):1366–78. doi: 10.1002/jbm.a.37127

31. Wang S, Gu Z, Wang Z, Chen X, Cao L, Cai L, et al. Influences of mesoporous magnesium calcium silicate on mineralization, degradability, cell responses, curcumin release from macro-mesoporous scaffolds of gliadin based biocomposites. *Sci Rep* (2018) 8(1):174. doi: 10.1038/s41598-017-18660-9

32. Zhang H, Han L, Xue X. Rational design of multifunctional CuS nanoparticle-PEG composite soft hydrogel-coated 3D hard polycaprolactone scaffolds for efficient bone regeneration. *Adv Funct Mater* (2022) 32:2202470. doi: 10.1002/adfm.202202470

33. Han L, Wang S, Xue X. Neutrophil-erythrocyte hybrid membrane-coated hollow copper sulfide nanoparticles for targeted and photothermal/ anti-inflammatory therapy of osteoarthritis. *Comp Part B: Eng* (2022) 237:109855. doi: 10.1016/j.compositesb.2022.109855

34. Geng Z, Sang S, Wang S, Meng F, Li Z, Zhu S, et al. Optimizing the strontium content to achieve an ideal osseointegration through balancing apatite-forming ability and osteogenic activity. *Mater Sci Eng C Mater Biol Appl* (2022) 133:112647. doi: 10.1016/j.msec.2022.112647

35. Niu Y, Cao L, Wei J, Ma Y, Song S, Weng W, et al. Development of a bioactive composite of nano fluorapatite and poly(butylene succinate) for bone tissue regeneration. *J Mater Chem B* (2014) 2(9):1174–81. doi: 10.1039/c3tb21371d

36. Su J, Cao L, Yu B, Song S, Liu X, Wang Z, et al. Composite scaffolds of mesoporous bioactive glass and polyamide for bone repair. *Int J Nanomed* (2012) 7:2547–55. doi: 10.2147/IJN.S29819

37. Xue X, Hu Y, Wang S, Chen X, Jiang Y, Su J. Fabrication of physical and chemical crosslinked hydrogels for bone tissue engineering. *Bioact Mater* (2022) 12:327–39. doi: 10.1016/j.bioactmat.2021.10.029

38. Hu Y, Deng Y, Xue X. Recent advances in design of functional biocompatible hydrogels for bone tissue engineering. *Adv Funct Mater* (2021) 19(31):2009432. doi: 10.1002/adfm.202009432

39. Metavarayuth K, Maturavongsadit P, Chen X, Sitasuwan P, Lu L, Su J, et al. Nanotopographical cues mediate osteogenesis of stem cells on virus substrates through BMP-2 intermediate. *Nano Lett* (2019) 19(12):8372–80. doi: 10.1021/acs.nanolett.9b02001

40. Chen W, Zhou Z, Chen D, Li Y, Zhang Q, Su J. Bone regeneration using MMP-cleavable peptides-based hydrogels. *Gels* (2021) 7(4):199. doi: 10.3390/gels7040199

41. Chen S, Chen X, Geng Z, Su J. The horizon of bone organoid: A perspective on construction and application. *Bioact Mater* (2022) 18:15–25. doi: 10.1016/j.bioactmat.2022.01.048

42. C. X. G. Z. REN X. Bone-targeted biomaterials: Strategies and applications. *Chem Eng J* (2022) 446:137133. doi: 10.1016/j.cej.2022.137133

43. Salmen J, Banys-Paluchowski M, Fehm T. Bone-targeted therapy. *Geburtshilfe Frauenheilkd* (2015) 75(6):584–7. doi: 10.1055/s-0035-1546151

44. Wang Z, Li M, Yu B, Cao L, Yang Q, Su J. Nanocalcium-deficient hydroxyapatite-poly (e-caprolactone)-polyethylene glycol-poly (e-caprolactone) composite scaffolds. *Int J Nanomed* (2012) 7:3123–31. doi: 10.2147/IJN.S31162

45. Gao Q, Wang L, Wang S, Huang B, Jing Y, Su J. Bone marrow mesenchymal stromal cells: Identification, classification, and differentiation. *Front Cell Dev Biol* (2021) 9:787118. doi: 10.3389/fcell.2021.787118

46. Hu Y, Li X, Zhi X, Cong W, Huang B, Chen H, et al. RANKL from bone marrow adipose lineage cells promotes osteoclast formation and bone loss. *EMBO Rep* (2021) 22(7):e52481. doi: 10.15252/embr.202152481

47. Wang L, Zhang H, Wang S, Chen X, Su J. Bone marrow adipocytes: A critical player in the bone marrow microenvironment. *Front Cell Dev Biol* (2021) 9:770705. doi: 10.3389/fcell.2021.770705

48. Barth C, Massard C, Vignot S. [Bone targeted therapies: new agents]. *Bull Cancer* (2013) 100(11):1215–21. doi: 10.1684/bdc.2013.1834

49. Cui Y, Guo Y, Kong L, Shi J, Liu P, Li R, et al. A bone-targeted engineered exosome platform delivering siRNA to treat osteoporosis. *Bioact Mater* (2022) 10:207–21. doi: 10.1016/j.bioactmat.2021.09.015

50. Hu Y, Li X, Zhang Q, Gu Z, Luo Y, Guo J, et al. Exosome-guided bone targeted delivery of antagomir-188 as an anabolic therapy for bone loss. *Bioact Mater* (2021) 6(9):2905–13. doi: 10.1016/j.bioactmat.2021.02.014

51. Song H, Li X, Zhao Z, Qian J, Wang Y, Cui J, et al. Reversal of osteoporotic activity by endothelial cell-secreted bone targeting and biocompatible exosomes. *Nano Lett* (2019) 19(5):3040–8. doi: 10.1021/acs.nanolett.9b00287

52. Sun J, Yin Z, Wang X, Su J. Exosome-laden hydrogels: A novel cell-free strategy for in-situ bone tissue regeneration. *Front Bioeng Biotechnol* (2022) 10:866208. doi: 10.3389/fbioe.2022.866208

53. Ren X, Liu H, Wu X, Weng W, Wang X, Su J. Reactive oxygen species (ROS)-responsive biomaterials for the treatment of bone-related diseases. *Front Bioeng Biotechnol* (2021) 9:820468. doi: 10.3389/fbioe.2021.820468

54. Zhou D, Zhang H, Xue X, Tao Y, Wang S, Ren X, et al. Safety evaluation of natural drugs in chronic skeletal disorders: A literature review of clinical trials in the past 20 years. *Front Pharmacol* (2021) 12:801287. doi: 10.3389/fphar.2021.801287

55. Li X, Wang L, Huang B, Gu Y, Luo Y, Zhi X, et al. Targeting actin-bundling protein l-plastin as an anabolic therapy for bone loss. *Sci Adv* (2020) 6(47): eabb7135. doi: 10.1126/sciadv.abb7135

56. Krappinger D, Bizzotto N, Riedmann S, Kammerlander C, Hengg C, Kralinger FS. Predicting failure after surgical fixation of proximal humerus fractures. *Injury* (2011) 42(11):1283–8. doi: 10.1016/j.injury.2011.01.017

57. Ponce BA, Thompson KJ, Raghava P, Eberhardt AW, Tate JP, Volgas DA, et al. The role of medial comminution and calcar restoration in varus collapse of proximal humeral fractures treated with locking plates. *J Bone Joint Surg Am* (2013) 95(16):e113(1–7). doi: 10.2106/JBJS.K.00202

58. Lescheid J, Zdero R, Shah S, Kuzyk PR, Schemitsch EH. The biomechanics of locked plating for repairing proximal humerus fractures with or without medial cortical support. *J Trauma* (2010) 69(5):1235–42. doi: 10.1097/TA.0b013e3181beed96

59. Zhu L, Liu Y, Yang Z, Li H, Wang J, Zhao C, et al. Locking plate fixation combined with iliac crest bone autologous graft for proximal humerus comminuted fracture. *Chin Med J (Engl)* (2014) 127(9):1672–6. doi: 10.3760/cma.j.issn.0366-6999.20133104

60. Civinini R, Capone A, Carulli C, Matassi F, Nistri L, Innocenti M. The kinetics of remodeling of a calcium sulfate/calcium phosphate bioceramic. *J Mater Sci Mater Med* (2017) 28(9):137. doi: 10.1007/s10856-017-5940-5

61. Jung HS, Jang S, Chung HY, Park SY, Kim HY, Ha YC, et al. Incidence of subsequent osteoporotic fractures after distal radius fractures and mortality of the subsequent distal radius fractures: a retrospective analysis of claims data of the Korea national health insurance service. *Osteoporos Int* (2021) 32(2):293–9. doi: 10.1007/s00198-020-05609-4

62. Ostergaard PJ, Hall MJ, Rozental TD. Considerations in the treatment of osteoporotic distal radius fractures in elderly patients. *Curr Rev Musculoskelet Med* (2019) 12(1):50–6. doi: 10.1007/s12178-019-09531-z

63. Meiners J, Jurgens C, Magerlein S, Wallstabe S, Kienast B, Faschingbauer M. Osteoporotic fractures of the distal radius. what is new?. *Chirurg* (2012) 83 (10):892–6. doi: 10.1007/s00104-012-2341-7

64. Kainz H, Dall Ara E, Antoni A, Redl H, Zysset P, Weninger P. Calcium phosphate cement augmentation after volar locking plating of distal radius fracture significantly increases stability. *Eur J Orthop Surg Traumatol* (2014) 24(6):869–75. doi: 10.1007/s00590-013-1285-z

65. Kim JK, Koh YD, Kook SH. Effect of calcium phosphate bone cement augmentation on volar plate fixation of unstable distal radial fractures in the elderly. *J Bone Joint Surg* (2011) 93(7):609–14. doi: 10.2106/JBJS.J.00613

66. Donovan RL, Smith JRA, Yeomans D, Bennett F, White P, Chesser TJS. Epidemiology and outcomes of tibial plateau fractures in adults aged 60 and over treated in the united kingdom. *Injury* (2022) 53(6):2219–25. doi: 10.1016/j.injury.2022.03.048

67. He Q, Sun H, Shu L, Zhan Y, He C, Zhu Y, et al. Tibial plateau fractures in elderly people: an institutional retrospective study. *J Orthop Surg Res* (2018) 13 (1):276. doi: 10.1186/s13018-018-0986-8

68. Ollivier M, Bulaid Y, Jacquet C, Pesenti S, Argenson JN, Parratte S. Fixation augmentation using calcium-phosphate bone substitute improves outcomes of complex tibial plateau fractures. *A matched cohort study Int Orthop* (2018) 42 (12):2915–23. doi: 10.1007/s00264-018-3926-7

69. Sain A, Garg S, Sharma V, Meena UK, Bansal H. Osteoporotic distal fibula fractures in the elderly: How to fix them. *Cureus* (2020) 12(1):e6552. doi: 10.7759/cureus.6552

70. Lee KM, Chung CY, Kwon SS, Won SH, Lee SY, Chung MK, et al. Ankle fractures have features of an osteoporotic fracture. *Osteoporos Int* (2013) 24 (11):2819–25. doi: 10.1007/s00198-013-2394-6

71. Cao H, Li YG, An Q, Gou B, Qian W, Guo XP, et al. Short-term outcomes of open reduction and internal fixation for sanders type III calcaneal fractures with and without bone grafts. *J Foot Ankle Surg* (2018) 57(1):7–14. doi: 10.1053/j.jfas.2017.05.037

72. Duymus TM, Mutlu S, Mutlu H, Ozel O, Guler O, Mahirogullari M. Need for bone grafts in the surgical treatment of displaced intra-articular calcaneal fractures. *J Foot Ankle Surg* (2017) 56(1):54–8. doi: 10.1053/j.jfas.2016.08.004

73. Cao L, Weng W, Song S, Mao N, Li H, Cai Y, et al. Surgical treatment of calcaneal fractures of sanders type II and III by a minimally invasive technique using a locking plate. *J Foot Ankle Surg* (2015) 54(1):76–81. doi: 10.1053/j.jfas.2014.09.003

74. Wang F, Wang LF, Miao DC, Dong Z, Shen Y. Which one is more effective for the treatment of very severe osteoporotic vertebral compression fractures: PVP or PKP? *J Pain Res* (2018) 11:2625–31. doi: 10.2147/JPR.S179022

75. Rong Z, Zhang F, Xiao J, Wang Z, Luo F, Zhang Z, et al. Application of cement-injectable cannulated pedicle screw in treatment of osteoporotic thoracolumbar vertebral compression fracture (AO type a): A retrospective study of 28 cases. *World Neurosurg* (2018) 120:e247-e258. doi: 10.1016/j.wneu.2018.08.045

76. Liu T, Li Z, Su Q, Hai Y. Cement leakage in osteoporotic vertebral compression fractures with cortical defect using high-viscosity bone cement during unilateral percutaneous kyphoplasty surgery. *Med (Baltimore)* (2017) 96 (25):e7216. doi: 10.1097/MD.0000000000007216

77. Chen X, Ren J, Zhang J, Li S, Liu Z. Impact of cement placement and leakage in osteoporotic vertebral compression fractures followed by percutaneous vertebroplasty. *Clin Spine Surg* (2016) 29(7):E365-70. doi: 10.1097/BSD.0b013e3182aa28d6

78. Landham PR, Baker-Rand HL, Gilbert SJ, Pollintine P, Annesley-Williams DJ, Adams MA, et al. Is kyphoplasty better than vertebroplasty at restoring form and function after severe vertebral wedge fractures? *Spine J* (2015) 15(4):721–32. doi: 10.1016/j.spinee.2014.11.017

79. Aydogan M, Ozturk C, Karatoprak O, Tezer M, Aksu N, Hamzaoglu A. The pedicle screw fixation with vertebroplasty augmentation in the surgical treatment of the severe osteoporotic spines. *J Spinal Disord Tech* (2009) 22(6):444–7. doi: 10.1097/BSD.0b013e31818e0945

80. Edwards BJ, Song J, Dunlop DD, Fink HA, Cauley JA. Functional decline after incident wrist fractures–study of osteoporotic fractures: prospective cohort study. *BMJ* (2010) 341:c3324. doi: 10.1136/bmj.c3324

81. Lucado AM, Li Z. Static progressive splinting to improve wrist stiffness after distal radius fracture: a prospective, case series study. *Physiother Theory Pract* (2009) 25(4):297–309. doi: 10.1080/09593980902782389

82. Highsmith MJ, Nelson LM, Carbone NT, Klenow TD, Kahle JT, Hill OT, et al. Outcomes associated with the intrepid dynamic exoskeletal orthosis (IDEO): A systematic review of the literature. *Mil. Med* (2016) 181(S4):69–76. doi: 10.7205/MILMED-D-16-00280

83. Quacinella M, Bernstein E, Mazzone B, Wyatt M, Kuhn KM. Do spatiotemporal gait parameters improve after pilon fracture in patients who use the intrepid dynamic exoskeletal orthosis? *Clin Orthop Relat Res* (2019) 477 (4):838–47. doi: 10.1097/CORR.0000000000000487

84. Ruffing T, Muhm M, Winkler H. [Pediatric calcaneal fracture after supination trauma: conservative therapy with an orthosis]. *Unfallchirurg* (2013) 116(11):1030–2. doi: 10.1007/s00113-012-2291-z

85. Pfeifer M, Kohlwey L, Begerow B, Minne HW. Effects of two newly developed spinal orthoses on trunk muscle strength, posture, and quality-of-life in women with postmenopausal osteoporosis: a randomized trial. *Am J Phys Med Rehabil* (2011) 90(10):805–15. doi: 10.1097/PHM.0b013e31821f6df3

86. Pfeifer M, Begerow B, Minne HW. Effects of a new spinal orthosis on posture, trunk strength, and quality of life in women with postmenopausal osteoporosis: a randomized trial. *Am J Phys Med Rehabil* (2004) 83(3):177–86. doi: 10.1097/01.phm.0000113403.16617.93

87. Murata K, Watanabe G, Kawaguchi S, Kanaya K, Horigome K, Yajima H, et al. Union rates and prognostic variables of osteoporotic vertebral fractures treated with a rigid external support. *J Neurosurg Spine* (2012) 17(5):469–75. doi: 10.3171/2012.7.SPINE122

88. Meccariello L, Muzii VF, Falzarano G, Medici A, Carta S, Fortina M, et al. Dynamic corset versus three-point brace in the treatment of osteoporotic compression fractures of the thoracic and lumbar spine: a prospective, comparative study. *Aging Clin Exp Res* (2017) 29(3):443–9. doi: 10.1007/s40520-016-0602-x

COPYRIGHT

© 2022 Zhang, Hu, Chen, Wang, Cao, Dong, Shi, Chen, Xiong, Zhang, Zhang, Yu, Chen, Wang, Tong, Liu, Zhang, Zhou, Niu, Yang, Zhang, Wang, Chen, Jia, Yang, Zhang, Zhang, Miao, Sun, Shen, Yu, Yang, Zhang, Wang, Liu, Zhang and Su. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.